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Protocol

A Mobile Intervention to Promote Low-Risk Drinking Habits in Young Adults: Protocol for a Randomized Controlled Trial

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Abstract

Background: Young adults' drinking habits commonly exceed recommendations for low-risk drinking, which may have a negative effect on their mental, social, and physical health. As smartphones are highly accessible to young adults, mobile apps could be used to support young adults to develop low-risk drinking habits and improve their general health.

Objective: The objective of this study is to evaluate the effectiveness of Boozebuster, a self-guided mobile app based on healthy lifestyle–related components that aim to develop and maintain low-risk drinking habits among young adults.

Methods: This two-arm, parallel-group randomized controlled trial will investigate whether a 6-week self-guided mobile intervention (Boozebuster) targeting drinking behavior is more effective than a minimal intervention consisting of an educational website on alcohol use and its consequences for young adults. We will recruit 506 young adults (aged 18-30 years) from the Netherlands via an open recruitment strategy by using an open access website. All outcomes will be self-assessed through questionnaires. The primary outcome is the quantity and frequency of alcohol consumption in standard drinks (10 g ethanol per standard drink) per month (timeline follow-back [TLFB]). Secondary outcomes include binge-drinking sessions per month, alcohol-related problem severity (Rutgers Alcohol Problem Index), cannabis use frequency and quantity in grams (TLFB), depressive symptoms (Center for Epidemiological Studies Depression Scale), perceived stress (Perceived Stress Scale), engagement (Twente Engagement with eHealth Technologies Scale), readiness to change (Readiness to Change Questionnaire), mental well-being (Warwick-Edinburgh Mental Wellbeing Scale), trauma and COVID-19–related trauma (Short-Form Posttraumatic Stress Disorder Checklist for Diagnostic and Statistical Manual of Mental Disorders, 5th Edition), impulsivity (Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency Impulsive Behavior Scale), study or work performance (Individual Work Performance Questionnaire), and treatment adherence. Baseline (T0), 6-week postbaseline (T1), and 3-month postbaseline (T2) assessments will be conducted and analyzed on the basis of the intention-to-treat principle using multilevel mixed modeling analyses.

Results: Recruitment began in September 2020. We received 933 registrations via our study information website; 506 participants have completed the T0 assessment, 336 participants have completed the T1 assessment, and 308 participants have completed the T2 assessment as of May 2021. The study is still in progress, and results will be reported in 2021 and 2022.

Conclusions: Self-guided mobile interventions based on a lifestyle approach might be an attractive approach for young adults due to their preference on self-reliance, healthy living, and increased perceived anonymity. Such interventions are yet understudied, and it is known that interventions addressing solely problem drinking are less appealing to young adults. We hypothesize that the Boozebuster mobile app will effectively reduce drinking levels compared to an alcohol educational website (control condition). If effective, our intervention could be an inexpensive and scalable public health intervention to improve drinking habits in young adults.

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International Registered Report Identifier (IRRID): DERR1-10.2196/29750

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KEYWORDS

alcohol; lifestyle; drinking; young adults; digital; mobile app; COVID-19

Introduction

It is well known that the prevalence of alcohol consumption among young adults is high and that their drinking habits commonly exceed low-risk drinking guidelines [1]. A study by the Dutch National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu) showed, for example, that 8.9% of young adults were considered problem drinkers, defined as individuals who drink more than 21 standard glasses of alcohol per week for males and more then 14 standard glasses of alcohol per week for females. Alcohol consumption among young adults is characterized by a drinking pattern that differs from the general population. Specifically, we know that young adults are more likely to binge drink, especially during the weekends [2]. In addition, binge drinking occurs in about 11.4%-19.4% of young adults (18-29 years of age) compared to approximately 7.7% of the general population [3]. Consequently, young adults' drinking patterns pose a significant negative effect on young adults' mental, social, and physical health [4].

According to the literature, face-to-face interventions delivered in individual or group settings targeting young adults' drinking patterns are effective [5,6]. However, given that young adults commonly avoid traditional counseling services due to perceived stigma and their preference for self-reliance [7,8], a potential solution to overcome these obstacles might be to provide self-guided digital interventions, which require limited resources compared to traditional prevention and treatment services.

Ample digital interventions that are aimed to reduce drinking levels in young adults, mostly in university settings located in the United States or Australia, have been previously evaluated. The majority of these interventions consist of internet-based single-session interventions, based on personalized normative feedback (PNF), that aim to correct erroneous perceptions of peer drinking levels by assessing personal drinking levels and consequently comparing them with drinking levels in similar-aged peer groups [9]; general alcohol education programs that are commonly incorporated within general education curriculums and provide educational modules about alcohol use, its dangers, and often focus on ensuring students comply with the law [10]; or brief interventions that screen for problematic drinking patterns and present feedback motivating individuals to alter those patterns [11].

The majority of the above-described digital interventions are delivered via a computer or web browser. However, it has been claimed that mobile apps are more suitable for young adults given the flexibility, interactivity, and their spontaneous nature [12]. However, a recent review assessed mobile apps developed with the purpose of managing alcohol consumption found that the evidence is promising but still inconclusive given the mixed results [13].

Although single-session interventions can reach a high number of individuals due to their appealing, limited time requirement, they are associated with a few important disadvantages such as the relatively small effect sizes produced and the limited longevity of those effects. For example, meta-analyses assessing single-session interventions show small effect sizes when compared to assessment only, attention-matched, or active controls ranging from g=0.18 to g=0.29 [5,14-18]. In addition, studies that assess long-term outcomes often show that those effects cease to exist in follow-up periods [19]. Lifestyle medicine is a relatively new approach for the potential prevention, promotion, and management of mental health conditions. It involves the use of environmental, behavioral, and psychological principles to improve physical and mental well-being by modifying lifestyle factors such as diet, physical activity, relaxation, sleep, and stress [20]. Although lifestyle modification has been extensively studied in particular regarding the prevention of chronic diseases [21], research about its value in curbing drinking among young adults is very limited. However, studies have shown that digital lifestyle interventions that target multiple behaviors may increase and prolong the effectiveness of behavioral change interventions targeting young adults [22-24].

Therefore, in our intervention, we decided to incorporate relevant lifestyle components that have been shown to be perceived as relevant and important for our target group's general well-being [25-27]. Such lifestyle-related topics include sleeping habits, mood, and perceived stress. We expect that by providing young adults with relevant lifestyle components in addition to the alcohol-related intervention content, we have a potential to increase and prolong effect sizes regarding drinking outcomes, while retaining the acceptability and reach of single-session interventions.

Methods

Study Design

We will conduct a two-arm, parallel-group randomized controlled trial (RCT) comparing a 6-week mobile app (Boozebuster) with an active educational website control condition. Participants in the Boozebuster condition will receive access to the self-guided mobile app; participants in the control condition will receive access to an educational website containing information about the effects and consequences of alcohol use on health. The Scientific and Ethical Review Committee of the Faculty of Behavioral and Movement Sciences of the Vrije Universiteit Amsterdam has approved the study protocol, informational letter, and informed consent process. The primary and secondary outcomes in addition to the exact timepoints at which each measure will be applied is presented in Table 1. The study is registered with the Netherlands Trial Registry (NL8828).

Table 1. Overview of study measurements, timepoints, and instruments.

Outcome measures	Baseline (T0)	6-week postbaseline (T1)	3-month postbaseline (T2)
Sociodemographics	✓		
Alcohol consumption, frequency, and quantity (TLFB[a])	✓	✓	✓
Binge-drinking frequency	✓	✓	✓
Cannabis consumption, frequency, and quantity (TLFB)	✓	✓	✓
Depressive symptoms (CES-D[b] Scale)	✓	✓	✓
Perceived stress (PSS[c])	✓	✓	✓
Alcohol-related problem severity (RAPI[d])	✓	✓	✓
Readiness to change (RCQ[e])	✓	✓	
Task performance (IWPQ[f])	✓	✓	✓
Engagement (TWEETS[g])	✓	✓	
Mental well-being (WEMWBS[h])	✓	✓	✓
Short-form PCL-5[i]	✓	✓	✓
Short-form PCL-5 – COVID-19	✓	✓	✓
UPPS-P[j] Impulsive Behavior Scale	✓	✓	✓

[a]TLFB: timeline follow-back.

[b]CES-D: Center for Epidemiological Studies Depression.

[c]PSS: Perceived Stress Scale.

[d]RAPI: Rutgers Alcohol Problem Index.

[e]RCQ: Readiness to Change Questionnaire.

[f]IWPQ: Individual Work Performance Questionnaire.

[g]TWEETS: Twente Engagement with eHealth Technologies Scale.

[h]WEMWBS: Warwick-Edinburgh Mental Wellbeing Scale.

[i]PCL-5: Posttraumatic Stress Disorder Checklist for Diagnostic and Statistical Manual of Mental Disorders, 5th edition.

[j]UPPS-P: Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency.

Inclusion Criteria

Young adults will be eligible for the RCT if they meet the following criteria: (1) aged between 18 and 30 years, (2) willingness to develop healthy lifestyle behaviors and low-risk drinking habits, (3) provision of informed consent digitally, (4) proficiency in reading and writing in Dutch, (5) access to an Android or IOS device with connection to the internet, and (6) possession of an email address. We did not apply a minimum drinking severity inclusion criterion. Our reasoning for not screening drinking severity is based on the fact that the Dutch drinking guidelines recommend an alcohol consumption level of zero or no more than 1 alcoholic drink per day.

Recruitment

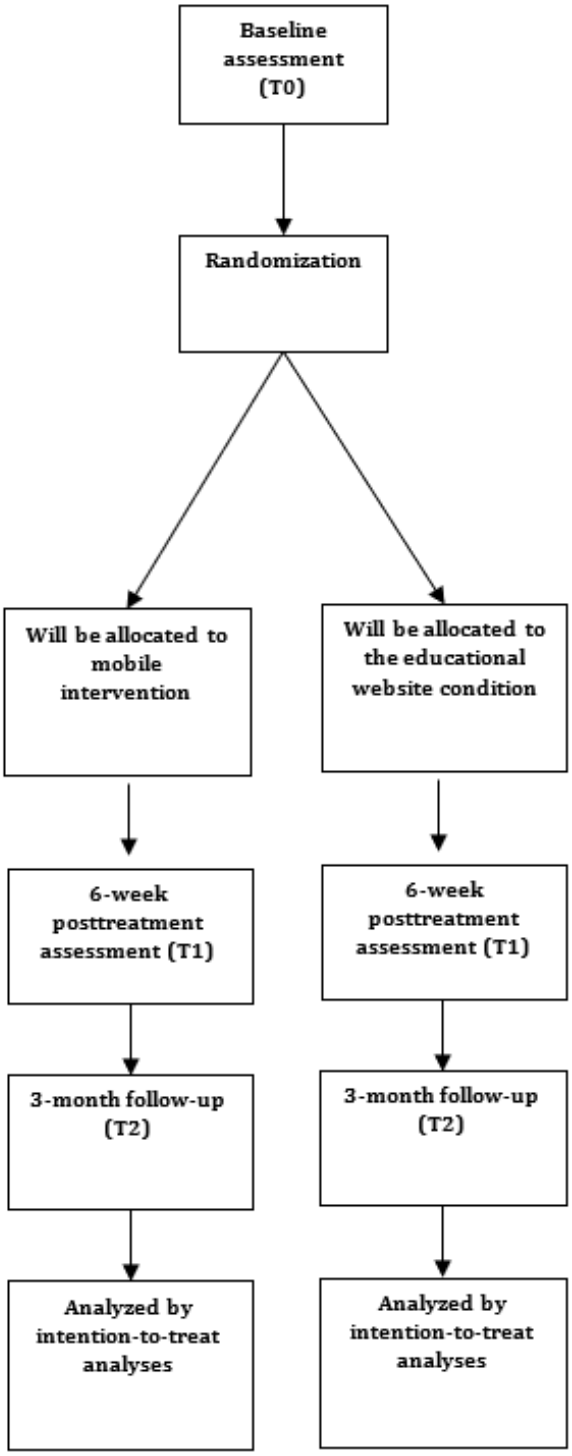
We will make use of an open recruitment strategy, specifically, by means of advertisements on social media and health-related websites and via posters on educational facilities. These advertisements contain a link to our study information website [28]. Interested respondents can apply by leaving their email address, and they will be consequently contacted via email by the research team. The participants will be invited to complete a baseline assessment (T0), 6-week postbaseline assessment (T1), and 3-month postbaseline assessment (T2) via the computerized Castor Electronic Data Capture (EDC) system [29]. All participants will be offered an incentive of €10 (US $12.2) for completing the T1 assessment and an additional €10 (US $12.2) incentive for completing the T2 assessment.

Randomization

First, participants will be screened, asked to fill out the baseline assessment (T0), and then randomized into either the mobile intervention or the educational website group. The allocation sequence will be automatically generated via the computerized Castor EDC system by using a 1:1 allocation ratio with random block sizes of 4 and 6, which also ensures allocation sequence concealment. Participants will be informed about the outcome of the randomization via email by a member of our research team. Initial stratification will be into two groups according to gender (ie, male and female). Within these two groups, participants will be further stratified into two groups categorized by adherence or nonadherence to the Dutch drinking guidelines. Nonadherence will be defined as the consumption of more than 7 drinks per week or at least one binge-drinking session (≥5 drinks for male participants and ≥4 drinks for female participants) in the past 30 days. This will create four strata. Because of the nature of our study design, blinding of group

allocation for participants is not possible. Figure 1 provides an overview of the trial flow.

Figure 1. Overview of the participant flow for the randomized controlled trial.



Sample Size

Previous meta-analyses assessing drinking reduction in young adults compared to assessment only, attention-matched, or active controls [17,18] found small effect sizes of about g=0.25. Although we expect the Boozebuster intervention to outperform previous interventions in reducing the quantity and frequency of alcohol consumption in comparison to the control condition at the posttest assessments, we decided to base our sample size calculation on this conservative effect estimate. These estimations would result with α=.05 and 1–β=.80 in a sample size of 253 per study arm (ie, N=506).

Intervention

Boozebuster is a mobile app aimed at developing low-risk drinking habits in young adults according to the Dutch drinking

guidelines. It has been developed by Vrije Universiteit Amsterdam in collaboration with the Institute for Systems and Computer Engineering, Technology and Science [30]. Boozebuster is based on the Moodbuster platform, which is being used for a variety of research projects funded by the European Union [31,32].

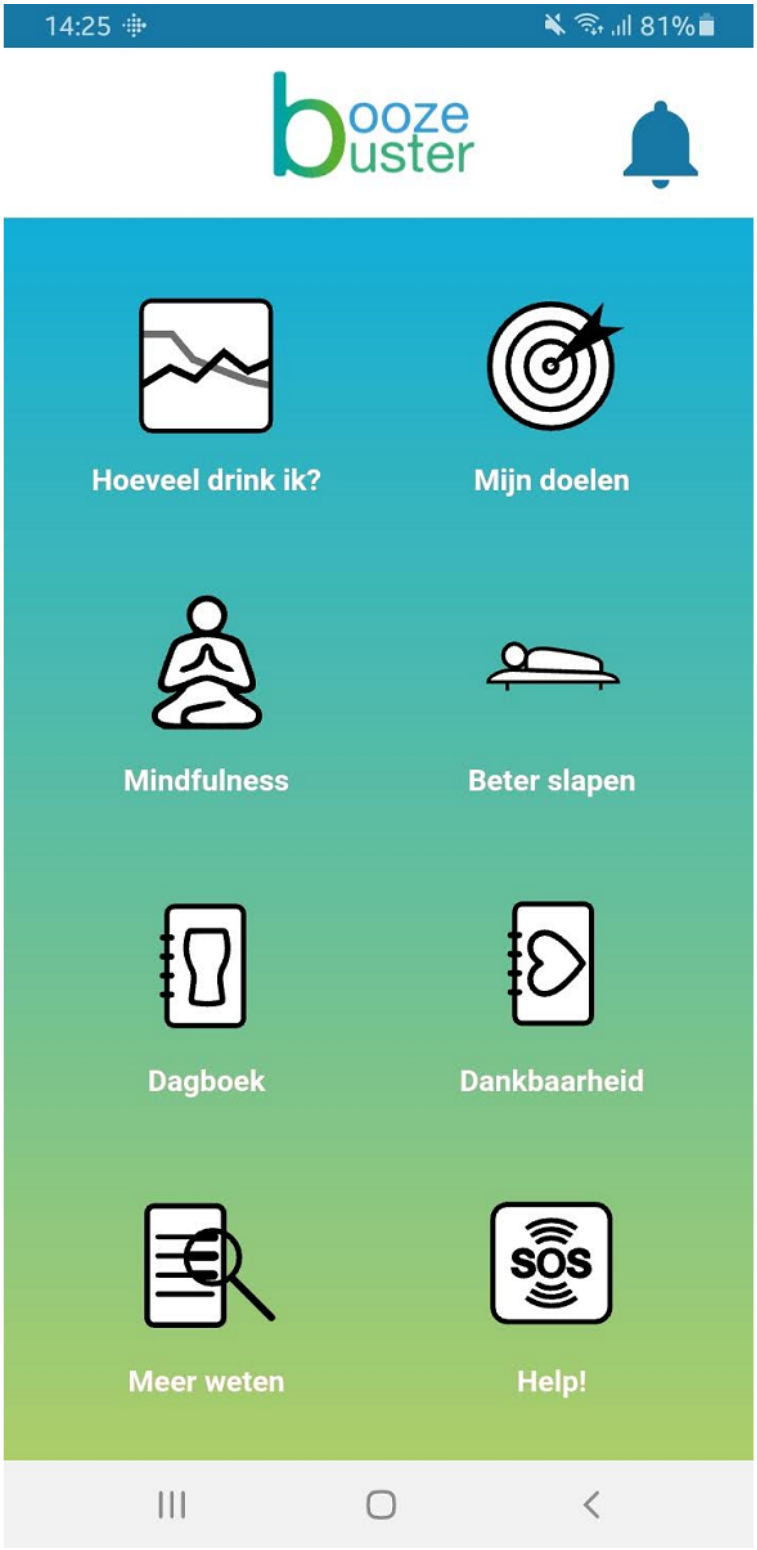
Boozebuster focuses on the importance of the individuals' motivation, self-efficacy, and environmental constraints with regard to drinking. The behavioral change techniques used include PNF [18], motivational interviewing [33], cognitive behavioral therapy [34], goal setting [35], self-monitoring [36], protective behavioral strategies [37], and mindfulness [38].

Boozebuster contains a total of seven modules and was developed with the following rationale in mind: the PNF module serves as the first assessment of young adults' drinking patterns and compares it with peer norms and the official Dutch drinking guidelines [39]. This procedure creates awareness among the individuals about their alcohol consumption in relation to their peers and has shown to be an effective approach in initiating drinking-related changes [40]. The incorporated motivational interviewing module motivates the individuals to change their alcohol-related behaviors by assisting them in building confidence in their abilities for achieving their goals. In addition, Boozebuster includes a variety of lifestyle support modules, such as relaxation, improving sleep, drinking diary, gratitude diary, and an emergency button specifically designed to provide recommendations for acute cravings. These modules provide individuals with tools to deal with cravings, peer pressure, and stress that might otherwise interfere with their drinking-related goals.

Participants in the Boozebuster group will be able to monitor their daily alcohol consumption via ecological momentary assessments (EMA) [41] in terms of the amount of standard drinks consumed, their mood via daily mood ratings on a scale of 1 (low) to 10 (high), and their sleep quality via daily sleep quality ratings on a scale of 1 (low) to 10 (high). Participants will also be able to monitor their progress on the three abovementioned key behaviors (ie, drinking, mood, and sleep) via visual feedback (ie, visualization of their scores) through the mobile app.

Participants are free to use Boozebuster during the 6-week study duration as frequently as desired. The reason we opted for a 6-week period is because it is the recommended timeframe in which alcohol-related changes can occur and be measured [42]. Hence, participants will be stimulated and motivated to engage with our intervention via the daily reminders of the EMA function during the 6 weeks of study participation. Figure 2 provides an overview of the Boozebuster mobile app and its modules.

Figure 2. Screenshot of the Boozebuster mobile app (home screen).



Educational Website Condition

Participants in the control condition will receive access to an educational website containing information on the effects and consequences of alcohol use on health. Only participants allocated to the control condition will have access to this website.

Outcome Measures

Given that applied outcome measures in the alcohol intervention literature vary considerably we decided to follow the advice and included key outcomes based on the recommendation of the Outcome Reporting in Brief Intervention Trials on Alcohol (ORBITAL) framework [43].

Primary Outcomes

Alcohol Consumption, Frequency, and Quantity

The primary outcome is the quantity and frequency of alcohol consumption in terms of standard drinks (10 g ethanol per standard drink) per month; this will be assessed through the timeline follow-back (TLFB) method [44], which measures alcohol consumption during the prior 30 days in terms of number of standard drinks. The TLFB is widely used in obtaining data on the frequency of occurrence of drinking behavior, has been evaluated in various clinical and nonclinical populations, and has been shown to have good psychometric characteristics [45,46].

Secondary Outcomes

Intervention Adherence

Intervention adherence will be calculated descriptively based on the percentage of participants who completed the main PNF and motivational interviewing module.

Readiness to Change

The Readiness to Change Questionnaire (RCQ) [47] is a 12-item self-report questionnaire assessing participants' readiness to change according to the three stages of change: precontemplation, contemplation, and action. The items are rated on a 5-point scale from –2 (totally disagree) to 2 (totally agree). The scores of each stage of change are calculated by adding the individual item scores of the relevant scale. The range of each scale is –8 through 0 to +8. A negative score indicates an overall disagreement with the items measuring the particular stage of change, whereas a positive score represents overall agreement. The RCQ has previously been applied in Dutch clinical settings and has proven to be a reliable and valid tool to measure an individual's readiness to change [48,49].

Binge Drinking

Participants will be asked to indicate the number of binge-drinking days defined as 4 (for females) or 5 (for males) standard drinks on one drinking occasion over the past 30 days.

Alcohol-Related Problem Severity

Alcohol-related problem severity will be assessed via the Rutgers Alcohol Problem Index (RAPI) [50]. The RAPI is an 18-item self-reporting scale that measures alcohol-related problems. The questions are answered on a 4-level scoring system, with higher scores indicating higher levels of alcohol-related problems. The total score is derived by summing the individual scores for each of the 18 items on a scale of 0 to 3; consequently, total scores range from 0 to 54. The RAPI is widely used to assess alcohol-related problems in adolescents and university students and is considered reliable and valid [50].

Cannabis Use Frequency and Quantity

Cannabis use frequency was assessed using the TLFB method [51]. Furthermore, we asked participants to estimate the quantity of cannabis consumed (in grams) during the previous 30 days. The TLFB method has shown to collect reliable and psychometrically sound information about individuals' daily cannabis use [52].

Depressive Symptoms

Depressive symptoms will be assessed via the Center for Epidemiological Studies Depression (CES-D) scale [53], a 20-item self-report scale designed to measure depressive symptoms. The CES-D has been tested in various settings and is considered a reliable and valid tool to measure depressive symptoms in a variety of populations also including young adults [54]. Responses are based on the frequency of occurrence of depressive symptoms. The questionnaire uses a 4-point ordinal scale: 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day). The scores of the CES-D scale range between 0 and 60, with cut-off scores of 16 and 20 indicative of mild depressive symptoms, scores between 21 and 25 are indicative of moderate depressive symptoms, and scores between 26 and 60 suggest severe depressive symptoms [55].

Mental Well-being

The Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) [56] is a 14-item self-report scale that measures positive mental well-being. The items are rated on a scale of 1 (none of the time) to 5 (all of the time). Higher scores indicate higher levels of positive mental well-being among respondents. The WEMWBS has been previously validated in a Dutch setting and has proven to be a reliable and valid tool to measure individuals' mental well-being [57].

Perceived Stress

The Perceived Stress Scale (PSS) [58] is a 10-item self-report scale that measures perceived stress. The questions are answered on a 5-level scoring system in which higher scores indicate higher levels of perceived stress. The total score is derived by summing the individual scores for each of the 10 items on a scale of 0 to 4; consequently, total scores range from 0 to 40. The PSS is considered a reliable and valid screening tool for perceived stress [59].

Study or Work Performance

The task performance scale is a 5-item self-report scale that measures study or work performance and is part of the Individual Work Performance Questionnaire [60]. The total score is derived by summing the individual scores for each of the 5 items on a scale of 0 to 4; consequently, total scores range from 0 to 20. The task performance scale is considered a reliable and valid screening tool for measuring study or work performance among adults [61].

Engagement

Engagement will be measured via the Twente Engagement with eHealth Technologies Scale (TWEETS) [62], a 9-item self-report scale that can be used to measure expectations of current or past engagement with digital interventions. In this study, the expected and past engagement will be assessed. The questions are answered on a 5-level scoring system in which higher scores indicate higher levels of treatment engagement. The total score is derived by summing the individual scores for each of the 9 items on a scale of 0 to 4; consequently, total scores range from 0 to 40. The TWEETS has shown to be a valid tool that possesses good psychometric qualities to assess engagement with eHealth technologies [63].

Short-Form Posttraumatic Stress Disorder Checklist for Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

The short-form version of the posttraumatic stress disorder (PTSD) Checklist for Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), or PCL-5 [64], is a 4-item self-report scale that screens for PTSD symptoms according to the DSM-5. The items are rated on a scale of 0 (not at all) to 4 (extremely). Higher scores indicate a higher likelihood for the screened individuals to fulfill the criteria of PTSD according to the DSM-5. However, the PCL-5 is meant to provide a provisional PTSD diagnosis in circumstances where a structured clinical interview is not feasible. The short-form PCL-5 has been previously validated in the Dutch population and has proven to be a reliable and valid tool [65].

Short-Form PCL-5 – COVID-19

Given the unprecedented situation that emerged due to the global COVID-19 pandemic, we decided to include a modified version of the short-form PCL-5 that measures only stressors tied to the COVID-19 pandemic. The short-form PCL-5 – COVID-19 scale that we used for this study is identical to the previously introduced short-form PCL-5; however, we specifically asked participants to indicate on this scale only stressors that are associated with the COVID-19 pandemic.

Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency Impulsive Behavior Scale

The reason we decided to include this measurement tool is due to the fact that impulsivity is a significant risk factor for the initiation, continuation, and problematic alcohol consumption [66]. Impulsivity will be assessed via the short-form Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency (UPPS-P) Impulsive Behavior Scale [67]. This short-form version of the UPPS-P is a 20-item self-report scale designed to measure factors that can lead to impulsive behaviors. The questionnaire items are scored on a scale of 1 (strongly disagree) to 4 (strongly agree). The UPPS-P contains five subscales, namely, positive urgency, negative urgency, (lack of) premeditation, (lack of) perseverance, and sensation seeking. The UPPS-P has been tested in healthy, student, and forensic psychiatry settings involving Dutch participants and is considered a reliable and valid tool [68].

Sociodemographic Variables

At baseline, sociodemographic variables such as sex, age, level of education, employment, and marital status will be assessed.

Statistical Analyses

After the data collection period, we will clean our data and assess it for accuracy and completeness. Missing data will be handled using either multiple regression imputation techniques or full information maximum likelihood estimation, depending on the amount of missing data and whether it is missing at random or not. All analyses for the primary and secondary outcomes will use linear mixed modeling regression analyses with the three time points nested within participants. For continuous outcomes, linear models will be used for normally distributed data and negative binomial models, for left-skewed data. For dichotomous outcomes, such as whether or not participants had a binge-drinking episode in the past 30 days, binary logistic regression will be used. All primary analyses will be conducted in line with the intention-to-treat (ITT) principle (ie, including all participants that are randomized). Sensitivity analyses will be conducted in line with the per-protocol principle (ie, intervention completers) and with study completers only. All statistical tests use a significance level α=.05. Time will be used as predictor and baseline measures will be included as covariates if appropriate. All analyses will be conducted using the R Statistical Package. Cohen *d* values will be used as the measure of effect size. Effect sizes of 0.8 are assumed to be large, effect sizes of 0.5 are assumed to be moderate, and effect sizes of 0.2 are assumed to be small [69]. In addition, several intervention effect moderators that might moderate drinking levels based on findings of previous studies will be investigated. In addition, potential moderators such as gender [70], readiness to change [71], engagement [72], and impulsivity [73] will be explored.

Results

Our study began recruitment in September 2020. We received 933 registrations on our study information website. Of these registrations, 506 participants have completed the baseline assessment, 336 participants have completed the 6-week postbaseline assessment (T1), and 308 participants have completed the 3-month postbaseline assessment (T2) as of May 2021. The study is still in progress. Results will be reported in 2021 and 2022.

Discussion

Study Overview

The majority of digital interventions aimed at reducing drinking levels in young adults were conducted in university settings in the United States or Australia, were delivered via a computer or web browser, and consisted of single-session interventions showing small effect sizes ranging from g=0.18 to g=0.29 [5,14-18]. Mobile apps with the purpose of managing alcohol consumption in young adults seem promising, but the evidence is still inconclusive given the mixed results [13].

To potentially enhance the effectiveness of such interventions, we decided to develop a self-guided mobile app supporting low-risk drinking habits among young adults from the general population, while incorporating relevant healthy lifestyle-related support components that may increase and prolong the effectiveness of our intervention but retain the acceptability and reach of single-session interventions [22-24].

Therefore, the present study aims at improving the existing knowledge on the effectiveness of mobile apps on alcohol reduction in young adults by employing lifestyle-related support components (ie, sleep, mood, and perceived stress). If our intervention proves to be effective, it could become an inexpensive and scalable public health intervention to improve drinking habits in young adults.

Potential Strengths and Limitations

Our study has a number of strengths such as the delivery of our intervention via the use of a mobile app, which seems to be a feasible and desirable delivery method for our target group [74,75]. Second, this study used an open recruitment strategy, which will enhance the generalizability of our results compared to studies that recruit only in university settings. Given the large sample size we aim to recruit, our study will provide a reliable estimate regarding the effectiveness of our mobile intervention.

Nevertheless, there are some limitations that are worthwhile mentioning. We are measuring all outcomes via self-report measures, and we have decided against using lengthy and costly diagnostic interviews in order to reach out to a large sample group and due to the preventive nature of our intervention. However, based on the literature, we know that self-report measures are reliable for actual drinking levels in our target population [76]; furthermore, we expect that the EMA function that we included for self-monitoring purposes will augment and improve our assessments by adding a dynamic dimension to it [41]. We expect a potential large dropout rate at posttest and 3-month follow-up assessments as commonly observed in web-based interventions with an open recruitment strategy [77]. To minimize drop-out, automated reminders for completing questionnaires will be sent via email to our participants and participants will be offered financial incentives for completing the follow-up assessments.

Conclusions

Providing young adults with a mobile app that promotes low-risk drinking habits while also providing lifestyle-related support components might be a promising approach to increase the reach, uptake, and effectiveness of behavioral change interventions targeting alcohol reduction in this population. We expect that the use of our mobile app will reduce drinking outcomes significantly compared to the use of the educational website. In addition, findings of the trial will be informative for future researchers developing interventions for young adults with regard to the reduction of alcohol consumption and improvement of associated lifestyle behaviors.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1183 KB - resprot_v10i6e29750_app1.pdf]

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Abbreviations

CES-D: Center for Epidemiological Studies Depression
EDC: Electronic Data Capture
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EMA: ecological momentary assessments
ITT: intention-to-treat
ORBITAL: Outcome Reporting in Brief Intervention Trials on Alcohol
PCL-5: Posttraumatic Stress Disorder Checklist for Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
PNF: personalized normative feedback PSS: Perceived Stress Scale
PTSD: posttraumatic stress disorder
PSS: Perceived Stress Scale
RAPI: Rutgers Alcohol Problem Index
RCT: randomized controlled trial
RCQ: Readiness to Change Questionnaire
TLFB: timeline follow-back
TWEETS: Twente Engagement with eHealth Technologies Scale
UPPS-P: Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency
WEMWBS: Warwick-Edinburgh Mental Wellbeing Scale

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Protocol

Motivation and Problem Solving Versus Mobile 360° Videos to Promote Enrollment in the National Diabetes Prevention Program's Lifestyle Change Program Among People With Prediabetes: Protocol for a Randomized Trial

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Abstract

Background: More than 88 million Americans are at risk of developing type 2 diabetes mellitus (T2DM). The National Diabetes Prevention Program's Lifestyle Change Program (DPP LCP) has been shown to be effective in reducing the risk of progressing from prediabetes to T2DM. However, most individuals who could benefit from the program do not enroll.

Objective: The aim of this trial is to test the real-world efficacy of 3 mobile phone–based approaches to increasing enrollment in the DPP LCP including a best-practice condition and 2 novel approaches.

Methods: We will conduct a 3-armed randomized clinical trial comparing enrollment and 1-month engagement in the DPP LCP among adults with prediabetes from 2 health care settings. Participants in the best-practice condition will receive SMS-based notifications that they have prediabetes and a link to a website that explains prediabetes, T2DM, and the DPP LCP. This will be followed by a single question survey, "Would you like the DPP LCP to call you to enroll?" Participants in the 2 intervention arms will receive the same best-practice intervention plus either 2 mobile 360° videos or up to 5 brief phone calls from a health coach trained in a motivational coaching approach known as Motivation and Problem Solving (MAPS). We will collect measures of diabetes-related knowledge, beliefs in the controllability of risk for T2DM, risk perceptions for T2DM, and self-efficacy for lifestyle change pre-intervention and 4 weeks later. The primary outcomes of the study are enrollment in the DPP LCP and 4-week engagement in the DPP LCP. In addition, data on the person-hours needed to deliver the interventions as well as participant feedback about the interventions and their acceptability will be collected. Our primary hypotheses are that the 2 novel interventions will lead to higher enrollment and engagement in the DPP LCP than the best-practice intervention. Secondary hypotheses concern the mechanisms of action of the 2 intervention arms: (1) whether changes in risk perception are associated with program enrollment among participants in the mobile 360° video group and (2) whether changes in self-efficacy for lifestyle change are associated with program enrollment among participants in the MAPS coaching group. Finally, exploratory analyses will examine the cost effectiveness and acceptability of the interventions.

Results: The project was funded in September 2020; enrollment began in February 2021 and is expected to continue through July 2022.

Conclusions: We are conducting a test of 2 novel, scalable, mobile phone–based interventions to increase enrollment in the DPP LCP. If effective, they have tremendous potential to be scaled up to help prevent T2DM nationwide.

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KEYWORDS

diabetes prevention program; mobile video; motivation and problem solving; program enrollment; participant engagement; prediabetes

Introduction

Background

Among US adults, 34.5% have prediabetes, placing them at increased risk of type 2 diabetes mellitus (T2DM) [1]. Extensive evidence has shown that therapeutic lifestyle changes can reduce the progression from prediabetes to T2DM by 58% [2]. To address this national epidemic, the Centers for Disease Control and Prevention (CDC) has established the National Diabetes Prevention Program's Lifestyle Change Program (DPP LCP) [3]. However, through 2019, only 0.4% of the 88 million adults in the United States with prediabetes have enrolled in the DPP LCP [4].

There are several reasons for low enrollment and engagement in the DPP LCP. First, many people with prediabetes are unaware of their risk for T2DM or do not believe that they are at risk of developing T2DM or its associated complications. Second, many individuals are not aware of the appropriate lifestyle changes that can prevent progression to T2DM [5-8]. This is important because risk perceptions are predictive of health behavior change [9]. Finally, several studies have identified practical barriers to enrolling in the DPP LCP, including the cost of enrollment, limited time for attendance, and difficulty with travel to and from DPP LCP sessions [10,11].

Most prior research on DPP LCP enrollment interventions has tested the effectiveness of medical providers notifying their patients of their prediabetes, counseling them, and referring them to the DPP LCP. These studies have reported DPP LCP enrollment rates of 8%-11% [12,13]. We believe there are significant limitations to this approach. First many providers do not notify their patients that they have prediabetes — only 15.3% of individuals with prediabetes report being told about their condition from a health professional [1]. Second, many providers do not currently counsel their patients about lifestyle changes, [14,15], likely because they do not feel they have the time or because they do not feel that such counseling will be effective [16,17].

In this project, we propose to address these issues by directly connecting with individuals with prediabetes through mobile phone–based interventions in a 3-armed randomized controlled trial. We will compare a best practice intervention with 2 novel interventions our research group has developed and pilot tested: mobile 360° videos and Motivation and Problem Solving (MAPS)–based phone counseling.

Aims and Objectives

Aim 1 is to conduct a 3-armed randomized clinical trial comparing enrollment and 1-month engagement in the DPP LCP among adults with prediabetes receiving risk notification and education alone, risk notification and education plus the mobile 360° video, and risk notification and education plus MAPS.

Aim 1.1 is to examine the mechanisms underlying the mobile 360° video by comparing changes in deliberative, experiential, and affective risk perceptions across study arms.

Aim 1.2 is to examine the mechanisms underlying MAPS by comparing changes in DPP LCP–related self-efficacy across study arms.

Methods

General Methods

As noted in the previous section, whether an individual enrolls in the DPP LCP is a multifactorial process that includes their awareness, knowledge, risk perception, and unique barriers. Our intervention is designed to address each of the factors. First, to address low awareness of prediabetes, individuals with a diagnosis of prediabetes within the past 5 years documented in their electronic health record (EHR) will be informed via text message that they have prediabetes and sent a link to the website, Do I Have Prediabetes [18], that includes 3 components: a self-assessment of risk, didactic pages about prediabetes and T2DM, and didactic pages about the National DPP LCP and its benefits.

Individuals will then be randomized to receive only the initial best practice intervention, the best practice plus the mobile 360° videos, or the best practice plus MAPS counseling. The proposed mechanism of action for the mobile 360° videos divides risk perceptions into *deliberative* risk perceptions (ie, the individual's estimates of the likelihood of developing a condition), *affective* risk perceptions (ie, the individual's level of worry about a particular risk), and *experiential* risk perceptions (ie, how easy it is to imagine developing a condition). The videos are hypothesized to increase participants' affective (emotional) and experiential (gist-based) risk perceptions and the likelihood of enrolling in the DPP LCP. The proposed mechanisms of action for MAPS counseling include increasing both motivation and self-efficacy (eg, by addressing practical barriers to enrolling and engaging in the National DPP LCP).

The DPP LCP is an evidence-based program that is available at hundreds of locations throughout the United States as well as online [19]. It is a therapeutic lifestyle change program that reduces the risk of progression to T2DM by 58% for high-risk individuals [20]. The year-long lifestyle change program is comprised of weekly group meetings for 6 months followed by monthly meetings for another 6 months (a minimum total of 22 hours over the year) [1].

Intervention

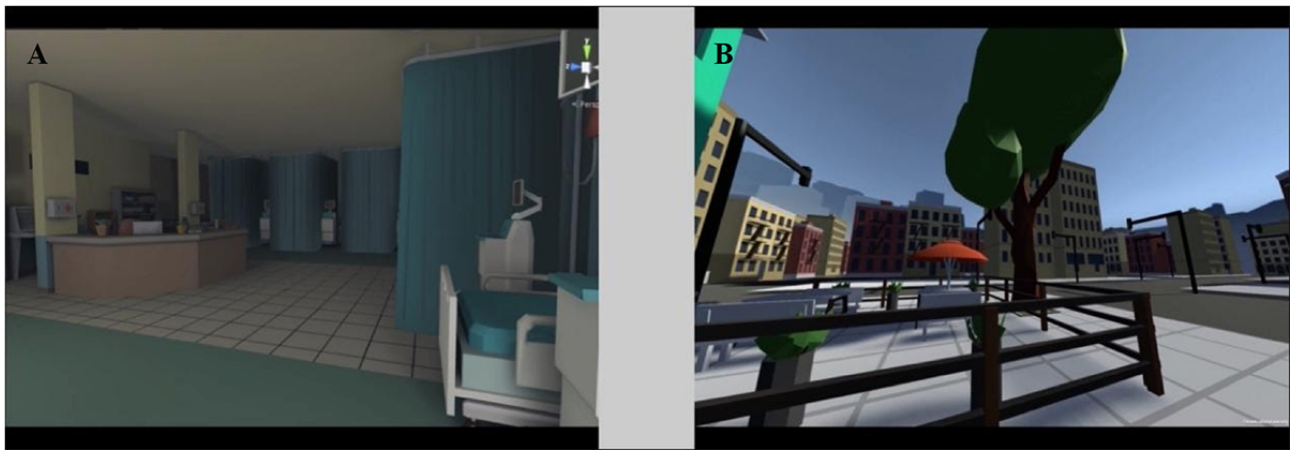
Best Practice Condition

In the best practice condition, we will send a text message to individuals who, according to their health records, have prediabetes. This message will notify them that they have prediabetes and refer them to a website that provides information about prediabetes and the effectiveness of the DPP LCP. This component of the intervention will increase participants' awareness of the condition and the DPP LCP without adding to the workload of primary care clinicians. Additionally, this is a process that can be automated to regularly reach new individuals with prediabetes within a health system. While it is not yet standard clinical practice to notify individuals with prediabetes of their condition and offer the DPP LCP to them, there is evidence that individuals with prediabetes who are notified about their status are more likely to engage in self-directed healthy lifestyle changes [21]. Additionally, the American Diabetes Association 2018 Standards of Medical Care in Diabetes recommend that all patients with prediabetes "should be referred to an intensive behavioral lifestyle intervention program modeled on the Diabetes Prevention Program." This recommendation has an evidence level of "A" [22].

Mobile 360° Videos

The mobile 360° videos (in which the viewer moves their phone to "look around" the world of the video) are intended to increase individuals' risk perceptions regarding the potential adverse outcomes that might occur should they develop T2DM. Our team has designed and pilot tested two 3-minute videos with accompanying voiceover (in either English or Spanish) and soundtrack. In the first video (Figure 1A), the narrator describes the effect of diabetes on health and family life as an individual progresses from having prediabetes to T2DM and having a heart attack. The second video (Figure 1B) provides a vicarious experience of the changes in vision that occur as diabetic retinopathy progresses and uses the visual metaphor of building height to change risk perceptions: As the viewer is transported through a cityscape from a roof to progressively higher roofs, they develop visual scotomas that worsen as the height of the buildings (reflecting their average glucose level) increases. Each video ends with a positive message that enrolling in the DPP LCP can reduce the risk of this potential negative future.

Figure 1. Screenshots of mobile 360° videos.



MAPS

MAPS is a hybrid counseling technique that combines motivational interviewing and social cognitive, practical problem-solving to enhance motivation and self-efficacy for behavior change. MAPS has been shown to help people effectively participate in evidence-based programs and change their health behaviors [23,24]. Aside from our pilot work (manuscript in progress for the MAPS pilot and manuscript under review for the mobile 360° videos), these interventions had not been previously evaluated as tools to promote the DPP LCP.

A standardized MAPS training and treatment manual has been developed and used in pilot work and will be utilized in this project. Coach training will include both online "classroom" instruction and practice coaching sessions with feedback from a MAPS expert (KL).

The MAPS counseling itself will focus on promoting enrollment and engagement in the DPP LCP by addressing each participant's unique values and barriers. MAPS uses a combination of motivational enhancement and social cognitive approaches based on motivational interviewing and practical problem-solving approaches. All participants will receive up to 5 telephone counseling calls lasting approximately 10 minutes during the 4 weeks following study enrollment. The timing of the MAPS counseling calls will be negotiated between the participant and health coach, as has been done for other MAPS trials. The MAPS counselor will also help each participant develop an individualized "wellness plan" that may not only include goals related to DPP LCP enrollment and engagement but also other potential stressors and concerns (eg,

transportation, interpersonal issues, family problems, financial concerns). Thus, MAPS will assist individuals with various life stressors that may ultimately affect their DPP LCP engagement. MAPS counseling will be conducted via telephone in Spanish or English, and information from each session will be documented in a secure REDCap database.

All MAPS counseling sessions will be audio-recorded, and the recordings will be uploaded into the study database (in REDCap). Ongoing training and monitoring of recorded calls will ensure that the delivered MAPS follows the protocol precisely. A MAPS expert will review at least one recording per coach per week and provide detailed feedback and guidance as necessary to the health coach.

Setting

Study participants will be recruited from 2 sites: University of Utah Health and the Midvale Community Building Community Clinic (CBC). University of Utah Health is the Mountain West's only academic health care system and includes 5 hospitals, 12 community clinics, and several specialty centers. The Midvale CBC is an outpatient community health clinic providing medical, dental, physical therapy, and mental health services to low-income and uninsured families, with a predominantly Spanish-speaking clientele.

Participants

Spanish- and English-speaking patients ages 18-89 years from University of Utah Health and the Midvale CBC will be invited to participate in the study.

Inclusion Criteria

Patients will be considered eligible for the proposed trial if (1) they are aged 18-89 years, (2) have a diagnosis of prediabetes within the past 5 years documented in the EHR (ICD-10 code R73.03), and (3) have an email or mailing address and a mobile telephone number on record with the health system.

Exclusion Criteria

Patients will be excluded from the study if they have any of the following diagnoses: T2DM (ICD-10-CM E11), type 1 diabetes mellitus (ICD-10-CM Diagnosis E10), diabetes mellitus due to underlying condition (ICD-10 E08), drug or chemical induced diabetes mellitus (ICD-10 E09); gestational diabetes (ICD-10 024.4), neonatal diabetes mellitus (ICD-10 P70.2), or post-pancreatectomy diabetes mellitus (ICD-10 E13). Individuals who are currently pregnant will be excluded from the trial. The rationale for this exclusion is that these women would be excluded from participating in the National DPP LCP. In addition, individuals who do not have an email address or mailing address or who do not own a smartphone will be excluded from the trial, simply because they could not complete the trial.

Study Design

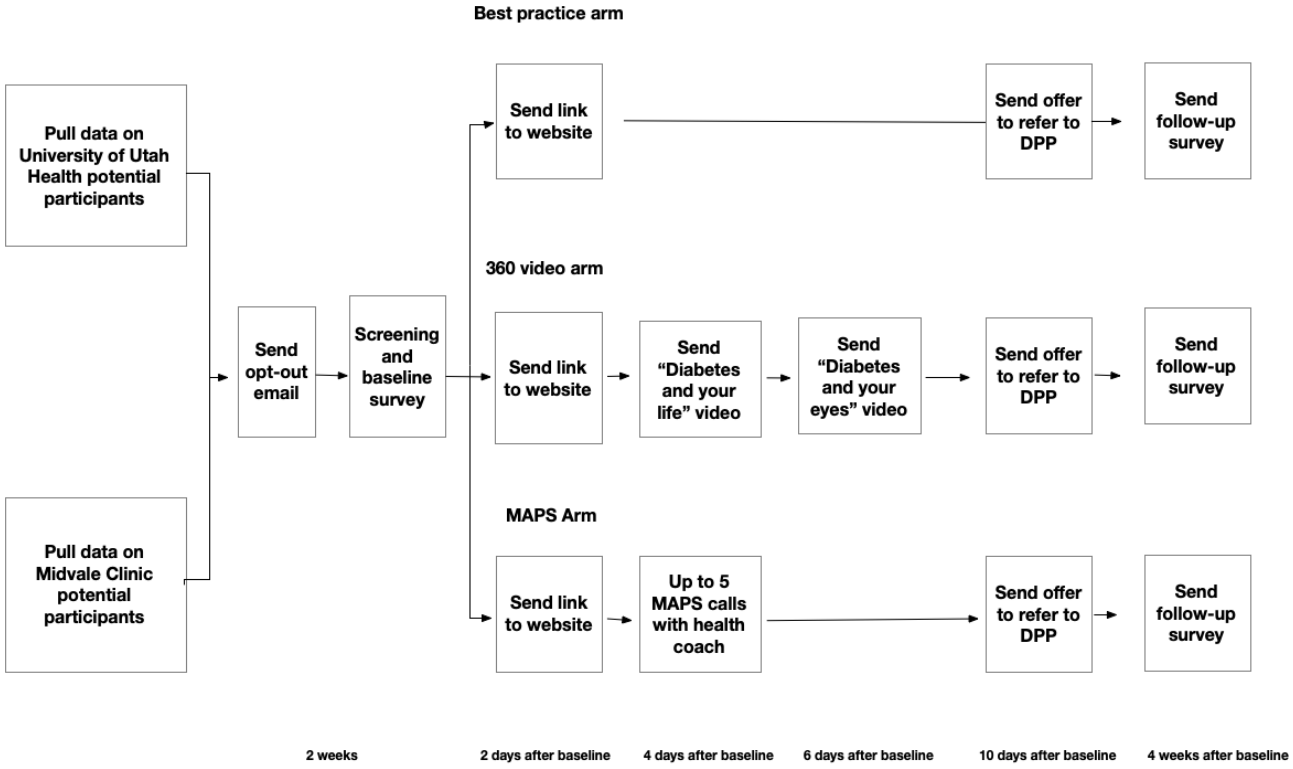
This is a 3-arm stratified randomized clinical trial comparing enrollment and 1-month engagement in the DPP LCP among adults with prediabetes receiving risk notification and education alone vs risk notification and education plus mobile 360° video vs risk notification and education plus MAPS. It should be noted that this study is not powered nor designed to compare the effectiveness of the mobile 360° videos vs MAPS nor does the design allow for testing of the additive value of mobile 360° videos plus MAPS.

Procedures

Overview

Figure 2 provides an overview of the study procedures. We will begin by pulling lists of potential participants (using the inclusion and exclusion criteria listed in the previous sections) from the EHR of each health system. Selected individuals will be given the option to opt-out of any study-related communication prior to phone contact. Hence, we will first contact potential participants by email (or by letter if they do not have an email address on record) with a brief description of the study and an explanation that they will be contacted on their mobile phone in 2 weeks if they do not opt out. This email will include a link to click if they want to be excluded from further study communication. All further communication will be with individuals who did not opt out and will be sent via SMS messages to their mobile phone.

Figure 2. Overview of study procedures. DPP: Diabetes Prevention Program; MAPS: Motivation and Problem Solving.



Screening and Baseline Survey

Potential participants who do not opt-out will then be sent an SMS message with a link to a survey. The survey will begin with a short eligibility screening section. Individuals who are screened out will be thanked for their time and informed that they do not meet the criteria for participating in the study.

Individuals who are not screened out will be directed to the consent cover letter and the remainder of the baseline survey. The baseline survey will collect information about demographics (age, sex, race/ethnicity, education, socioeconomic status), diabetes-related knowledge (11 items), and beliefs about the controllability of risk for type 2 diabetes (4 items) using 2 subscales on the risk perception for developing diabetes scale [25]. It will also collect information on self-efficacy related to DPP LCP participation as well as for diet, exercise, and weight loss (16 items) using the brief self-efficacy scales adapted from Wilson et al [26]. This will be followed by an 18-item scale of risk perceptions for T2DM that includes 6 items each to assess 3 different aspects of risk perception: deliberative, affective, and experiential risk perceptions [27].

Allocation to Condition

After completing the baseline survey, individuals will be allocated to the condition according to randomization tables generated by the projects statistician (YZ). These tables will be based on permuted block randomization, stratified by health system and sex, with block sizes randomly generated as 5, 10, or 15. In accordance with our planned sample sizes in each arm, each block will maintain a 1:2:2 ratio in sample size across the treatment groups (best practice, mobile 360° videos, and MAPS).

Risk Notification and Education

Two days after completing the baseline survey, all participants will be sent a hyperlink to the education website, Do I Have Prediabetes? [18]. This will be delivered as an iframe in a Qualtrics survey; in this way, we will be able to measure the number of participants who actually visit the website and the duration of time they spend on the site. After visiting the website, participants will be asked about which pages of the website they visited, what they learned, and what they liked and disliked about the website.

Mobile 360° Video

Four days after completing the baseline survey, participants randomized to the mobile 360° video arm will be sent the first video; 2 days later, they will be sent the second video. Up to 2 reminder texts 1 day apart will be sent to individuals who do not access the links for the videos. Similar to the educational website, the videos will be delivered as an iframe within a web-based survey. This will allow us to assess the duration of time spent watching the video and to collect immediate feedback on participants' impressions of each video.

MAPS Phone Calls

A health coach trained in MAPS will call the participants randomized to that group; the first call may be used to initiate MAPS coaching or to simply schedule the upcoming MAPS counseling sessions. Participants will be offered up to 5 coaching calls over 4 weeks, each lasting approximately 10 minutes. During these sessions, participants will explore their motivation and goals and how enrollment in the DPP LCP may fit with these goals. Additionally, MAPS coaches will help participants identify barriers to achieving their goals and troubleshoot ways

to address these barriers. If a participant enrolls in the DPP LCP, any remaining MAPS calls will serve to reinforce the positive change the individual has made, provide accountability, address ongoing challenges and barriers, and encourage continued engagement with the DPP LCP. All MAPS sessions will be audio-recorded, and at least 1 session per week per coach will be reviewed by a MAPS expert. Feedback will be provided to coaches as needed. This process will insure the fidelity of the MAPS intervention. Participants will have the option to tell the MAPS coaches that they would like to stop receiving calls at any point.

Offer to Refer to DPP LCP

Ten days after study enrollment, all participants will be sent a single question survey: “Would you like the DPP LCP to call you to help you enroll?” The contact information for participants who respond “yes” will be sent to the referral coordinator at their respective health system's DPP LCP, who will then call them to enroll. The rationale for this piece of the intervention is to mimic the current workflow for individuals to enroll — in most cases, a health care provider places a referral to the program via the EHR, and the program contacts the potential participant to enroll them. Due to the COVID-19 pandemic, both study sites have been offering the DPP LCP virtually, either as an asynchronous online program or through synchronous group sessions. During the study, participants will have the ability to select whatever DPP LCP format they prefer, including in-person sessions, if available.

Follow-Up Survey

The follow-up survey will be sent via text message to all participants 4 weeks after the baseline survey is completed. The survey will include all of the items described in the baseline survey (diabetes-related knowledge, beliefs about the controllability of diabetes, self-efficacy, and risk perceptions). The survey will conclude with a 9-item questionnaire about the practical barriers and facilitators that were relevant to choosing whether to enroll in the DPP LCP such as perceptions of the need for counseling to change one's lifestyle (which prior work suggests many individuals don't feel the need for) [28]; accessibility of the DPP LCP in terms of cost, location, time requirements, and scheduling [29]; and desire to participate in an online vs in-person DPP LCP [30,31]. This portion of the survey will provide space for free-text comments on each barrier and also ask for input on other barriers we did not anticipate. At the end of the follow-up survey, participants will be asked if they are willing to participate in a short phone-based semistructured interview about their experiences in the study. We will randomly select up to 40 individuals for these interviews; those who are interviewed will receive a US $20 electronic gift card.

We will use Qualtrics survey software for all questionnaires used in this study [32]. This platform allows us to automate the timing and delivery of each intervention component. This platform will allow us to assess the number of people contacted and the click rate of participants in each intervention component. Finally, the platform also provides a mechanism for participants to easily opt out of the trial at any time by responding “STOP” to any text message.

Each participant will be sent US $20 electronic gift cards upon completion of the baseline survey and follow-up survey (US $40 total for the study). To motivate completion of all study procedures, participants who complete both the baseline and follow-up questionnaires will be placed into a lottery for 1 of 5 US $100 electronic gift cards.

Measures

Outcome Measures

The primary outcomes of the study are DPP LCP enrollment and 4-week engagement, as defined by the CDC (Table 1). These data are currently collected by all CDC-recognized organizations offering the National DPP LCP and are a part of their required reporting for DPP LCP recognition.

Table 1. Centers for Disease Control and Prevention (CDC)–defined measure of enrollment and engagement in in-person and online Diabetes Prevention Program’s Lifestyle Change Programs (DPP LCPs).

Time point	In-person	Online
Milestone 1 (enrollment)	Registration for the program	Setting their password for the app
Milestone 2 (4-week engagement)	Attending at least 2 out of the first 4 sessions	Must do at least 2 of the following activities: (1) Complete 2 education modules; (2) send at least 1 in-app message and/or Group Wall post; (3) set or log at least 1 behavior; (4) log, plan, or research at least 3 meals; (5) log physical activity at least 3 times; (6) weigh in on 3 or more days during 2 out of the first 4 sessions

The DPP LCP at University of Utah Health is covered by some insurance plans and requires an out-of-pocket fee for those without coverage. The cost for the online program is currently US $504, and the cost for the in-person program is US $425. Some scholarships are available for those who meet income guidelines. These costs may change during the course of the study. The Midvale CBC’s program is offered free of charge and is currently funded by a grant. To minimize the problem of cost as a barrier to enrollment, University of Utah Health participants who are uninsured or underinsured may be invited to participate in the Midvale CBC program. Otherwise, all other participants will only be invited to attend the program offered by their health system.

Process Measures

If the mobile 360° videos and MAPS are successful in increasing enrollment and early engagement with the DPP LCP as they have been in our pilot work (manuscript for the Video pilot study submitted to JMIR Diabetes, 11/26/20; manuscript for

MAPS pilot in preparation), they have tremendous potential to be scaled up to help prevent T2DM nationwide. More than 80% of adults in the United States own a smartphone [33]. Therefore, health systems and DPP LCPs nationwide could implement these interventions. The scalability of the interventions depends, of course, not just on their efficacy but also on the effort that DPP LCPs must expend to implement them. Therefore, in this project, we will collect data on the person-hours required to implement each intervention at our 2 sites. This will inform our planned future work to test whether the intervention arms differ significantly in their effectiveness and cost effectiveness (Table 2).

Table 2. Process measures collected by study staff.

Measure	How measured
Number of participants who click on educational website link	Link is sent as a Qualtrics survey question; clicking on link results in data indicating a "click" was made.
Number of participants in the mobile 360° video group who click on each of the videos and time spent watching	Click rates from survey in which video is embedded and duration of time on each video
Number of participants in the MAPS group who respond to our initial attempts to connect for MAPS	Attempts to call will be documented by the health coach using a RedCAP survey.
Number of person-hours needed to train health coaches in MAPS	Documented hours for the duration of the training including practice sessions with KL
Number of person-hours required to deliver each MAPS session	The start and end time for each MAPS session will be documented by the health system using a REDCap survey.
Number of person-hours required to oversee MAPS sessions to insure fidelity to the protocol	Documented hours for the time spent by KL to review and provide feedback on a sample of recorded MAPS sessions

Statistical Analyses

Sample Size and Power Calculation

Statistical power for the primary analysis in Aim 1 was calculated using the statistical power calculation software PASS 14 [34]. Based on prior work on the effect of risk notification and education, we hypothesize that 2% of participants in the risk notification and education arm of the study will enroll in the DPP LCP. In the intervention arms, based on our pilot work, we hypothesize that enrollment in the DPP LCP will increase to 32% and 45% for the mobile 360° video and MAPS arms, respectively (manuscript for the video pilot study submitted to JMIR Diabetes, 11/26/20; manuscript for MAPS pilot in preparation). We plan for a total sample size of 400; of whom, 80 will be randomized to risk notification and education alone, 160 will be randomized to risk notification and education plus mobile 360° video, and 160 will be randomized to risk notification and education plus MAPS. We calculated that this study will have >99% power to detect the hypothesized differences between the best practice arm and the intervention arms. To address the possibility of loss to follow-up, we are planning to recruit a total of 480 individuals into the trial.

Aim 1

We will use logistic regression to compare the effects of the 3 treatments on the likelihood of enrollment and 1-month engagement in the DPP LCP. The distributions of participants' demographics and baseline measures of risk perception and self-efficacy will be summarized and compared by treatment groups using chi-squared tests for categorical variables and *F* tests for continuous variables. If participants' demographics and baseline measures of risk perception are not balanced across the 3 treatment groups at baseline, we will use inverse probability of treatment weighting with propensity scores to create a synthetic sample and compare the difference in the causal average treatment effects across the 3 treatment groups [35]. We will calculate standardized differences to check whether the distribution of baseline covariates is independent of treatment groups conditional on the propensity score. We will conduct intention-to-treat analysis to account for noncompliance. We will summarize missing data for all variables in the dataset. We will employ multiple imputation to examine the impact of any missing values in a sensitivity analysis. All analyses will be conducted using statistical programming language R, and statistical significance will be defined at alpha=.05.

Aim 1.2

To examine the mechanisms underlying the mobile 360° video by comparing changes in deliberative, experiential, and affective risk perceptions across study arms, we will calculate the changes in risk perception scores across all 3 treatment groups using the scoring procedures described by Ferrer et al [27]. We will then use Baron and Kenny's [36] procedure to determine if the efficacy of the mobile 360° videos is mediated by changes in affective and experiential risk perceptions as hypothesized. The Baron and Kenny procedure assumes that the mediating factor is also randomly assigned to individuals in addition to the randomized baseline intervention (ie, sequential ignorability). However, the sequential ignorability assumption may not hold in this study even after adjusting for observed covariates. The potentially unmeasured confounders for the association between mediating factors and outcome may lead to biased inference. To reduce such bias, we will also employ 2 alternative casual modeling approaches, the structural mean model [37] and principal stratification [38,39], to evaluate how the impact of mobile 360° videos on DPP enrollment is mediated by risk perceptions.

Aim 1.3

To examine the mechanism of the MAPS intervention by comparing changes in DPP LCP–related self-efficacy across study arms**,** we will calculate the changes in self-efficacy across all 3 treatment groups using the scoring procedures described by Wilson et al [26]. We will then use a similar mediation procedure to the aforementioned to determine if the efficacy of MAPS is mediated by changes in self-efficacy for DPP LCP enrollment and engagement and self-efficacy for health behavior change as hypothesized [37]. Our hypothesis is that if MAPS increases participants' self-efficacy, then enrollment in the DPP LPC will increase.

Process Measure Analysis

In addition to the efficacy data collected in the trial, the study team will collect a series of process measures (Table 2). We will summarize the distribution of these measures, conduct univariate analysis to explore the association between participants' demographics and process measures, and calculate preliminary estimates of the cost of delivering each intervention component (person-time times the salary for that role) in order to prepare for future work that will compare the cost-effectiveness of our interventions at scale.

Results

The project was funded in September 2020. The institutional review board approved the study on January 13, 2021. Enrollment began on March 10, 2021 and is expected to continue through July 31, 2022. As of April 27, 2021, 39 individuals had begun the study.

Discussion

In this project, we will conduct a 3-arm randomized controlled trial intended to compare the efficacy of a best-practice approach and 2 novel interventions on enrollment and engagement in the DPP LCP. These interventions will be delivered directly to individuals with prediabetes through their mobile phones. To standardize the offer of referral to the DPP LCP, all participants will receive an offer to be referred to the National DPP LCP 10 days after completing the baseline survey. Our primary outcome will be participants' enrollment and 1-month engagement in the National DPP LCP.

Strengths

This study is a randomized trial targeting patients with prediabetes within 2 health systems, including a community clinic serving primarily low-income, Spanish-speaking patients and a large academic medical center. The interventions will be delivered by mobile phones, making them scalable to large, diverse populations if found to be effective. The interventions will be delivered in English and Spanish, expanding the generalizability of study findings. The use of a theoretical framework for the study and validated questionnaires to elucidate the mechanism of action of the 2 novel interventions is a strength, as is the collection of process measures.

Limitations

This study is not powered nor designed to compare the effectiveness of the mobile 360° video vs MAPS nor does the design allow for testing of the additive value of mobile 360° video plus MAPS. Because each of these interventions is quite novel, we felt that first they should have demonstrated incremental efficacy over the best-practice condition. If these interventions are found to be incrementally effective, future trials will be designed to compare the effectiveness of these interventions head-to-head as well as to evaluate a combination of the interventions (ie, via a sequential multiple assignment randomized trial [SMART] design). In addition, the differences in number of contacts between the best-practice condition, the video condition, and the MAPS condition may present a confound, making it unclear if outcomes differ due to number of contacts or intervention content. Finally, in this trial, we are only able to assess 1-month DPP LCP engagement. Future work should explore whether these interventions impact longer-term (12 months) engagement and health outcomes.

Contingency Plans

Potential challenges we may encounter include difficulties with recruitment and retention. If we have difficulties with recruitment, we will expand our recruitment population to individuals with A1C levels between 5.7% and 6.4% rather than just those with a documented prediabetes ICD-9 code. If we have challenges with recruitment, we will revisit the frequency and timing of contact with participants. If many returned surveys have significant amounts of missing data, we will follow up with participants and ask them to respond to missing items. Additionally, if we are unable to meet our recruitment goal at the smaller Midvale CBC, we will enroll uninsured or underinsured Spanish-speaking patients from the University of Utah to supplement the Midvale sample.

Future Work

All of the data will be used to inform the design of a large, SMART in which individuals will first receive risk notification and education; then, nonresponders will be randomized to mobile 360° video or nothing, and subsequent nonresponders will be randomized to MAPS phone counseling. Primary outcomes will be enrollment and 1-year engagement in the DPP LCP. Secondary outcomes will include changes in an objective measure of risk for T2DM including hemoglobin A_{1c} and weight. In this future trial, we will also compare the cost effectiveness of these interventions.

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Conflicts of Interest

None declared.

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Abbreviations

CBC: Community Building Community Clinic
CDC: Centers for Disease Control and Prevention
DPP LCP: Diabetes Prevention Program's Lifestyle Change Program
EHR: electronic health record
MAPS: Motivation and Problem Solving
SMART: sequential multiple assignment randomized trial
T2DM: type 2 diabetes mellitus

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Protocol

Feasibility and Efficacy of Delivering Cognitive Behavioral Therapy Through an Online Psychotherapy Tool for Depression: Protocol for a Randomized Controlled Trial

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Abstract

Background: Major depressive disorder (MDD) is a prevalent and debilitating mental health disorder. Among different therapeutic approaches (eg, medication and psychotherapy), psychotherapy in the form of cognitive behavioral therapy (CBT) is considered the gold standard treatment for MDD. However, although efficacious, CBT is not readily accessible to many patients in need because of hurdles such as stigma, long wait times, high cost, the large time commitment for health care providers, and cultural or geographic barriers. Electronically delivered cognitive behavioral therapy (e-CBT) can effectively address many of these accessibility barriers.

Objective: This study aims to investigate the efficacy and feasibility of implementing an e-CBT program compared with in-person treatment for MDD. It is hypothesized that the e-CBT program will offer results comparable with those of the in-person treatment program, regarding symptom reduction and quality of life improvement.

Methods: This nonrandomized controlled trial intervention will provide e-CBT for MDD through the Online Psychotherapy Tool, a secure, cloud-based, digital mental health platform. Participants (aged 18-65 years) will be offered 12 weekly sessions of an e-CBT program tailored to MDD to address their depressive symptoms. Participants (n=55) will complete predesigned modules and homework assignments while receiving personalized feedback and interacting with a therapist through the platform. Using clinically validated symptomology questionnaires, the efficacy of the e-CBT program will be compared with that of a group (n=55) receiving in-person CBT. Questionnaires will be completed at baseline, at week 6 and week 12, and at a 6-month follow-up. Focus groups will be conducted to investigate personal, cultural, and social factors impacting the accessibility and feasibility of implementing a web-based psychotherapy tool from a patient and care provider perspective. Inclusion criteria include diagnosis of MDD, competence to consent to participate, ability to speak and read English, and consistent and reliable access to the internet. Exclusion criteria include active psychosis, acute mania, severe alcohol or substance use disorder, and active suicidal or homicidal ideation.

Results: Ethics approval was obtained in January 2019, and recruitment of participants began in June 2019. Recruitment has been conducted via social media, web-based communities, and physician referrals. To date, 52 participants have been recruited

to the e-CBT group, and 48 patients have been recruited to the in-person CBT group. Data collection is expected to be completed by March 2021, and analyses are expected to be completed by June 2021, as linear regression (for continuous outcomes) and binomial regression analysis (for categorical outcomes) are still being conducted.

Conclusions: The results of this study can provide valuable information for the development of more accessible and scalable mental health interventions with increased care capacity for MDD, without sacrificing the quality of care.

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KEYWORDS

mental health; depression; psychotherapy; cognitive behavioral therapy; online; internet; electronic; virtual; mental health care

Introduction

Background and Rationale

More than 264 million people globally have depression, with major depressive disorder (MDD) being one of the most prevalent mental health disorders [1]. In addition, depression is the largest contributor to global disability and is associated with an estimated economic cost of more than US $2.5 trillion globally [2-6]. Given the large prevalence and the debilitating nature of this mental disorder, discovering effective and accessible treatments for depression is essential and urgently needed.

There are different therapeutic approaches for treating MDD, from medication to psychotherapy. Although pharmacotherapy has been widely investigated and various medications are used to treat MDD, approximately one half of primary care patients only respond partially to medication, with residual symptoms persisting in most cases [7]. Furthermore, many patients using medications for MDD experience adverse effects (eg, weight change, sexual side effects, and sleep problems) or develop addiction or dependency on these medications [8]. These challenges discourage many patients from taking their medications and render this therapeutic path moot as a first-line treatment for MDD.

The current frontline treatment for MDD is in-person psychotherapy, more specifically, cognitive behavioral therapy (CBT) [9-11]. This traditional form of CBT uses a structured format to focus on altering cognitive processing based on the theory that maladaptive behaviors affect an individual's perceptions, emotions, and thoughts [12]. By altering these maladaptive behaviors, a patient's thoughts and beliefs can be positively impacted, allowing for a cyclical improvement in cognition and behavior. CBT allows patients to learn the necessary skills to better cope with situations in their lives by better interpreting their thoughts, thereby influencing their emotions. By positively influencing thoughts, mood, behavior, or physical reactions, a positive effect is seen in other areas of one's life. Through CBT programming, patients can learn skills such as breathing techniques, thought records, activity scheduling, and goal setting, which can give them the tools they need to better control their emotions.

Although CBT is efficacious for treating mood and anxiety disorders, the barriers associated with this treatment make it extremely inaccessible. An effective round of CBT usually requires a large time commitment (ie, 12-15 weekly sessions), making CBT a costly solution for patients. In addition, given the time commitment from the clinicians, there are often extremely long wait times for individuals to receive treatment. Additional barriers to CBT include cultural and language barriers, especially within more culturally diverse countries, geographic isolation in rural areas, and social isolation, particularly in the context of the COVID-19 pandemic. Public stigma, high financial costs, lack of after-hour resources, and confidentiality concerns are also common concerns associated with receiving CBT [13,14]. Therefore, new innovative solutions are needed to make this effective and safe treatment option more accessible to patients in need without sacrificing the quality of care.

Electronically delivered cognitive behavioral therapy (e-CBT) presents itself as a remedy to these barriers. Owing to the structured nature of CBT, it can be effectively delivered remotely in the form of e-CBT. e-CBT offers results comparable with those of the in-person CBT, while increasing treatment adherence and yielding high treatment satisfaction [15,16]. Recent findings have supported the notion of implementing e-CBT for MDD, showing significant improvements in symptoms in various settings [17-19]. The use and accessibility of the internet have continued to grow globally, with more than 40% of the population having access to the internet and more than 2.5 billion individuals currently using the internet [20,21]. Given the increased accessibility to and use of web-based resources, internet-based delivery of mental health treatments can make help accessible and available at any time or place, helping underserved populations, geographically isolated individuals, and people looking for treatment outside of their work hours. In addition, delivering mental health care on the web provides a secure and private environment that could lower the stigma of receiving care, which is particularly useful for patients with MDD who usually show low help-seeking behaviors [22-24]. Furthermore, receiving care on the web allows patients to save time or financial burdens commuting to weekly appointments.

Several forms of e-CBT have been used, including self-help (unguided and self-directed), guided self-help (clinicians provide limited support), and *live* psychotherapy (clinician has the same role as in-person CBT through video conferencing). A meta-analysis [25] revealed that although self-help e-CBT can

have varying degrees of efficacy, therapist engagement increases treatment efficacy up to 4 times [26,27]. Therefore, a supervised form of e-CBT is required. Although this supervision can be achieved in *live* psychotherapy through videoconference, the time commitment for clinicians is identical to, if not greater than, that needed for in-person CBT [11]. From this, we can see that an asynchronous form of e-CBT delivery must be used where therapist supervision can be achieved without the strenuous time commitment of in-person CBT. Asynchronous e-CBT has been delivered in previous research; however, these studies used email as the primary method of communication between therapists and patients [28,29]. Although this offers the benefits of therapist engagement, email is an insecure and unsustainable form of patient-clinician communication [30]. This can be achieved by using predesigned and clinically validated therapy content coupled with asynchronous therapist interaction through a secure platform. In doing so, a high standard of care can be achieved without repeating general concepts to all patients, thus saving time.

This study aims to evaluate the efficacy and feasibility of delivering a supervised e-CBT program with streamlined processes for delivering care. By using predesigned therapeutic content, clinicians can skip repeating general concepts across multiple patients and focus on personalizing the treatment. This practice can significantly lower the time commitment from the clinical staff, which lowers the cost of care and increases the capacity, thereby shortening the wait time. Moreover, by validating the therapeutic content and clinical process in this clinical trial, we ensure that a high quality of care is delivered on a routine basis. The predesigned content will be delivered through a secure web-based platform, the Online Psychotherapy Tool (OPTT; OPTT Inc), designed by the lead author. The platform allows clinicians to schedule their interactions and activities with patients, track patient participation, and access analytical tools to improve the quality of care. Clinicians can personalize treatment plans for each patient, similar to *live* psychotherapy, without the time commitment needed for live and face-to-face treatment. By delivering e-CBT for MDD through this web-based platform, the aim is to provide patients with more accessible, affordable, and efficacious treatment options for their problems.

Objectives

This study aims to implement an e-CBT program to improve symptoms in patients with MDD. This study also aims to deliver this care program through a secure web-based platform structured as a web-based mental health clinic. This e-CBT program will be delivered using a digital care plan (ie, therapeutic content, feedback templates, care procedures, and instructions) specifically designed to address problems faced by patients with MDD. Using qualitative focus groups to collect personal, social, and cultural information from patients and health care providers, the accessibility and feasibility of the program can be better understood.

Methods

Study Design

For this study, an open-label, nonrandomized controlled trial study design will be used to compare the efficacy and feasibility of the web-based program with the in-person treatment option in a controlled manner. Blinding will not be possible, as patients will be aware of whether their treatment is occurring in person or remotely. Qualitative focus groups will be conducted with patients to gather personal, social, and cultural factors. These focus groups will be conducted to allow for a natural and open conversation on how participant factors can impact the treatment experience with the program. Additional focus groups will be conducted with therapists to gather information regarding the feasibility of implementing a web-based psychotherapy tool. This will be done to better understand how web-based treatment compares with in-person in terms of usability, time efficiency, and perceived connectedness to patients. These focus groups will occur posttreatment.

Quantitative analyses of e-CBT treatment efficacy will be conducted using standardized and clinically validated symptomology questionnaires. This data collection will occur at baseline, at week 6 and week 12 (posttreatment), and at a 6-month follow-up. In addition, a qualitative analysis of focus group interviews will be conducted with theme extraction. We hypothesize that the e-CBT program will offer results comparable with those of the in-person treatment program regarding symptom reduction and quality of life improvement. On the basis of this design, both the efficacy and feasibility of the e-CBT program can be evaluated and compared with in-person treatment for MDD. All study procedures have been approved by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (HSREB; file number 6020045).

Participants

Patients (N=110; 55 e-CBT participants and 55 in-person CBT participants) aged between 18 and 65 years will be recruited from Queen's University from the outpatient psychiatry clinic at both the Kingston Health Sciences Center sites (Hotel Dieu Hospital and Kingston General Hospital) as well as from Providence Care Hospital located in Kingston, Ontario, Canada. Additionally, family doctors, physicians, clinicians, and self-referrals will be accepted. Once informed consent is provided, a psychiatrist from the research team will evaluate participants through a secure video appointment to make or confirm a diagnosis of MDD using the Diagnostic and Statistical Manual of Mental Disorders, 5th edition [31].

The inclusion criteria for the study are as follows: aged at least 18 years at the start of the study, diagnosed with MDD according to Diagnostic and Statistical Manual of Mental Disorders, 5th edition by an attending psychiatrist from the research team, competence to consent to participate, ability to speak and read English, and consistent and reliable access to the internet. Exclusion criteria are as follows: active psychosis, acute mania, severe alcohol or substance use disorder, and/or active suicidal or homicidal ideation. If a participant is receiving another form of psychotherapy, they will also be excluded from the study to

avoid any confounding effect on the efficacy of this e-CBT program. Participants are eligible for the study if they are receiving pharmacotherapy. However, they must be receiving the same drug and dosage for the duration of the study. If eligible for the study, participants will choose between the e-CBT program (n=55) or the in-person CBT offered individually through this program at Hotel Dieu Hospital (n=55).

During the informed consent process, all participants will be explained that this program is not a crisis resource and that they will not always have access to their therapist. In the case of an emergency, participants will be directed to the proper resources (eg, emergency department or crisis lines), and this event will be reported to the principal investigator of the study. The reasoning behind having a nonrandomized design and allowing patients to choose their treatment is to mimic a real-world setting in which patients have autonomy in their treatment decisions. We recognize that this could be a limitation of this study. We plan to conduct a randomized controlled trial in the future.

Procedures

The e-CBT care plan consists of 12 weekly sessions of approximately 30 slides and interactive content delivered through OPTT (refer to Multimedia Appendix 1 for the sample module). The e-CBT module content mirrors in-person CBT content, including different weekly topics, general information, skill overviews, and homework. The efficacy of the therapeutic content has previously been tested through email administration and has been shown to reduce depressive symptoms significantly [32]. Participants are instructed to go through the content and complete homework at the end of the session, which helps them practice the skills they learned through that session. Homework is submitted through OPTT and reviewed by the therapist assigned to the participant, who will provide personalized feedback within 3 days of submission. Therapists have access to predesigned session-specific feedback templates to use as a basic structure to write their feedback. By doing so, the time needed to respond to each patient is reduced, and therefore, the number of patients each therapist can handle increases. At the same time, by using a structured format in responding to patients, more standardized quality of care can be ensured. The general structure of the feedback template is as follows: validating the participant's time and effort, reviewing the event they have used in their homework, summarizing the previous module's content, and discussing the participant's homework submission and how they could improve it. In addition to these points, the feedback will emphasize specific content from the participant's submission, reassuring them that their therapist is reading and understanding their challenges. All feedback submissions are finished with a personalized signature from the therapist, helping to develop a rapport between the therapist and the participant. On average, developing this feedback takes a therapist 15 to 20 minutes per patient. In addition to the weekly feedback, participants have the option to message their therapist through the platform throughout the week regarding any questions or concerns they may have. All technical issues are handled directly by OPTT's technical support team.

Participants in the in-person CBT group will attend weekly sessions at Hotel Dieu Hospital (12 weeks), where they will receive standardized individual (one-on-one) CBT for MDD from a trained therapist. All content covered and skills taught will mirror the e-CBT program. Similar to the e-CBT group, participants will be assigned weekly homework assignments that they will complete during the week and hand over at the start of their next session. At this time, participants will receive personalized feedback from their therapist for their previous week's homework.

At the end of the study, a few participants and health care providers (ie, 8 participants and 2 providers) will be recruited for focus groups. The focus group prompts will pertain to experience and expectations of service during the study and how they think the service could be improved.

Web-Based Module Content

Both e-CBT modules and in-person CBT sessions are designed to instill constructive and balanced coping strategies in the participants. During the program, we focus on essential thinking and behavioral skills to help patients become more engaged in day-to-day activities. The sessions focus on the connection between thoughts, behaviors, emotions, physical reactions, and the environment. In addition, we will evaluate negative beliefs and thought processes and their relationships with 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 allows them to adjust the way they behave and think about their problems in a way that is not as negative and replaces those thoughts and behaviors with potentially more realistic and productive ones. The 12 e-CBT sessions will follow the themes listed below:

1. *What is depression?* Provides expectations for the course and introduces the concepts of CBT and depression.
2. *5-part model:* Introduces the 5-part model (how situations, thoughts, feelings, physical reactions, and behaviors are connected and how they interact with each other).
3. *Situation, thoughts, feelings, physical reactions, and behaviors:* Provides further detailed exploration of the 5-part model and how changes in an area affect the other parts.
4. *Rating feelings and thought records:* Highlights the first 3 columns of a thought record (a tool used to help understand the connection between feelings, behaviors, and thoughts), which are situation, feelings, and automatic thoughts associated with the situation.
5. *Automatic thoughts:* Explains the role of automatic thoughts and how they influence feelings. Provides ways to identify thoughts and specifically identify the most dominant thoughts in stressful situations.
6. *Evidence:* Focusing on columns 4 and 5 of the thought record, which are designed to help gather evidence that supports or does not support the identified automatic thought.
7. *Alternative and balanced thinking:* Focus on the final 2 columns of the thought record that reflect on the evidence columns to help find alternative and more balanced views of the situation. The final column has the patient rerate their feelings based on the completion of the thought record.

8. *Experiments:* Explains the importance of conducting experiments to believe the alternative and balanced thoughts from the thought record to initiate changes in negative thinking patterns.
9. *Action plans:* Centered around using the thought record to identify a problem that needs to be solved and providing a framework for creating a plan for solving the problem.
10. *Strategies for stressful situations:* Overview of helpful strategies that can be used in stressful situations, including distraction activities and helpful breathing techniques.
11. *Activity scheduling:* Explains activity records and how using one can inform the patient on their mood changes and help reinforce scheduling positive activities into their day.
12. *Review:* Summarizes the main concepts of CBT and the tools and skills that the patient should continue to practice beyond completion of the final session.

Training

All therapists are research assistants hired by the principal investigator. All therapists undergo training in psychotherapy and receive additional training from a psychiatrist from the research team before any interaction with participants. During this training, therapists complete feedback on practice homework, which is reviewed by a psychiatrist from the research team to ensure adequate quality of work. All therapists are supervised by the lead psychiatrist, who is an expert in electronically delivered psychotherapy [23,24]. Feedback is always reviewed by the lead psychiatrist, before submission to the participants.

Outcome Evaluation

The primary outcomes that will be measured include changes in symptoms of depression based on the following clinically validated symptomology questionnaires: Patient Health Questionnaire-9 (PHQ-9) and the Quick Inventory of Depressive Symptomatology Questionnaire [33,34]. An additional measurement of quality of life change will be made based on the Quality of Life and Enjoyment Questionnaire [35]. All questionnaires were shown to be reliable and highly valid. Questionnaires will be collected directly through OPTT before treatment (baseline), after session 6, after the final session (week 12), and after a 6-month follow-up. Participants will not be offered incentives to increase the completion of the questionnaires. OPTT will collect use statistics (ie, log-ins per day and amount of time spent logged in) to help better understand the relationship between engagement and treatment outcomes.

Through the focus groups, health care providers will be asked about the feasibility of providing the electronic-delivered psychotherapy program and how it compares with in-person psychotherapy delivery. They will be asked to make their judgments based on variables such as time commitment, connectedness to patients, and benefits and drawbacks. From the focus group interviews with the participants, personal, social, and cultural factors (eg, gender, sexuality, background, supportive resources, and structural or social barriers) will be extracted using an interpretive phenomenological analysis approach. In addition, any adverse events and adherence to the intervention will be reported.

Ethics and Data Privacy

All procedures have been approved by the Queen's University HSREB. For privacy purposes, participants are only identifiable by an ID number on the platform, and hard copies of the consent forms with participants' identities are stored securely on site and will be destroyed 5 years after study completion. Participants' data are only accessible by the care providers directly assigned to that participant, and only anonymized data are provided to the analysis team members. Participants have the option to withdraw from the study at any point and request for their data to be removed from the analysis. However, as the collected data are considered a medical record, it will not be permanently deleted for 10 years after treatment.

The web-based platform used for the study (OPTT) is Health Insurance Portability and Accountability Act, Personal Information Protection and Electronic Documents Act, and Service Organization Control-2 compliant. In addition, all servers and databases are hosted in the Amazon Web Service Canada cloud infrastructure, which is managed by Medstack to ensure that all provincial and federal privacy and security regulations are met. OPTT does not collect any identifiable personal information or internet protocol addresses for privacy purposes. OPTT only collects anonymized metadata to improve its service quality and provide advanced analytics to the clinician team. OPTT encrypts all data, and no employees have direct access to participants' data. All encrypted backups are kept in the S3 storage that is dedicated to Queen's University, located in Kingston, Ontario, Canada.

Data Analysis

This is a confirmatory study with previously established objectives and analyses. Initially, all data are examined for missing, nonsensical, and outlying variables. Missing data are treated as missing and not imputed (ie, will be analyzed on a per-protocol basis). The participants in this study were intentionally oversampled to account for dropouts or withdrawals. On the basis of previous research, an anticipated dropout rate of up to 30% was factored in. Using the PHQ-9 as the primary outcome, a 30% change is considered clinically significant. Therefore, a sample size of 55 participants in each arm of the study would be sufficient for detecting significant results with P=.05 and a power of 0.95. Data collection occurs at baseline (preintervention), in the middle of the study (week 6), immediately after the intervention (week 12), and at a 6-month follow-up. Using Mann-Whitney U tests, demographic information can be compared between participants who complete the program and those who withdraw prematurely in the hope of identifying possible differences between the two. Moreover, an intention-to-treat analysis will be conducted to evaluate the clinical effects of treatment on participants who withdraw prematurely. Linear regression analysis (for continuous outcomes) and binomial regression analysis (for categorical outcomes) will be used to identify variables associated with the outcome measures (PHQ-9, Quick Inventory of Depressive Symptomatology Questionnaire, and Quality of Life and Enjoyment Questionnaire). This will occur over the 4 measurement time points while controlling for demographic variables, including age and gender. In addition, a comparative

analysis between both groups' questionnaire scores will be conducted at all data collection time points using group and paired two-tailed *t* tests.

Other quantitative measures for the e-CBT group will be gathered by extrapolating recorded information directly through the OPTT platform (eg, the number of log-ins per day and the amount of time spent logged in). Qualitative measurement analyses will be conducted to inquire about the role of personal, social, and cultural factors in enabling or constraining the use of e-CBT. The findings will identify factors related to the utility, feasibility, and accessibility of e-CBT from the perspectives of users and providers. Interpretive qualitative methods are ideal for gathering in-depth descriptions of user experience and meaning.

Results

This study received ethics approval from the Queen's University HSREB in January 2019, and the recruitment of participants began in June 2019. Participant recruitment has been conducted through social media advertisements, physical advertisements, and physician referrals. To date, 52 participants have been recruited in the e-CBT arm, and 48 participants have been recruited in the in-person CBT arm. Data collection is expected to be concluded by the end of March 2021, and data analyses are expected to be completed by June 2021.

Discussion

Comparison With Prior Work

MDD is a debilitating mental illness. Although treatment options are available, these modalities are either not efficacious for patients, inaccessible, or not scalable to a large population. Therefore, an innovative treatment that is efficacious and accessible while having an increased care capacity is needed. Developing a web-based psychotherapy tool with predesigned therapy modules and care processes can drastically increase care capacity for an overwhelmed mental health care system without sacrificing the quality of care. In this study, we aim to evaluate the feasibility and efficacy of this method of care delivery. By evaluating both the efficacy (through validated symptomology questionnaires) and feasibility (using focus groups), we can learn more about the real-world usefulness of e-CBT. Many of the current options for e-CBT are offered in nonsecure, nonscalable formats (email) or less effective (self-help) modalities, and by using this web-based platform, we can fill the gaps in the literature surrounding a large-scale psychotherapy clinic format for e-CBT delivery. Through the focus group findings, we can continue to better understand the accessibility issues associated with the remote delivery of mental health treatments and use these findings to develop more accessible options for patients. If proven feasible and efficacious, a web-based psychotherapy clinic can provide significant financial savings to the health care system through efficient use of clinician time, while providing an equitable and accessible method of treatment delivery for patients.

Conclusions

The outcomes of this study will be shared as a preprint through bioRxiv for the rapid dissemination of the findings. We will also hold multiple web-based workshops for other clinicians interested in implementing this approach and provide technical and academic support to deploy this solution in their respective practices. This will ensure that the findings can be efficiently incorporated into clinical practice across the country. This protocol and future publications or findings will be reported using the guidance for reporting interventional development studies in health research framework and the template for intervention description and replication [36,37].

Conflicts of Interest

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

Multimedia Appendix 1
Sample electronically delivered cognitive behavioral therapy module session.
[PDF File (Adobe PDF File), 3875 KB - resprot_v10i6e27489_app1.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
e-CBT: electronically delivered cognitive behavioral therapy
HSREB: Health Sciences and Affiliated Teaching Hospitals Research Ethics Board
MDD: major depressive disorder
OPTT: Online Psychotherapy Tool
PHQ-9: Patient Health Questionnaire-9

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Protocol

The Impact of a Novel Mimicry Task for Increasing Emotion Recognition in Adults with Autism Spectrum Disorder and Alexithymia: Protocol for a Randomized Controlled Trial

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Abstract

Background: Impaired facial emotion expression recognition (FEER) has typically been considered a correlate of autism spectrum disorder (ASD). Now, the alexithymia hypothesis is suggesting that this emotion processing problem is instead related to alexithymia, which frequently co-occurs with ASD. By combining predictive coding theories of ASD and simulation theories of emotion recognition, it is suggested that facial mimicry may improve the training of FEER in ASD and alexithymia.

Objective: This study aims to evaluate a novel mimicry task to improve FEER in adults with and without ASD and alexithymia. Additionally, this study will aim to determine the contributions of alexithymia and ASD to FEER ability and assess which of these 2 populations benefit from this training task.

Methods: Recruitment will primarily take place through an ASD community group with emphasis put on snowball recruiting. Included will be 64 consenting adults equally divided between participants without an ASD and participants with an ASD. Participants will be screened online using the Kessler Psychological Distress Scale (K-10; cut-off score of 22), Autism Spectrum Quotient (AQ-10), and Toronto Alexithymia Scale (TAS-20) followed by a clinical interview with a provisional psychologist at the Federation University psychology clinic. The clinical interview will include assessment of ability, anxiety, and depression as well as discussion of past ASD diagnosis and confirmatory administration of the Autism Mental Status Exam (AMSE). Following the clinical interview, the participant will complete the Bermond-Vorst Alexithymia Questionnaire (BVAQ) and then undertake a baseline assessment of FEER. Consenting participants will then be assigned using a permuted blocked randomization method into either the control task condition or the mimicry task condition. A brief measure of satisfaction of the task and a debriefing session will conclude the study.

Results: The study has Federation University Human Research Ethics Committee approval and is registered with the Australian New Zealand Clinical Trials. Participant recruitment is predicted to begin in the third quarter of 2021.

Conclusions: This study will be the first to evaluate the use of a novel facial mimicry task condition to increase FEER in adults with ASD and alexithymia. If efficacious, this task could prove useful as a cost-effective adjunct intervention that could be used at home and thus remove barriers to entry. This study will also explore the unique effectiveness of this task in people without an ASD, with an ASD, and with alexithymia.

Trial Registration: Australian New Zealand Clinical Trial Registry ACTRN12619000705189p; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=377455

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KEYWORDS

alexithymia hypothesis; training facial expression emotion recognition; mimicry task; autism spectrum disorder; interoception; facial expression; emotion; emotion recognition; autism; spectrum disorder; mimicry; therapy; protocol; expression; disability

Introduction

Background

Behavioral and cognitive neuroscience has elaborated a range of emotion-related difficulties with emotion recognition [1], empathy [2], and regulation of emotions in autism spectrum disorder (ASD) [3]. However, these abnormalities are not observed in all people with ASD [4]. Traditionally, these emotion-processing difficulties have been viewed as inevitable correlates of ASD, but recent research suggests that their presence is variable and better explained by co-occurring alexithymia. This suggestion is termed the alexithymia hypothesis [5] and is gaining significant support [6]. Alexithymia is a personality construct that relates to the inability to distinguish or describe the subjective feelings in the body produced by emotion. Alexithymia is related to both empathy [7] and emotion recognition [8] deficits. Severe degrees of alexithymia are manifested in up to 65% of adults with ASD [9].

The 2 forms of alexithymia, type 1 and type 2 [10], differ on the affective and cognitive dimensions [11]. Type 1 alexithymia includes high levels of both dimensions, whereas type 2 alexithymia only includes high levels of the cognitive dimension. Type 1 relates to reduced emotional reactivity (or a severe downregulation of emotional experience), and type 2 is typical emotional reactivity, but a reduced ability to interpret and describe that emotion [12].

Simulation Theories

Simulation theories [13] may explain how these emotion processing deficits occur in alexithymia. Simulation theories refer to the perception of a facial expression triggering a simulation of that expression's corresponding emotion within the perceiver. This simulation is then used to understand the perceived facial expression meaning to facilitate emotion recognition and empathy [14,15].

Alexithymia can explain the failure of this simulation process. Studies suggest that reduced emotion recognition accuracy in alexithymia is related to reduced activity in the insula (a small region within the cerebral cortex) [16]. The insula is related to the cognitive processing of emotions and generation of emotions [17,18], which are both required for simulation to work. The insula has also been noted as a critical relay station between the action representation system, which represents the vision of facial expressions, and limbic areas, which generate emotion [19]. In alexithymia, it has been found that the insula is hypoactive [12]. Therefore, when a facial expression is seen, the insula may fail to relay this information to the limbic area, which typically simulates the observed emotion.

The simulation process may also fail in alexithymia due to an inability to access the emotional information generated by a simulation. There are 2 explanations as to why people with alexithymia may not be able to access the simulation information. The first explanation is because of the inability to describe emotions in the self and differentiate them from bodily sensations, which is the hallmark of alexithymia [20]. Second, significant interoceptive deficits have been observed in alexithymia, which explains why people with alexithymia cannot accurately assess their current emotional state [21,22]. This interoceptive deficit would suggest that, even if an emotion was generated during simulation, people with alexithymia would not be able to appraise and understand this simulated emotion. Therefore, the simulation process would not provide any information about what the other person is feeling.

Another way that alexithymia may explain a failure of the simulation process is if people with alexithymia have trouble assigning the simulated emotion as belonging to the “sender” of the emotional expression [23], which is termed self-other distinction. If an emotion is simulated, but not tagged as belonging to the “sender,” then the simulation cannot aid recognition of the sender's emotion.

While alexithymia is a key element in explaining the failure of this simulation process, it does not provide a finer mechanistic explanation. However, theories proposed within predictive coding frameworks (PCFs) are beginning to provide a compelling explanation.

Predictive Coding Frameworks, Interoception, and Self-Other Distinction

PCFs suggest that the brain uses complex mathematical models to predict the most likely truths occurring in ourselves and our worlds [24,25]. These models are continually updating to increase efficiency and accuracy at explaining the most probable cause of sensory inputs [24]. Quattrocki and Friston [26] proposed a PCF theory that suggests that the causal factor of ASD is an aberrant oxytocin system. They proposed that the neuropeptide oxytocin has 2 functions. First, it has a role in prescribing the perceived accuracy of an interoceptive signal within the body. The perceived accuracy of an interoceptive signal is important because, if a top-down prediction and bottom-up stimulus do not match up, the brain will rely more heavily on the information source it perceives to be most accurate.

Therefore, when generating a model of the current state of the self or body, oxytocin mediates how much weight will be given to an interoceptive stimulus versus predictive models of the body’s current state. Second, oxytocin has a role in enabling the plasticity required for the brain to generate a model of the emotional and social “self.” Without these models, an over

reliance would be put on bottom-up information, as described by Pellicano and Burr [27].

Two constructs implicated in forming a distinction between the self and others were introduced in the earlier paragraphs: interoception and the self. Interoception is the perception of one's own internal state, including the perception of sensations such as thirst, stress, temperature, sleepiness, and heartbeat. One use of these sensations is for inferring emotional states and generating a model of the embodied "self" [25]. The embodied "self" is the physical body belonging to an individual, which the brain distinguishes as separate from other matter in the environment [28]. These bottom-up stimuli inform limbic brain regions and are suggested to assimilate with higher-order models of the self in the insula, anterior cingulate cortex, and ventromedial prefrontal cortices [29,30]. Therefore, these 3 areas are responsible for producing top-down predictions of perceptual information that has an emotional valence (ie, "gut feelings"). These emotionally valenced predictions are key components of the subjective emotional experience and self-awareness [25]. Quattrocki and Friston [26] suggested that one way in which models of the self can be weak is due to an aberrant oxytocin system. They suggest that an aberrant oxytocin system results in a failure to attribute less accuracy to interoceptive cues, which leads to a biased use of interoceptive cues over top-down prediction models. This biased use of interoceptive cues results in the models of the self being underdeveloped, lacking efficiency and accuracy. Underdeveloped models of the self make the ability to form a self-other distinction exceedingly difficult, and therefore, the ability to attribute an emotion to another person is compromised. Consequently, any emotional presentation generated via simulation for either empathy or emotion recognition may be experienced, however, not able to be attributed to the other person.

Facial Mimicry and Oxytocin

Facial mimicry and oxytocin may aid these interoceptive and emotional processing symptoms. Aoki and colleagues [31] showed that activity in the insula could be increased during emotion recognition tasks in people with ASD. They found that oxytocin significantly increased emotion recognition (P=.043) and increased activity in the insula during these tasks (P=.004). This study did not measure alexithymia; however, emotion recognition deficits in ASD have been found to become insignificant after accounting for alexithymia [32]. Therefore, this relationship between emotion recognition, oxytocin, and activity in the insula may actually be more applicable to alexithymia than to ASD.

One natural way to increase oxytocin has been suggested by Delaveau et al [33] by using mimicry. Mimicry referrers to copying the movements of another person. Delaveau et al [33] found that when mimicking and being mimicked, there was increased activity in the insula, similar to the results of Aoki and colleagues [31]. Paired with prior behavioral studies [34], the authors suggested that these results may be due to mimicry increasing the salience of social cues through the modulation of brain regions related to self-other processing. Further, they suggested that the systematic use of mimicry may provide therapeutic benefits. Given that both oxytocin and self-other processing have been implicated as key targets for the emotional processing problems observed in alexithymia, an intervention that includes mimicry may be a novel and simple therapeutic method.

Lewis and Dunn [35] offered support for the effectiveness of instructed mimicry in their emotion recognition study. They found that instructions to mimic a facial expression improved the recognition of that emotional expression selectively for people with high autistic traits. This finding was similar to that of Luminet et al [36] who found that oxytocin selectively benefits people high in alexithymia on a similar task. Additionally, other studies have shown that by restricting facial mimicry, facial emotion expression recognition (FEER) decreases (eg, [37-39]).

Study Aims

The first aim of this study is to evaluate the efficacy of an instructed mimicry task condition to improve FEER compared to a control condition and also from baseline to posttest in adults with and without alexithymia and ASD. The second aim of the study is to confirm findings by Cook et al [32] that FEER is related to alexithymia and not ASD. As an ancillary aim, the study will also collect data for further research on how eye-gaze patterns in type 1 alexithymia and type 2 alexithymia uniquely relate to FEER in the same sample.

Methods

Study Design

The study design is a mixed factor 2x2x2 within-between design. Participants who meet inclusion and exclusion criteria will be randomized to a control task or the experimental task. Inclusion and exclusion criteria and pretrial control variables will be collected during an online screening stage and during an in-person clinical interview. Baseline outcomes will be assessed directly before the control task or experimental task. They will then be assessed again during the control and experimental tasks. The study will conclude with a brief measure of satisfaction of the task and a debriefing session. See Multimedia Appendix 1 for a step-by-step workflow of a participant through the study.

Participants

We will recruit through local ASD support groups, online social media, and noticeboard advertisements (eg, at Federation University Australia). We will also use snowball recruiting to better penetrate the ASD community. Participants with an ASD (based on the assessments described in the Assessment section) will be assigned to the ASD group. Other participants will be assigned to the alexithymia-matched general population group (AM group).

The researchers will also use the 20-item Toronto Alexithymia Scale (TAS-20) total scores [40] to match the ASD group with the AM group without an ASD. Specifically, the number of participants in each group meeting criteria for alexithymia will be matched as indicated by TAS-20 scores ≥61, which is how groups have been matched in similar studies (eg, [32]).

The inclusion criterion is that participants are 18 years of age and older. The ASD group also has the added inclusion criterion of a confirmed ASD based on the assessment described in the Assessment section. Exclusion criteria include the participant having another mental health condition (other than an ASD if in the ASD group) diagnosed by a clinician and that the Kessler Psychological Distress Scale (K10) [41] indicates a significant level of distress (cut-off score of 22).

Assessments

The main aim of the current study is to assess the efficacy of the intervention in the general population and an ASD population, but also if people with high levels of alexithymia gain additional benefit. Further, this study will aim to replicate the study by Cook et al [32], which suggested that alexithymia, not ASD, predicts poor FEER. This requires having a general population group and another group with people with ASD, with both groups being matched on levels of alexithymia. Therefore, participants will be prescreened online to facilitate creating this composition of participants. During the online screening stage, participants will choose to consent in the study, complete the TAS-20, and indicate if they have an ASD or if they have been diagnosed with an ASD. During this screening stage, participants will also complete demographic information, the Autism Spectrum Quotient (AQ-10) [42], and the K-10.

Participants will then be invited to a clinical interview with a provisional psychologist (PP) at the Federation University Psychology Clinic who will confirm a reported diagnosis of ASD and complete an observational assessment that gives a diagnostic indication of an ASD. Participants who have reported a diagnosis will be asked what instrument was used and if the PP can request a copy of the results. The PP will also complete the Autism Mental Status Exam 2.2 (AMSE) [43,44]. The AMSE is an 8-item observational assessment that takes place during a clinical interview and predicts ASD classification on the Autism Diagnostic Observation Schedule (ADOS) [45]. During this clinical interview, participants will also be administered the Depression Anxiety Stress Scales-21 (DASS-21) [46] and the Wechsler Abbreviated Scale of Intelligence (WASI-II) [47] to assess depression, anxiety, and IQ, which will be used as control variables in the analyses of the results.

Assessor Training and Supervision

The PPs will have pre-existing training in conducting clinical interviews, including mental status examination, as well as administration of symptom measures and cognitive testing. They will be supervised by approved supervisors and endorsed clinical psychologists with extensive clinical experience (at least 10 years) working with and diagnosing people who have an ASD. All psychologists will participate in the AMSE training [48], which entails working through the AMSE manual, examples, and posttests. The viewing, rating, and discussion of additional videos of adults with ASD will enhance interrater reliability and ensure understanding of diagnostic criteria.

Clinical interviews will be recorded, and AMSE scoring decisions will be made with one or, where it is difficult to reach consensus, both of the supervisors. Participants who meet AMSE criteria and have a confirmed historical diagnosis will be included in the ASD group.

Measures

During the screening stage of the study, participants complete the K-10, TAS-20, AQ-10, and several single-item questions pertaining to demographic variables and known presence of other mental conditions. In the clinical interview with the PP, participants will be administered the DASS-21 and WASI-II, and the clinician will also use this time to complete the AMSE observational measure. Indication of context and time-point for each measure can be seen in Table 1.

Table 1. Study design and measures.

Concept	Measure	Instrument	Condition/ time point				
			Online screening stage	Clinical interview stage	Experiment stage		
					Pretest	During Experimental task	Posttest
Primary outcome	FEER[a] ability	FEER task Improvement score	-	-	X	X	-
Secondary Outcome	Acceptance / Enjoyment of task	Task satisfaction Questionnaire	-	-	-	-	X
Eligibility	Psychological distress	K-10[b]	X	-	-	-	-
	Depression and Anxiety	DASS-21[c]	-	X	-	-	-
	Predict ASD[d] classification on the ADOS[e]	AMSE[f]	-	X	-	-	-
	Predict ASD classification	AQ-10[g]	X	-	-	-	-
	Alexithymia	TAS-20[h]	X	-	-	-	-
Control variables	Alexithymia	BVAQ[i]	-	-	X	-	-
	IQ	WASI-2[j]	-	X	-	-	-
	Demographics	Demographic information	X	-	-	-	-

[a]FEER: facial emotion expression recognition.

[b]K-10: Kessler Psychological Distress Scale.

[c]DASS-21: Depression Anxiety Stress Scales-21.

[d]ASD: autism spectrum disorder.

[e]ADOS: Autism Diagnostic Observation Schedule.

[f]AMSE: Autism Mental Status Exam.

[g]AQ-10: Autism Spectrum Quotient.

[h]TAS: Toronto Alexithymia Scale.

[i]BVAQ: Bermond–Vorst Alexithymia Questionnaire.

[j]WASI-2: Wechsler Abbreviated Scale of Intelligence.

K-10

The K-10 [41] is a measure of psychological distress. It consists of 10 items measured using 5 values that ask how often a specific feeling was felt over the past 4 weeks. Possible answers range from 1 “None of the time” to 5 “All of the time,” with higher values indicating more distress. Possible scores range from 10, indicating no distress, to 50, indicating severe distress. A cut-off score of 19 will be used to indicate the presence of case-level anxiety or depression [49]. The K-10 is a reliable and valid measure of psychological distress with high discriminant validity [41].

TAS-20

The 20-item TAS-20 [40] is the most widely used measure of alexithymia. It consists of 20 items, with each item being rated on a 5-point Likert scale between “strongly disagree” (1) and “strongly agree” (5). Higher scores designate higher degrees of alexithymia with a possible score ranging between 20 and 100. Cut-off scores have been developed with scores ≤50 suggesting no alexithymia, scores between 51 and 60 indicating borderline alexithymia, and scores ≥61 suggesting alexithymia [50]. The TAS-20 has been demonstrated to be a valid and reliable measure of alexithymia [40] with an internal consistency of α=.81 and test-retest reliability of .77 (P<.01).

Bermond–Vorst Alexithymia Questionnaire

The Bermond–Vorst Alexithymia Questionnaire (BVAQ) [11] is also a measure of alexithymia that aims to assess the alexithymia construct more comprehensively across 2 subdimensions, namely the cognitive and the affective. Measuring these 2 subdimensions aids in distinguishing between participants with type 1 and type 2 alexithymia. In total, there are 40 items rated on a 5-point Likert scale, with higher scores indicating higher levels of alexithymia. This model of alexithymia and the BVAQ have demonstrated strong validity and reliability [10,11].

DASS-21

The DASS-21 [46] is a self-report questionnaire that is designed to measure depression, anxiety, and stress/tension levels. Each of the 3 subscales contains 14 items that are scored on a 4-point

Likert style scale, which ranges from 0, “did not apply to me at all,” to 3, “applied to me very much, or most of the time.” Total scores are calculated by summing the scores from the 3 subscales, with higher scores indicating more of that construct. The DASS has good convergent and divergent validity, with strong internal consistency and reliability, with Cronbach alphas observed at .94, .87, and .91 for depression, anxiety, and stress, respectively [51]. Additionally, the DASS has established normative data for adults with an ASD [52].

AMSE

The AMSE 2.2 [43] is an 8-item clinician observational assessment that aims to structure the documentation and observation of social, communicative, and behavioral function in people with ASD. The AMSE takes place during a clinical interview without adding extra work or time during the examination. Scores higher than 4 predict ADOS [53] classification with a sensitivity of 94% and specificity of 81% [44]. Interrater agreement is high at 0.97, and internal consistency was fair with a Cronbach α of .72 [43].

WASI-II

The WASI-II [47] is an individual, clinician-administered measure of cognitive intelligence based on the Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV) [54]. The WASI-II includes 4 subtests: block design, vocabulary, matrix reasoning, and similarities. It produces 3 metrics: Full-Scale IQ, Verbal IQ, Performance IQ. The WASI-II correlates highly with the WAIS-IV and has good reliability and validity [55].

AQ-10

The AQ-10 [42] is a short-form, 10-item, self-assessment instrument for measuring autistic traits based on the AQ-10 [56]. Each of the 10 items contains a statement such as “I find it easy to 'read between the lines' when someone is talking to me.” Responses are made on a 4-point scale ranging from “Definitely Agree” to “Definitely Disagree.” One point is scored if the respondent selects “Definitely Agree” or “Slightly Agree” on each of items 1, 7, 8, and 10. One point is scored for “Definitely Disagree” or “Slightly Disagree” on each of items 2, 3, 4, 5, 6, and 9. The AQ-10 has good construct validity and adequate internal consistency with a Cronbach alpha of .85 [42].

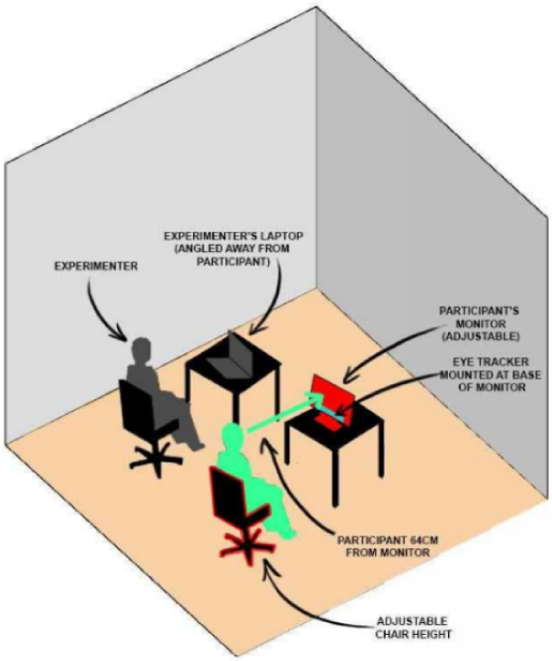
Questionnaire of Task Satisfaction

In addition to these measures, a self-developed questionnaire of satisfaction, acceptance, and enjoyment of the task will also be designed to assess how viable this method of training is for people with alexithymia and ASD (Multimedia Appendix 2). It will include 5 statements about the study task, with responses on a 5-point scale. Responses will range from 1 (Not very true) to 5 (Very true). Higher scores for each question indicate that the statement applied more strongly to the individual. Examples of the items are “The task made me uncomfortable” and “I feel like this task helped me.”

Equipment

The Tobii Pro x3-120 Eye Tracker (TPX3) is a screen-based eye tracker that tracks the gaze point on a screen. The TPX3 has been certified to meet European standard EN 62471, which indicates that it is not harmful to the human eye. The TPX3 has a sampling rate of 120 Hz and a large head movement box (area where the user’s head can move and still be tracked). Only the gaze point 2D coordinates on the screen for each eye will be used. The TPX3 will attach to the bottom of a computer monitor that is ~64 cm in front of the participant. Both the chair and the participant’s screen can adjust for height to make sure the participant’s head is within the head movement box as indicated in Figure 1. The chair and screen height will be adjusted based on the setup procedure within the iMotions software prior to running the iMotions software eye-tracker calibration process.

Figure 1. Physical layout of experiment and eye-tracker.



Primary Outcome

The primary outcome being assessed is an increase in FEER. This will be measured by comparing the percent of correctly identified facial emotion expressions from the baseline assessment task to the instructed mimicry experimental task. Additionally, the percent of correctly identified expressions will also be compared between the control condition and the intervention condition. This will provide 2 primary metrics: before-after percent improvement and control group to experimental group percent improvement.

Intervention

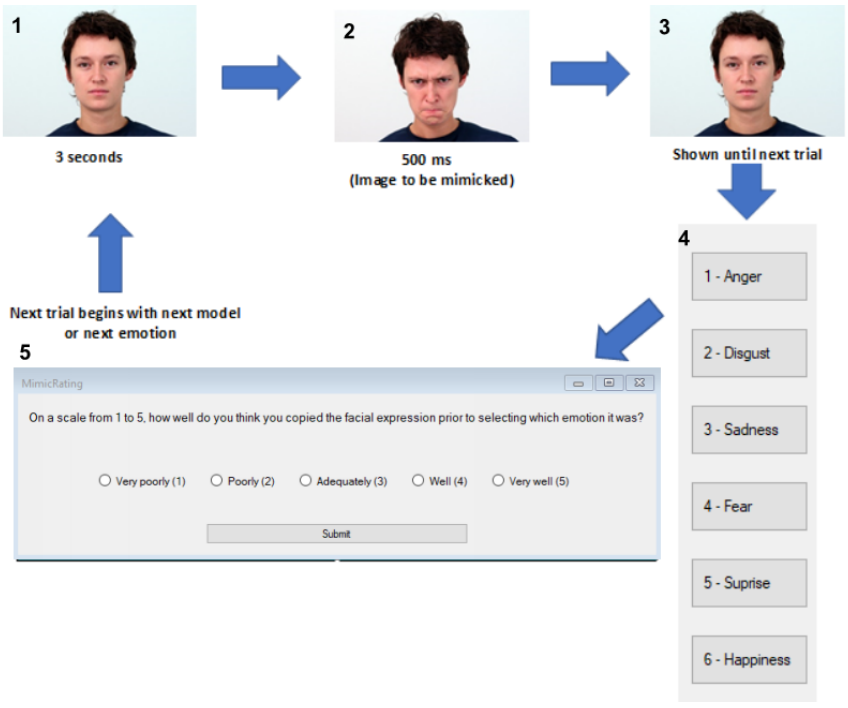
The task will be delivered in-person at the Federation University Psychology Clinic in Ballarat, Australia, by the primary author in a small counselling room. The room will have 2 computers on a desk, each with separate monitors and peripherals (one for the participant and the other for recording eye-tracking data). Participants will take part in the task 1 participant at a time based on a mutually agreed upon time and date. Participants will only undergo this task once, and it is expected to take approximately 30 minutes based on prior testing where a small neurotypical group took approximately 25 minutes to complete the task in a usability test. The intervention is a software-based FEER training task that presents a series of different facial expressions and requires individuals to firstly mimic and then select which emotional expression they saw. The software runs on Microsoft Windows 10 and requires only minimal system requirements and a mouse.

The intervention task condition will begin with the software presenting a basic description of 6 facial expressions (fear, sadness, happiness, anger, disgust, surprise) and tips on how to spot each expression. Next, participants will be verbally advised by the experimenter and by on-screen text that a series of emotion recognition trials will begin shortly. Further, they will be told that after each emotion is displayed that they should try their best to mimic (copy) the observed facial expression with their own face. Once they have mimicked the expression, they should then use the 6 labelled buttons on the right-hand side (or associated keyboard shortcut) to choose which emotion was displayed. After selecting the answer using 1 of the 6 buttons, a 5-point Likert scale on the computer screen will ask the participant "How well did you mimic the expression?" with responses ranging from 1 "not very well" to 5 "very well." This will repeat for each of the 36 trials. The trials will include various models of both men and women depicting the 6 emotions.

The sequence of each trial in the task is depicted in Figure 2 with accompanying numbered indexes. Each trial will begin with a neutral expression image displayed on the screen (index 1). After this image has been displayed for 3 seconds, it will quickly swap to another image from the same model, except this image will depict an emotional expression (eg, angry or sad, index 2). After 500 milliseconds, this image will be replaced with the original neutral image (index 3), and the 6 buttons with emotion labels will appear on the right-hand side (index 4). Once the participant selects the emotion using the 6 buttons, the trial will conclude with the 5-point rating of how well the participant felt they copied the expression (index 5).

In a task that aims to test or train FEER ability, it is important to ensure that the emotional stimuli tested against are true exemplars of the emotion they purport to signal. It is also important that the expressive images in the baseline test and the experimental tasks are similar in recognition difficulty. This will reduce the risk of improvements being attributed to easier expressions in the experimental tasks compared to the baseline task. This task used the Warsaw Set of Emotional Facial Expression Pictures (WSEFEP) [57]. See Multimedia Appendix 3 for a description of these pictures and how pictures were selected for each condition. See Figure 2 for an example of the pictures.

Figure 2. Task sequence and stimulus example.



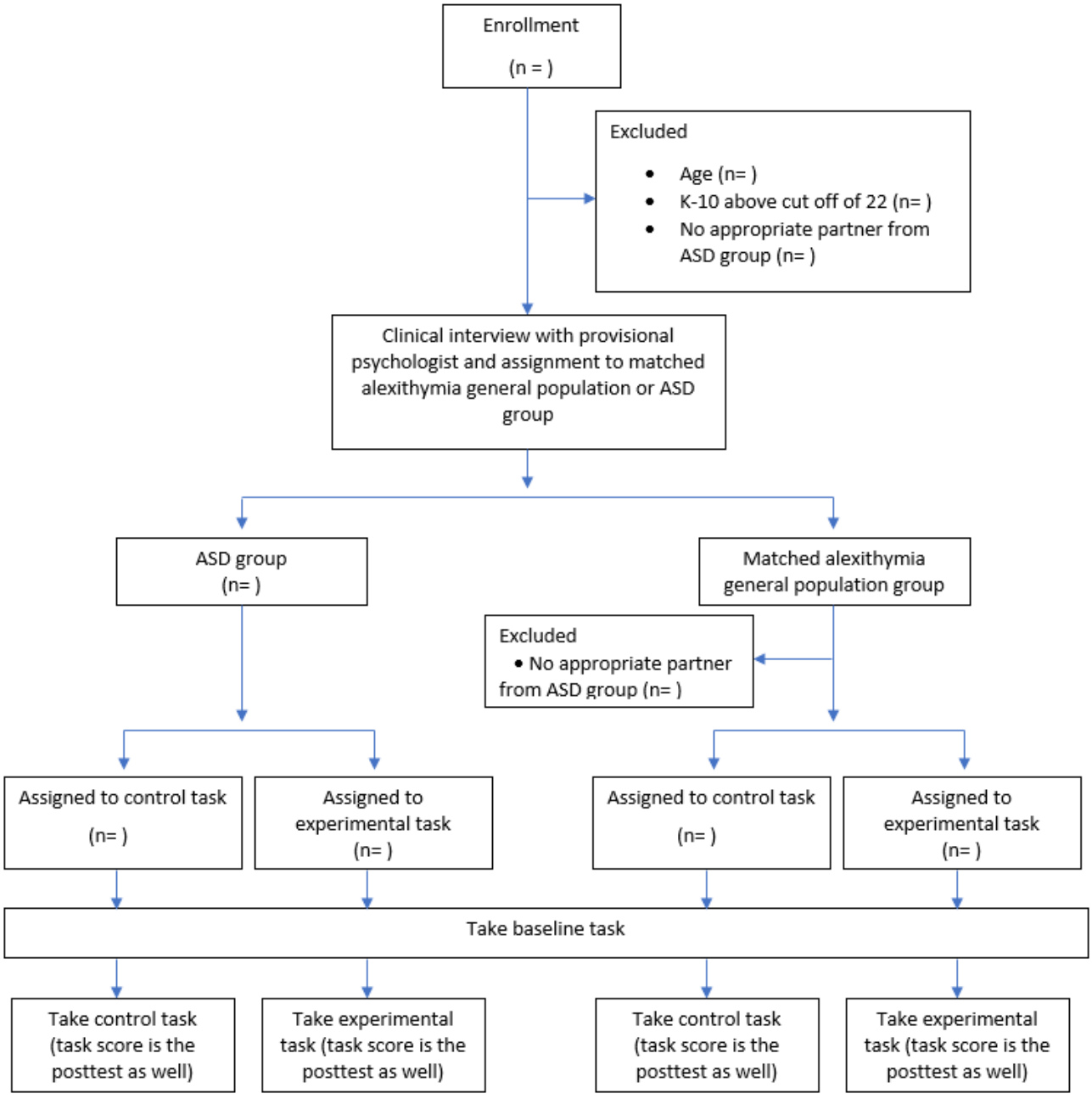
Comparator/Control Group

This study includes both a before-after, within-group comparator and a between-groups control group. To make the before-after comparison, participants will first partake in a baseline assessment task of emotion recognition before randomization to one of the experimental conditions. This baseline assessment task will be the same as the intervention task; however, participants will not be instructed to mimic the facial expressions prior to selecting an expression.

In addition to the before-after comparator, there will be a control condition. The control condition will also undergo the baseline assessment task; however, instead of participating in the mimicry intervention task, they will undergo a similar task with no mimicry element. This task will be identical to the instructed mimicry intervention task; however, instead of being instructed to mimic the facial expression, they will be instructed to "pay particular attention to the entire face prior to selecting an expression." This instruction is aimed to match for attention levels.

A final point of comparison will be that participants will be first broken up into 2 groups, namely the AM group and ASD group. This comparison will provide the ability to analyze if any intervention effects only occur or are stronger in people with ASD, alexithymia, or the general population. The participant flow diagram can be seen in Figure 3.

Figure 3. Participant flow diagram. ASD: autism spectrum disorder; K-10: Kessler Psychological Distress Scale.



Randomization

Participants will be randomized using permuted block randomization with stratification across age and gender to receive either the control or experimental task condition with equal numbers from both the ASD group and AM group receiving each task.

Sample Size Calculation

Based on the effect sizes of 2 previous studies measuring similar constructs and similar tasks [32,35], to achieve a medium to large effect (eg, Gpower f^2 test = 0.27) with a significance of 5% (P=.05) and power of 80%, a sample size of 58 will be required to demonstrate statistical significance for the primary hierarchal regression and analysis of variance (ANOVA). Given an expected attrition of 10%, a total of 64 participants will be recruited.

Statistical Analyses

The data will be analyzed using SPSS, Version 25. Alexithymia will be analyzed to aid in matching the AM group and ASD group on alexithymia. To ensure that the ASD and AM groups, and also the experimental and control groups, are comparable, means and standard deviations of participant characteristics will also be compared with tests of difference.

The study design is a mixed factor, 2x2x2, within-between design (see Table 2), and therefore, the most appropriate test of difference is a mixed factorial ANOVA, set up according to Table 2 with IQ, depression, and anxiety variables added as covariates. This will provide analyses of whether the instructed mimicry intervention task was effective by comparing baseline scores to posttest scores. Additionally, it will provide the ability to compare posttest scores between the control group and the intervention group. Finally, this analysis will have the additional ability to discern these differences based on group (ASD group and AM group).

In addition to the mixed factorial ANOVA, a hierarchical regression analysis will also be conducted (see Table 3) to determine the predictive ability of alexithymia on the primary outcome variable.

Table 2. Experimental group and intervention design.

Time point	ASD[a] group (n=~32)		AM[b] group (n=~32)	
	Control task condition (n=~16)	Mimicry task condition (n=~16)	Control task condition (n=~16)	Mimicry task condition (n=~16)
Pretest	FEER[c] task score	FEER task score	FEER task score	FEER task score
Posttest (the intervention task is the posttest)	FEER task score	FEER task score	FEER task score	FEER task score

[a]ASD: autism spectrum disorder.

[b]AM: alexithymia-matched general population.

[c]FEER: facial emotion expression recognition.

Table 3. Hierarchal regression stages for analysis.

Stage	Variables
Stage 1	IQ, age, gender
Stage 2	+Autism
Stage 3	+Alexithymia
Stage 4	+Intervention

Hypotheses

It is hypothesized that the condition that receives the mimicry task will show significantly better emotion recognition improvement scores (posttest minus baseline); the degree of alexithymia will negatively predict baseline scores; the degree of alexithymia will predict improvement scores (posttest minus baseline); when matched on alexithymia, the general population and ASD population will not significantly differ in emotion recognition improvement scores (posttest minus baseline); and when matched on alexithymia, the AM group and ASD group will not significantly differ on baseline emotion recognition scores.

Results

Ethics Approval and Trial Registration

This study will meet the ethical guidelines outlined in the National Statement on Ethical Conduct in Human Research (NHMRC, ARC & UA) [58]. This study has been granted full approval from the Federation University Australia Human Research Ethics Committee (Project # A19-036) and is registered with the Australian New Zealand Clinical Trial Registry (ACTRN: ACTRN12619000705189).

Timeline

As of June 2021, the project has not begun recruitment. The project is predicted to begin participant recruitment in the third quarter of 2021, with data collection beginning as eligible consenting participants make contact.

Discussion

This paper describes, to our knowledge, the first study to assess an instructed mimicry task to increase emotion recognition ability in people with alexithymia and ASD. Despite the formulation of the alexithymia hypothesis, very few studies have assessed the impact of alexithymia in interventions aimed at increasing social functioning and in particular, emotion recognition. Additionally, to our knowledge, no other study has explored the benefits of instructed mimicry on emotion recognition in people with ASD and alexithymia. This mixed factor, 2x2x2, within-between design will assess the efficacy of the instructed mimicry task to increase FEER. This study design will enable the assessment of baseline and improvement scores individually for people with and without ASD while controlling for levels of alexithymia. This will allow analyses of how this intervention uniquely benefits ASD without the interference of alexithymia, which is known to frequently co-occur in ASD [9]. If this task is successful at increasing emotion recognition, it could provide easily accessible training to those with ASD, alexithymia, and other disorders that typically have high rates of alexithymia such as schizophrenia [59].

One proposed benefit of this intervention for people with alexithymia and ASD is that the software does not require supervision. This will likely benefit these populations as they typically enjoy computer-based interaction rather than social interaction, as indicated by previous studies (eg, [60]). This has the added benefit of improving access to the task as it could be used on a home computer, which may eliminate a key barrier to treatment.

Despite the benefits of this task and study design, some limitations are present. First, matching the ASD and AM groups on levels of alexithymia improves our ability to exclude alexithymia as a contributing factor of emotion recognition accuracy. Unfortunately, it also means that other confounding factors may have been systematically introduced when matching on alexithymia. This limitation will make it difficult to attribute any benefits of the intervention task specifically to autism. Additionally, when comparing emotion recognition accuracy, it will limit our ability to suggest whether emotion recognition difficulties are related to ASD or to alexithymia, as per the alexithymia hypothesis.

A second limitation is the once-off nature of this intervention. While similar tasks have shown improvement over one session (eg, [61]), it would be ideal to administer the intervention several times over a longer time period and measure in between. Given that the primary variable, emotion recognition, is measured during the task (the intervention task is the posttest), this could be done by having participants complete the task at home for a specific amount of time and intervals.

In summary, it has been suggested that emotion recognition problems in ASD are instead due to co-occurring alexithymia. This study matches an ASD and non-ASD general population group (the AM group) on alexithymia to improve the ability to detect if this is true. Further, this study design will aid in detecting if the instructed mimicry intervention benefits people specifically with ASD or if it more broadly aids people with alexithymia. If successful, this adjunct intervention will be cost-effective and easy to implement while also removing entry barriers as it could be used at home on a personal computer.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Workflow of participants through in-person segments of study.
[DOCX File , 28 KB - resprot_v10i6e24543_app1.docx]

Multimedia Appendix 2
Questionnaire of Task Satisfaction.
[DOCX File , 19 KB - resprot_v10i6e24543_app2.docx]

Multimedia Appendix 3
Selection process of pictures to match task difficulty between the baseline task and the experimental task.
[DOCX File , 25 KB - resprot_v10i6e24543_app3.docx]

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Abbreviations

ADOS: Autism Diagnostic Observation Schedule
AM: alexithymia-matched general population
AMSE: Autism Mental Status Exam
ANOVA: analysis of variance
AQ-10: Autism Spectrum Quotient
ASD: autism spectrum disorder
DASS-21: Depression Anxiety Stress Scales-21
FEER: facial emotion expression recognition
K-10: Kessler Psychological Distress Scale
PCF: predictive coding framework
PP: provisional psychologist
TAS: Toronto Alexithymia Scale
WAIS-IV: Wechsler Adult Intelligence Scale - Fourth Edition
WASI-II: Wechsler Abbreviated Scale of Intelligence
WSEFEP: Warsaw Set of Emotional Facial Expression Pictures

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Protocol

Assessing the Pregnancy Protective Impact of Scheduled Nonadherence to a Novel Progestin-Only Pill: Protocol for a Prospective, Multicenter, Randomized, Crossover Study

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Abstract

Background: Progestin-only contraceptive pills (POP) are commonly reserved for women with medical comorbidities but in actuality, POPs can be safely used by anyone wanting to prevent pregnancy. This wide safety profile makes them an ideal candidate for being available over the counter without a prescription, but adherence issues may be more common with over-the-counter use. We need a better understanding of the ability of POPs to prevent pregnancy when adherence issues occur in the form of a missed or delayed pill.

Objective: This study aims to determine cervical mucus characteristics following a 6-hour delayed pill intake or after one missed pill as compared to typical daily use of norgestrel 75 mcg.

Methods: This prospective, multicenter, randomized, crossover study assesses the effect of norgestrel 75 mcg (Opill) on cervical mucus and ovarian activity during reported compliant daily use, after a 6-hour delayed intake mid cycle, and after a mid-cycle missed pill. Subject participation will last approximately 4.5 months. We will recruit at 2 US sites: Oregon Health & Science University, Portland, Oregon and University of California Davis Health, Sacramento, California. Reproductive-aged subjects with regular menstrual cycles (21-35 days), BMI <32 kg/m2, and proven ovulation (screening luteal phase progesterone >3 ng/mL [>10 nmol/L]) are eligible to enroll. Participants cannot be at risk for pregnancy during the study period and not use other hormonal methods. Norgestrel 75 mcg will be taken at the same time daily except for one day in each of treatment periods 2 and 3, when the pill will be taken either 6 hours late (delayed pill) or omitted completely (missed pill). Every 3-4 days, we will monitor subjects for follicular activity with transvaginal ultrasound (TVUS) examination, cervical mucus, and blood sampling for ovarian hormones and gonadotropins. Subjects will undergo serial cervical mucus sampling on the days with missed and delayed pill intake at 8 hours after pill intake on the day before the delayed or missed pill, 3 hours following the scheduled time of pill intake if intake was delayed, 6 hours after the scheduled time if intake was omitted, and on the next day 30 minutes before the time of scheduled pill intake. The primary objective of the study is to determine the effect of a delayed or omitted pill intake on cervical mucus characteristics based on a modified Insler score compared to reported daily use.

Results: Our protocol was successfully approved by a central institutional review board (Advarra, Columbia, MD), received ethical approval on March 23, 2018, and was registered with ClinicalTrials.gov (NCT03585712). As of January 2020, the study completed enrollment of 52 subjects. Analyses are pending.

Conclusions: Our protocol was approved by a central review board, and study procedures were successfully executed with completed proposed enrollment.

Trial Registration: ClinicalTrials.gov NCT03585712; https://clinicaltrials.gov/ct2/show/NCT03585712

International Registered Report Identifier (IRRID): DERR1-10.2196/29208

(JMIR Res Protoc 2021;10(6):e29208) doi:10.2196/29208

KEYWORDS

protocol; missed pill; progestin-only pills; contraception; pharmacokinetics

Introduction

Oral contraceptives are the most widely used hormonal method of contraception in the United States [1]. Progestin-only pills (POP) are commonly prescribed for individuals with contraindications to estrogen, such as those who are breastfeeding or with medical comorbidities. Almost anyone, with or without a comorbidity, can safely use POPs to prevent pregnancy [2]. This wide safety profile makes them an ideal candidate for being available over the counter without a prescription [3-5]. For successful use, users need a full understanding of the ability of POPs to prevent pregnancy when adherence issues occur in the form of a missed or delayed pill. Studies of combined estrogen-progestin pills are reassuring that short lapses in adherence do not put a user at increased risk for pregnancy; however, we lack similar information for low-dose POPs [6]. These studies are essential to applying for over-the-counter status with the US Food and Drug Administration. POPs are a well-established method of contraception and considered an effective method of birth control with a perfect and typical use failure rate of 0.3% and 9%, respectively [7]. Impenetrable cervical mucus is considered the dominant mechanism for pregnancy prevention with POP use [8]. Timely pill intake is thought to be critical for this mechanism of action, but data are not available to assess the temporality of this effect with low-dose POPs, such as norgestrel 75 mcg (active enantiomer, levonorgestrel), the focus of our proposed studies. POPs also suppress ovarian activity, but the extent of suppression is contingent on progestin potency and dose; but again, data linking pharmacokinetic and pharmacodynamic data for a POP containing norgestrel 75 mcg do not exist [9].

Current clinical guidance recommends that taking POPs more than 3 hours late is considered a missed pill due to concern regarding diminishing effects on cervical mucus [10]. However, that may not be case for all POPs; more detailed studies of cervical mucus qualities over the time period of a missed or delayed pill may prove that a 3-hour cutoff is too short and provide POP users with a wider window for maintaining efficacy should they miss taking their pill on time. Our proposed studies, outlined in the protocol described here, have been designed to determine the impact of the POP-containing norgestrel 75 mcg on cervical mucus and ovarian activity as well as levonorgestrel levels during a treatment period of typical and nonperfect adherence.

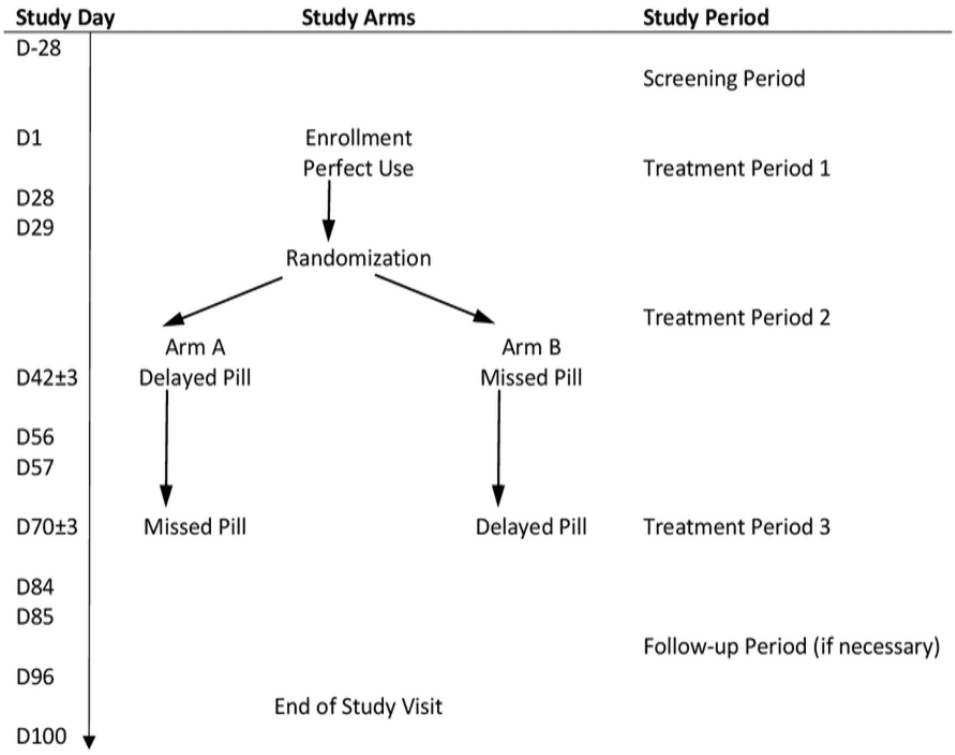
The primary objective of the study is to determine the effect on cervical mucus characteristics following a 6-hour delayed pill intake or after 1 missed pill as compared to typical daily use of norgestrel 75 mcg (see Box S1 in Multimedia Appendix 1). Our secondary objectives focus on other pharmacodynamic and pharmacokinetic endpoints including ovarian activity and levonorgestrel levels with typical and nonperfect adherence to POPs.

Methods

Study Design

This is a prospective, multicenter, randomized, crossover study (Figure 1).

Figure 1. Study design.



Study Population

The study population will consist of healthy, reproductive-aged women with regular menstrual cycles.

Inclusion Criteria

We will recruit healthy subjects aged 18-35 years old with a BMI no greater than 32 kg/m^2 with regular menstrual cycles (21-35 days) and proven ovulation as documented by a luteal phase progesterone >3 ng/mL (>10 nmol/L) during screening (see Box S2 in Multimedia Appendix 1). Subjects must have an intact uterus and both ovaries. Participants cannot not be at risk for pregnancy during the study period (eg, heterosexually abstinent, using condoms or permanent contraception). Subjects must be willing and able to understand and give informed consent and, in the opinion of the investigator, able to follow all study requirements. Subjects recently postpartum or postabortal must have 1 full menstrual cycle (2 bleeding episodes) and meet the other inclusion criteria prior to enrollment. Subjects previously using intrauterine or noninjectable hormones must have had at least 1 menstrual cycle without the treatment prior to screening. For those having used injectable contraception (depot medroxyprogesterone acetate), their last injection must be at least 9 months before screening.

Exclusion Criteria

In general, our exclusion criteria include any of the common reasons an individual should not be taking contraception, including pregnancy or anything that would confound or adversely influence our endpoints. A complete list of exclusion criteria can be found in Box S2 in Multimedia Appendix 1.

Randomization and Allocation Concealment

All subjects will receive the same study drug, norgestrel 75 mcg, during 3 consecutive treatment cycles lasting 28 days each. Treatment cycle 1 will be the planned “perfect use” cycle for all participants with no scheduled delayed or missed pill. We will randomize subjects during the first visit of treatment cycle 2 in a 1:1 ratio with 13 blocks with a block size of 4 for each site, to either Arm A (delayed pill to be done during treatment cycle 2 and missed pill in treatment cycle 3) or Arm B (missed pill in treatment cycle 2 and delayed pill in treatment cycle 3). The centralized study coordinating center will computer-generate the randomization scheme; site-based study staff will not have access to the scheme, but once allocated, both site staff and subjects will know their allocated arm (Figure 1).

Participant Recruitment and Enrollment

Participants will be recruited from 2 research centers in the United States with competitive recruitment planned between the 2 centers. Subjects will be recruited from clinics serving reproductive-aged women for gynecologic care and reproductive health services (including the clinics’ database) as well as through institutional review board–approved research recruitment efforts (eg, newsletters, in-services, tear ads, social network ads). Referrals from previous or ongoing participants will be accepted. This study’s ClinicalTrials.gov registration number is NCT03585712. Subjects will be selected for the study according to the inclusion and exclusion criteria (see Box S2 in Multimedia Appendix 1), will be provided information about the study and study procedures directly from the study staff, and if eligible and agree to participate, will undergo and sign informed written consent.

Intervention

Subject participation will be 4.5 months, which includes up to 1 month for screening, 3 separate 28-day treatment cycles, and up to 2 weeks for follow-up and end-of-study processes. All participants will receive the study drug, norgestrel 75 mcg (Opill), in the form of a pill taken orally once daily. The study drug will be provided in boxes containing 1 blister pack of 28 tablets, which corresponds to 28 days of study drug (1 pill per day, single dose). Participants will be provided with 2 boxes at the start of treatment period 1 (one as back up) and 1 box each at the end of treatment periods 1 and 2.

Sample Size

Since this is an exploratory study with no working hypothesis to confirm or reject, the sample size is not based on a power calculation. This study will screen approximately 70 subjects to achieve at least 45 completed subjects.

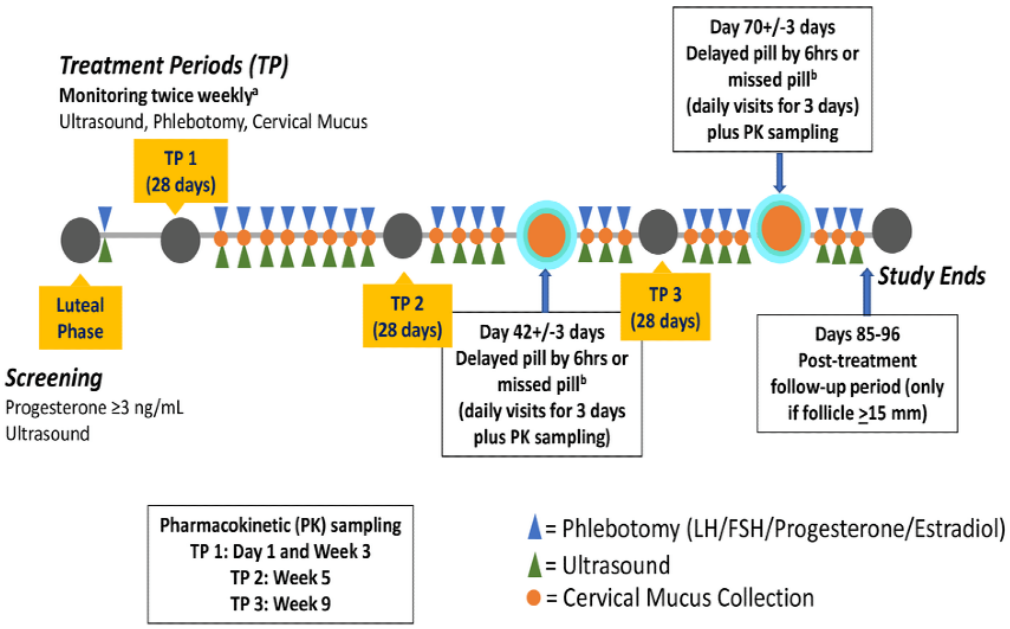
Sample Collection

Serial sampling over the 3 separate 28-day treatment cycles will be necessary to obtain the key pharmacodynamic and pharmacokinetic endpoints for this study: cervical mucus, ovarian follicular activity, gonadotropins and ovarian hormones, and plasma levonorgestrel levels. Subjects will prospectively track any vaginal bleeding experienced.

The integrity of the data for this study is contingent on subject compliance with study drug and procedures. The subjects will be instructed to bring their study drug packs to each visit. Compliance will be assessed by monitoring the study drug present or absent from the medication packs at each visit and at the end of each treatment period and by information recorded prospectively by an electronic diary (daily text messaging to report daily pill intake [yes/no], the time, and bleeding). During treatment cycles 2 and 3 when either the delayed or missed pill will occur, the delayed pill intake will be directly observed by study staff, and the missed pill will be removed from the blister package by the study staff and placed in a small container, labeled, and retained in order to monitor accountability.

Study visits occur approximately every 3-4 days but will increase to every other day when a follicle >15 mm is observed during transvaginal ultrasonography examination (TVUS; for a maximum of 3 visits) and to daily visits around the time of the delayed or missed pill (Figure 2). Cervical mucus, blood sampling, and ovarian monitoring via TVUS will be performed at each visit. Cervical mucus will be collected by aspiration using the SelectMucus Endocervical Aspirator (Cooper Surgical, Trumbull, CT). The cervical mucus assessment will be made by a limited number of trained clinic personnel to limit variability. A centralized in-person training will be organized to maintain a high level of consistency for these evaluations. The cervical mucus sampling will be performed prior to the TVUS examination. We will utilize the modified Insler score to evaluate cervical mucus samples based on consistency (viscosity), ferning, spinnbarkeit, and cellularity, each scored on a 4-point scale (0-3; see Box S3 in Multimedia Appendix 1) [11]. Cervical mucus is considered protective for pregnancy when the total score is ≤4.

Figure 2. Study Procedures. [a]If follicle is ≥15mm, then visits are changed to every other day for 3 extra visits; [b]Three consecutive visits at the time of delayed/missed pill.



TVUS examinations will be performed by licensed and trained study personnel using a transducer of at least 5 mHz. Standard measurements will include documentation of the largest follicle's maximum measurements in 3 dimensions and average size if it is ≥10 mm, postovulatory image, and any ovarian or follicular abnormalities. A cross-sectional picture of each ovary, even if no follicles >10 mm are present, will also be taken. A postovulatory image will be defined as the abrupt disappearance of the follicle-like structure or reduction of size in the leading follicle by >4 mm at 2 consecutive visits or visualization of a hemorrhagic corpus luteum. Determination of ovarian status will be categorized based on size of follicle and estradiol and progesterone levels according to a modified Hoogland score

(Multimedia Appendix 2) by an independent adjudication committee [12,13].

Staff will obtain blood samples for the gonadotropin (luteinizing hormone, follicle-stimulating hormone) and ovarian hormone levels (estradiol, progesterone) during the weekly visits. Levonorgestrel levels will be drawn in treatment cycle 1 on Day 1 and the first visit of week 3, in treatment cycle 2, and in treatment cycle 3.

Adjudication Committee

An adjudication committee, comprised of experts in cervical mucus assessment and ovarian activity who are not affiliated with either of the study sites, will convene at study end before database lock. This committee will define whether the data collected for a subject were evaluable or relevant and then define ovarian status based on ovarian activity parameters (Multimedia Appendix 2) and the level of conception protection based on cervical mucus (modified Insler score) and ovarian (modified Hoogland score) activity and their temporal relationship.

Duration of Trial

It was anticipated that the study will be completed in approximately 19 months. As of January 2020, the study completed enrollment of 52 subjects across 2 sites. Analyses are expected to be complete by July 2021.

Ethical Approval and Dissemination

We utilized a central institutional review board (Advarra, Columbia, MD) and received ethical approval on March 23, 2018. The study was registered with clinicaltrials.gov (NCT03585712) prior to enrollment of the first participant. We plan to present the data at international conferences and publish results in peer-reviewed journals.

Confidentiality

The information on individual subjects arising from this study is considered confidential and will be transmitted to the sponsor only in a form that will not permit identification of the individual. Identifiable information will remain secure and confidential within the research team. Regulatory and sponsoring agencies may request access to the study records and related medical records of each participating subject; the subject's identity will remain confidential to the extent permitted by the applicable laws and regulations. The results of the research will be released to public agencies including regulatory agencies, clinical investigators, and research organizations without reference to items identifiable to a particular subject. The results will be published such that the identity of the subjects will not be disclosed and cannot be ascertained. National and international agencies and sponsoring agencies may request access to the medical records of each participating subject, and if requested, the subject's identity will remain confidential. All records will be kept in a secure storage area with limited access.

Discontinuations and Withdrawal

A subject is considered to have completed the clinical trial after they have completed 3 separate 28-day treatment periods and the end-of-study visit. Subjects may be discontinued due to an adverse event (AE) or serious adverse event (SAE), a major protocol violation, suspected drug interaction, change in health status, pathologically changed laboratory values, or noncompliance with the study drug or the visit schedule. Subjects must be discontinued if they withdraw consent, are lost to follow-up, at trial closeout, have a confirmed pregnancy, are diagnosed with gonorrhea or chlamydia or pelvic inflammatory disease during the study, have a suspected unexpected SAE related to the study drug, or have a serious problem leading to need for critical care or surgery. Subjects have a right to withdraw from the study at any time for any reason and will be informed of this right upon entering the study.

Outcomes

The primary objective of the study is to determine the effect on cervical mucus score following delayed pill intake (by 6 hours) or after a missed pill as compared to reported daily use of norgestrel 75 mcg by measuring the difference in cervical mucus score between the day of a delayed pill or missed pill, the day after, and the day before.

The secondary objectives are as follows. To assess cervical mucus protection, we will evaluate the duration of effect of a cervical mucus score ≤4 after last pill intake of norgestrel 75 mcg after reported perfect use. Cervical mucus is considered protective when achieving a Modified Insler score ≤4 (see Box S3 in Multimedia Appendix 1). We will evaluate and compare the proportion of subjects with a protective cervical mucus score during reported daily use of norgestrel 75 mcg, during a treatment period with a delayed intake of 6 hours, and during a treatment period with a missed pill. We will evaluate and compare the ovarian activity of norgestrel 75 mcg as categorized by a modified Hoogland score (Multimedia Appendix 2) during reported perfect daily use, during a treatment period with a delayed intake of 6 hours, and during a treatment period with a missed pill. We will assess conception protection of norgestrel 75 mcg by evaluating if a protective cervical mucus score plus ovarian quiescence is maintained during reported daily use, during a treatment period with a delayed intake of 6 hours, and during a treatment period with a missed pill. We will determine plasma levonorgestrel pharmacokinetics after a single dose of norgestrel 75 mcg, at steady state, and after a delayed intake and after a missed pill. We will assess the safety of norgestrel 75 mcg taken daily for 12 weeks (SAE/AEs, bleeding patterns, abnormal blood chemistry or blood count parameters).

Data Management and Statistical Analysis

Data will be prospectively collected and entered into a secure, centralized, electronic data capture system as soon as possible after the information is collected. Any outstanding entries must be completed immediately after the final examination.

We will analyze 4 populations of interest: (1) full-analysis population consisting of all evaluable subjects, who will be classified into 4 analysis populations depending on the question of interest: cervical mucus primary and secondary objectives, ovarian activity, and conception protection; (2) a per-protocol population composed of subjects from the full-analysis population having completed the study without major protocol violations or deviations and good compliance who will also be classified into 4 analysis populations: cervical mucus primary

and secondary objectives, ovarian activity, and conception protection; (3) intent-to-treat consisting of all subjects randomized; (4) a safety population that consists of all subjects who took at least 1 dose of the study drug.

Adverse Events

AE and SAE reporting will be in accordance with good clinical practice guidelines [14].

Results

Our protocol was successfully approved by a central institutional review board (Advarra, Columbia, MD), received ethical approval on March 23, 2018, and registered with ClinicalTrials.gov (NCT03585712). As of January 2020, the study completed enrollment of 52 subjects across 2 sites. Analyses are pending.

Discussion

Lapses in adherence are a common occurrence with daily dosing of any medication [15]. Studies demonstrate that, over time, contraceptive pill users have more difficulty with strict adherence [16,17]. Current clinical guidance recommends that POP users who take their pill 3 hours late should consider that a missed pill, but these recommendations are not specific to a POP containing norgestrel 75 mcg nor are they based on updated methods of monitoring pharmacodynamic endpoints [8]. Our protocol focuses on obtaining baseline pharmacodynamics of daily norgestrel 75 mcg utilizing serial monitoring plus 2 different types of adherence lapses, a delayed pill by 6 hours and a missed pill. A greater understanding of how a lapse might impact POPs and the risk for pregnancy is a critical gap in the literature that our study is designed to answer.

Our endpoints will be gathered using standard processes and by teams experienced in cervical mucus and ovarian activity monitoring, which will decrease variability in our outcome measures. Additionally, our randomized study design utilizing appropriate concealment and allocation techniques decreases the risk of bias that might occur with a nonrandomized design. Our inclusion and exclusion criteria are generalizable to the population of users who would use this pill outside of a research study except for the exclusion of individuals with a BMI >32 kg/m^2. Ideally, pregnancy would be the endpoint to determine if these adherence lapses increase the risk for pregnancy instead of the biomarkers of pregnancy that we are monitoring. However, it would be unethical to place patients at potential risk for pregnancy, and the sample size would not be feasible. Our outcomes will be based on subject compliance with study drug and study procedures. We plan to utilize several different compliance measures including daily self-report, frequent in-person visits, and study drug counts, but we are not collecting additional objective measures of compliance in the form of frequent serum levonorgestrel levels nor are we doing daily observed pill intake as this would not be feasible. Individuals that report nonadherence or are found to be nonadherent to study drug will be discontinued from ongoing study participation. For individuals with less obvious incursions but with pharmacodynamic endpoints that appear consistent with nonadherence (ovulation and favorable cervical mucus), we can retroactively perform levonorgestrel testing on the blood samples obtained.

Unintended pregnancy is considered a major public health issue that can adversely impact an individual's health and well-being as well as that of their community. Increased access to effective, safe methods of contraception, like increasing over-the-counter options, may help to decrease unintended pregnancy. We designed our proposed study to gain further critical information necessary to pursue over-the-counter status and to fill an important gap in the literature.

Acknowledgments

The study is funded by HRA Pharma, Paris, France.

Conflicts of Interest

AE reports honoraria and travel reimbursement from the American College of Obstetricians and Gynecologists, the World Health Organization, and Gynuity for committee activities and honoraria for peer review from the Karolinska Institute. AE receives royalties from Up to Date, Inc, and she has acted as a consultant to MedinCELL. Oregon Health & Science University receives research funding from Oregon Health & Science University Foundation, Merck, HRA Pharma, and National Institutes of Health where AE is the principal investigator. AH and PB are employees of HRA Pharma. MC serves on an Advisory Board for Evofem, Mayne, Merck, and Searchlight and is a consultant for Danco, Estetra, Mayne, Medicines360, and Merck. The Department of Obstetrics and Gynecology, University of California, Davis Health receives contraceptive research funding, from which MC is supported from HRA Pharma, Medicines360, Merck, and Sebela. BS and AG are regular consultants to HRA Pharma.

Multimedia Appendix 1
Supplementary materials: information regarding study outcomes, inclusion and exclusion criteria, and cervical mucus scoring.
[DOCX File , 28 KB - resprot_v10i6e29208_app1.docx]

Multimedia Appendix 2
Supplementary table: modified Hoogland score.

[DOCX File , 26 KB - resprot_v10i6e29208_app2.docx]

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Abbreviations

AE: adverse event
POP: progestin-only pills
SAE: serious adverse event
TVUS: transvaginal ultrasonography examination

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Protocol

Wireless Home Blood Pressure Monitoring System With Automatic Outcome-Based Feedback and Financial Incentives to Improve Blood Pressure in People With Hypertension: Protocol for a Randomized Controlled Trial

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Abstract

Background: Hypertension is prevalent in Singapore and is a major risk factor for cardiovascular morbidity and mortality and increased health care costs. Strategies to lower blood pressure include lifestyle modifications and home blood pressure monitoring. Nonetheless, adherence to home blood pressure monitoring remains low. This protocol details an algorithm for remote management of primary care patients with hypertension.

Objective: The objective of this study was to determine whether wireless home blood pressure monitoring with or without financial incentives is more effective at reducing systolic blood pressure than nonwireless home blood pressure monitoring (usual care).

Methods: This study was designed as a randomized controlled open-label superiority study. A sample size of 224 was required to detect differences of 10 mmHg in average systolic blood pressure. Participants were to be randomized, in the ratio of 2:3:3, into 1 of 3 parallel study arms :(1) usual care, (2) wireless home blood pressure monitoring, and (3) wireless home blood pressure monitoring with financial incentives. The primary outcome was the mean change in systolic blood pressure at month 6. The secondary outcomes were the mean reduction in diastolic blood pressure, cost of financial incentives, time taken for the intervention, adherence to home blood pressure monitoring, effectiveness of the framing of financial incentives in decreasing nonadherence to blood pressure self-monitoring and the adherence to antihypertensive medication at month 6.

Results: This study was approved by SingHealth Centralised Institutional Review Board and registered. Between January 24, 2018 and July 10, 2018, 42 participants (18.75% of the required sample size) were enrolled, and 33 participants completed the month 6 assessment by January 31, 2019.

Conclusions: Due to unforeseen events, the study was stopped prematurely; therefore, no results are available. Depending on the blood pressure information received from the patients, the algorithm can trigger immediate blood pressure advice (eg, Accident and Emergency department visit advice for extremely high blood pressure), weekly feedback on blood pressure monitoring, medication titration, or skipping of routine follow-ups. The inclusion of financial incentives framed as health capital provides a novel idea on how to promote adherence to remote monitoring, and ultimately, improve chronic disease management.

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KEYWORDS

telemedicine; home blood pressure monitoring; behavior change; hypertension; financial incentive; medication adherence; remote titration

Introduction

Hypertension is prevalent in Singapore, affecting 23.5% of adults between 18 to 69 years of age [1]. It is a major risk factor for cardiovascular morbidity and mortality [2,3] and is associated with significant health care cost [4,5]. The goal of hypertension management is to lower blood pressure to healthy ranges through lifestyle modifications such as restricting salt and alcohol intake, eating a healthy diet, losing weight, engaging in regular exercise, quitting smoking, and taking antihypertensive medication(s) [6].

For patients whose blood pressure remains high, doctors routinely recommend home blood pressure monitoring for better blood pressure control. Home blood pressure monitoring allows the doctor to monitor response to treatment, detect white-coat hypertension, and predict cardiovascular risk [7,8]. Nonetheless, adherence to home blood pressure monitoring and medication(s) remains low [9]. Even when patients adhere to home monitoring, the readings are not reviewed by the doctor until the patient's subsequent in-person visit, which may be several weeks later. To address this, telemonitoring [10-14] can be employed as it allows for health care providers to monitor and intervene [15], to increase adherence to blood pressure monitoring [16], or titrate blood pressure medication [17] as needed, potentially without requiring an in-person visit [18]. However, systematic reviews [19,20] on telemonitoring reveal that it produces only modest improvements, which suggests that other features are needed [21-25]. For example, features such as automatic reminders [26,27], weekly feedback [28], or clinical interventions in response to concerning blood pressure trends (eg, medication titration), and financial incentives can be considered.

Behavioral economic theory suggests that the high rates of nonadherence to lifestyle modifications result, at least in part, from patients not perceiving a clear cause and effect relationship between greater adherence and reduced likelihood of adverse health consequences (eg, cardiovascular disease and premature death) [29,30]. The financial cost, such as the cost of medication(s), and nonfinancial costs, such as eating healthy, exercising, medication adherence, and blood pressure monitoring efforts, occur today, whereas the benefits, such as reduced risk for major cardiovascular events, often appear distant and uncertain. As a result, and because many individuals with hypertension feel perfectly healthy, they do not internalize the costs of nonadherence until it is too late. This theory suggests that a strategy to improve adherence is by providing a short-term financial incentive—an immediate benefit to offset the costs associated with the behavior change. Similar economic incentives have been used successfully in several adherence-enhancing interventions [31-34].

Therefore, this study aimed to leverage the potential of wireless and mobile technology and introduce financial incentives to improve the effectiveness of home blood pressure monitoring. The primary objective of this study was to determine whether wireless home blood pressure monitoring, with or without financial incentives, is more effective at reducing systolic blood pressure than nonwireless home blood pressure monitoring that relies on patient self-report (usual care). The secondary objectives were to improve adherence to blood pressure monitoring and antihypertensive medication(s).

Methods

Trial Design

The study was designed as a randomized controlled open-label superiority study with 3 parallel arms. Patients with hypertension who were on antihypertensive medication were randomized to (1) usual care, (2) wireless home blood pressure monitoring only, and (3) wireless home blood pressure monitoring with financial incentives arms, in a ratio of 2:3:3. Participants were randomly stratified based on whether they had diabetes mellitus (diabetes) and by clinic. The study intervention was to last 6 months. This protocol conforms to CONSORT (Consolidated Standards of Reporting Trials [35]) guidelines; the checklist can be found in Multimedia Appendix 1.

Study Setting and Eligibility Criteria

Patients were recruited from Bedok and Marine Parade Polyclinics (SingHealth Polyclinics) in Singapore. Bedok and Marine Parade Polyclinics provide primary health care services to the eastern and southern region of Singapore. Hypertension management is one of the key services provided. Participant eligibility was based on the inclusion and exclusion criteria (Textbox 1).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

Participants had to fulfil all of the following:

- Diagnosed hypertension and on at least 1 antihypertensive medication
- Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg for patients without diabetes (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥85 mmHg for patients with diabetes), which was verified by the average of the last 2 of 3 blood pressure readings taken on the day of the screening visit at 3-minute intervals [36] (model: HEM-7130, Omron)
- Age from 21 to 70 years of age
- Singapore citizens or permanent residents
- Able to converse in English
- Has a compatible smartphone (iOS: versions 8.0 and higher, Android: versions 5.0 and higher) with data plan or regular Wi-Fi access
- Ability to perform self-monitoring of blood pressure as assessed by the clinical research coordinator
- Expecting to be a patient of Bedok or Marine Parade Polyclinics for the duration of the trial

Exclusion criteria

Patients with any of the following were not enrolled:

- Systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg which was verified by the average of the last 2 of 3 blood pressure readings taken on the day of the screening visit at 3-minute intervals (model: HEM-7130, Omron)
- Started on angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers within the last 3 months
- Clinically unstable heart failure
- Advanced kidney disease (estimated glomerular filtration rate <30 mL/minute CKD-EPI Creatinine formula [37]
- Acute kidney injury (ie, increase in serum creatinine ≥50% from baseline within the past week
- Confirmed glomerulonephritis
- Severe or overt macro albuminuria (urine albumin-to-creatinine ratio >30 mg/mmol or protein-to-creatinine ratio >0.5)
- Known liver disease (eg, liver cirrhosis)
- Atrial fibrillation
- On warfarin or anticoagulants (eg, novel oral anticoagulants)
- Underwent double mastectomy
- Pregnant
- Known allergy to epoxy resin
- Newly referred to specialist outpatient clinics or upon follow-up for complications related to hypertension
- Discharged from hospital within the last 3 months for complications related to hypertension
- Any other major debilitating disease or mental illness that precludes validity of informed consent or would result in the patient being unable to take their blood pressure independently
- Living in a household where another member has been recruited into the trial

Participant Recruitment, Timeline, and Study Arms

Overview

Participants were recruited via posters and referrals at Bedok and Marine Parade Polyclinics. A screening visit was arranged during which the study's purpose was explained and the screener administered. For eligible patients, the clinical research coordinator went through the participant information sheet, and if the patient agreed to participate, obtained informed consent (Multimedia Appendix 2).

Blood pressure was assessed at baseline and at month 6. Participants wore an ambulatory blood pressure monitor (model 7100, Welch Allyn) for 12 hours while awake (eg, 9 AM-9 PM). A period of 12 hours instead of 24 hours was chosen to reduce participant burden [38]. A diary was also given to participants to record antihypertensive medication adherence and physical activity (Multimedia Appendix 3, Figure S1). Participants were also issued a home blood pressure monitor and advised to monitor their blood pressure 3 times per week during the study. Medication Tracker (eCAP) was also issued, and participants were advised to store their most frequently prescribed antihypertensive medication in it. A demonstration of the study devices was given. The baseline questionnaire was administered (in paper format) at Bedok and Marine Parade Polyclinics, and the participant's responsibilities and adherence goals explained.

The study intervention began on the Monday following the valid baseline ambulatory blood pressure monitoring test (defined as having at least 70% of successful readings [39]). Participants also completed questionnaires at the 6-month assessment. Multimedia Appendix 4 contains the study timeline.

Arm 1: Usual Care

SingHealth Polyclinics have a structured framework for hypertension management. Patients who are newly diagnosed with hypertension would be prescribed antihypertensive medication if deemed necessary by the doctor. All patients are subsequently referred to a nurse who would provide further information on hypertension and come up with a lifestyle modification plan with the patient. Patients are then followed up by the doctors and nurses at 3- to 4-month intervals (or more), based on their blood pressure trend. Further education is given at these visits as needed. Patients with good blood pressure control can teleconsult with a trained nurse, alternating with in-person doctor's consultation at up to 6-month intervals if they monitor their blood pressure at home. There are in-house pharmacists who assist patients in understanding their medication doses and regimens. Regular blood tests (ie, electrolytes, renal function, lipids, and glucose) are also carried out annually to monitor the patient's response to treatment and to detect any disease progression and complications. Patients with evidence of disease progression and complications would be closely monitored and referred to the appropriate specialists if required.

Participants in the usual care arm were advised to use their existing blood pressure monitor. Participants who did not have a home blood pressure monitor were given a blood pressure monitor (HEM 7130, Omron). In order to properly identify the effect of contingent financial incentives, all participants received a participant leaflet (Textbox 2).

The clinical research coordinator also provided advice on self-management and education on how to interpret blood pressure readings according to a standard self-monitoring guideline (Multimedia Appendix 5). The self-monitoring instructions were adapted from the guidelines of the Healthy Singapore website, a website by the Singapore Ministry of Health which was discontinued in September 2016. Elevated blood pressure was defined as clinic-measured systolic blood pressure 140 mmHg or diastolic blood pressure 90 mmHg. Published home-based monitoring protocols however, state that for home blood pressure monitoring, systolic blood pressure ≥135 mmHg or diastolic blood pressure ≥85 mmHg is indicative of elevated blood pressure [40,41]. In addition, SingHealth Polyclinics guidelines recommend home blood pressure monitoring targets of <135/80 mmHg for patients with diabetes, and <135/85 mmHg for those without diabetes. We therefore worked with the SingHealth Polyclinics Telehealth Team to fine-tune the blood pressure cut-offs for the various categories in order to have the same blood pressure cut-offs as the intervention (Table 1).

Participants in Arm 1 recorded their blood pressure readings on the SingHealth Polyclinics home blood pressure charting form (in paper format) as part of usual care. For monitoring adherence to hypertensive medicines, an eCAP (Information Mediary Corp) was used. The eCAP device passively recorded the dates and times the bottle was opened; these data are stored in the memory via an radiofrequency identification tag. Data were extracted by scanning the eCAP device on a reader (CertiScan desktop). Participants were assessed for adherence within specified time windows (eg, if a participant's specified timing is 5 AM to 11 AM and 5 PM to 11 PM, a reading had to be logged within both windows for the participant to be considered adherent for that day).

Textbox 2. Participant leaflet.

Aim to achieve blood pressure readings in the normal range

Measure your blood pressure on at least 3 days each week

Recommendations:

1. It is best to measure your blood pressure in the morning, before you take your medication, coffee, tea, smoke or exercise. Please sit for at least 5 minutes before measuring your blood pressure.
2. It is also recommended that you measure your blood pressure before you sleep at night.

Get active

Eat better. Reduce your salt intake

Take your medication as prescribed by your doctor.

Table 1. Blood pressure classification.

Diabetes status	Very low	Low normal	Normal	Slightly high	Very high	Extremely high
No diabetes						
Systolic blood pressure (mmHg)	<90	90-99	100-134	135-159	160-179	≥180
Diastolic blood pressure (mmHg)	<50	50-59	60-84	85-99	100-109	≥110
Diabetes						
Systolic blood pressure (mmHg)	<90	90-99	100-134	135-159	160-179	≥180
Diastolic blood pressure (mmHg)	<50	50-59	60-79	80-99	100-109	≥110

Arm 2: Wireless Home Blood Pressure Monitoring System

Participants in Arm 2 used an asynchronous telehealth system that consisted of a wireless home blood pressure monitor and app (Figure 1). The study app comprised 3 parts: (1) instant home blood pressure monitoring advice, (2) weekly home blood pressure monitoring adherence feedback, and (3) 28-day continuous home blood pressure monitoring assessment.

The participants monitored their blood pressure using a wireless upper arm blood pressure monitor (iHealth KN-550BT [42]). The blood pressure monitor transmitted the readings via Bluetooth and internet to a smartphone app on the participants' smartphones. Participants received training from the clinical research coordinator on how to use the device and to upload their blood pressure readings. This smartphone app was available at no charge to study participants. Data were automatically sent to secure participant accounts, then pushed to a secure study app. The study app then sent feedback SMS text messages to the participants and automatically triggered interventions from the polyclinics depending on the blood pressure readings (Table 2).

Figure 1. Wireless home blood pressure monitoring system. BP: blood pressure; CRC: Clinical Research Coordinator; WiFHy: Wireless Monitoring and Financial Incentives for Uncontrolled Hypertension.

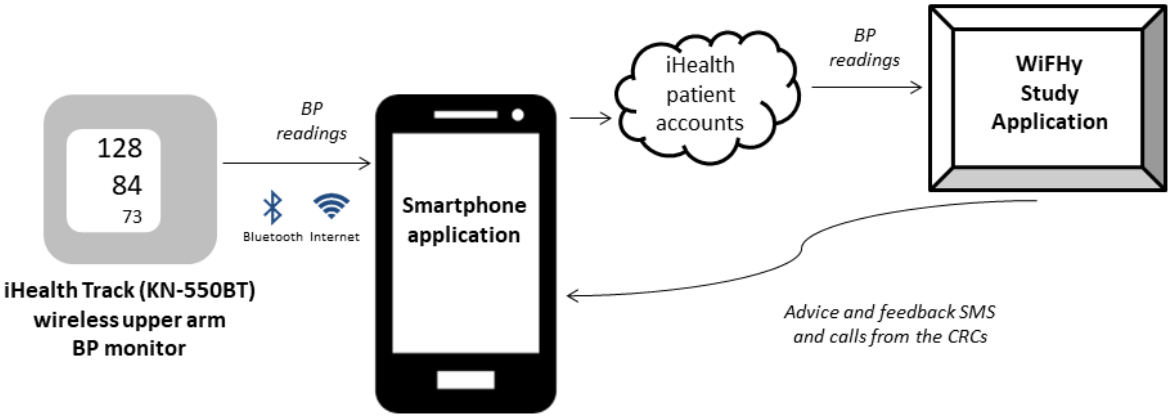

Table 2. Blood pressure–related procedures.

Part	Description
Part 1: Instant home blood pressure monitoring advice (Multimedia Appendix 6)	Each blood pressure reading was classified in the order of most abnormal to normal (ie extremely high, very high, slightly high, very low, low normal and normal) and displayed on the study website. Based on the blood pressure classification, the participant received SMS self-management advice. A colour coded protocol (Red protocol)[a] was activated for very low and extremely high blood pressure readings.
Part 2: Weekly home blood pressure monitoring adherence feedback (Multimedia Appendix 7)	Participants received automated praise, encouragement, or reminder SMS messages on the Monday of the following week at 8 AM throughout the intervention, with content that were dependent on their adherence to home blood pressure monitoring the week prior.
Part 3: 28-day continuous home blood pressure monitoring assessment (Multimedia Appendix 8)	The average of blood pressure readings over the past 28 days was calculated daily based on readings over the preceding 28 days. It was categorized in the order of most abnormal to normal and color coded[a]. The triggering of interventions based on the average blood pressure in the past 28 days is in line with previous studies that recommend using the average of a series of measurements for clinical decisions [43]. The 28-day continuous home blood pressure monitoring assessment occurred when the system detected a minimum of 8 blood pressure readings in the past 28 days.

[a]Color-coded protocols (Multimedia Appendix 8)—red: for very low and extremely high blood pressure; black: for very low or extremely high average blood pressure; gray: for low normal average blood pressure; green: for average blood pressure within the normal range just before scheduled clinic visit (participants were eligible to skip their upcoming clinic visit on approval of a doctor after review of the participant's clinical history and verification of the participant's current well-being by the clinical research coordinator); pink: for slightly high or very high average blood pressure (remote drug titration for participants on selected drugs); yellow: no readings for the past 28 days (the clinical research coordinator contacted the participant to determine the reason).

Remote Titration (Arm 2 and 3 Participants Only)

To be clinically more responsive to uncontrolled blood pressure, remote titration is integrated in this intervention as per the Joint National Committee 8 [44] recommendation to increase the dose of an initial drug if goal blood pressure is not reached within 1 month of treatment. This protocol for drug titration is based on an unpublished pilot program at Pasir Ris Polyclinic. Participants were eligible for remote titration if they were randomized to Arms 2 and 3 and prescribed (1) nifedipine LA ≤30 mg/day, (2) amlodipine ≤7.5 mg/day, (3) atenolol ≤75 mg every morning or (4) bisoprolol ≤7.5 mg every morning at baseline. For participants who were on more than 1 drug, the study doctor determined the drug to be titrated based on the drug selection workflow (Multimedia Appendix 8, Figure S4) and gave instructions on the dose increase to the participant. The participant was to increase the dose only if contacted by the clinical research coordinator to do so during the intervention. The doctor's instructions were also written in an individualized leaflet (Remote Titration Action Plan–Patient Information Leaflet; Multimedia Appendix 8, Figure A8.4.1.2) and given to the participant for reference. The clinical research coordinator also tagged the drug to be titrated and reinforced the doctor's advice. Participants were prescribed the full duration of the antihypertensive drugs until their next scheduled clinic visit. The drugs selected for remote titration were calcium channel blockers and beta blockers as these do not require monitoring of electrolytes.

On each working day, the clinical research coordinator logged-in to the study website, monitored the dashboard for flags and intervened accordingly. The clinical research coordinator unflagged the flag once the intervention had been carried out.

Study participants had doctor consultations at month 3 and at month 6 during the intervention period. For Arm 1 participants, the clinical research coordinator met with them prior to their doctor consultation and made a copy of their blood pressure readings for record. For Arm 2 and 3 participants, the clinical research coordinator passed them the blood pressure readings captured by the wireless monitoring system on the day of the doctor consultation for review by the doctor; except in cases where the visit was skipped due to good blood pressure control (green protocol).

Arm 3: Wireless Home Blood Pressure Monitoring System With Incentives

Participants in this arm received an intervention identical to those in Arm 2, with the addition of financial incentives for blood pressure monitoring. This arm was subdivided into 2 arms; participants were eligible to receive the same incentive amounts but framed differently. In the instant reward subarm, participants received SGD $3 (an exchange rate of approximately SGD $1 to US $0.75 was applicable at the time of publication) for each day they measured their blood pressure, up to 3 times per week (SGD $9 if they measured their blood pressure on at least 3 different days, SGD $6 if they measured their blood pressure on at least 2 different days, SGD $3 if they measured their blood pressure on at least 1 day, or no financial incentive if they did not measure their blood pressure). In the health capital subarm, participants received an initial health capital of SGD $72. Participants' health capital increased by SGD $6 on each week they measured their blood pressure on at least 3 different days. Participants' health capital decreased weekly by 10% per missing blood pressure reading. Health capital decreased by 10% if the participant measured their blood pressure on 2 different days, by 20% if the participant measures their blood pressure only on 1 day, and by 30% if the participant did not measure their blood pressure. Therefore, at the end of the 24-week intervention, Arm 3 participants could receive incentives up to SGD $216 for blood pressure monitoring.

Noncontingent study payments (Multimedia Appendix 9) to Arm 1 and 2 participants and incentive payments to Arm 3 participants (Multimedia Appendix 7, Table A7.4) in the form of supermarket vouchers were disbursed by the clinical research coordinator at the month 6 assessment.

Participant Withdrawal

During the study intervention, the clinical research coordinator reviewed the participants' medical records and contacted the participants via phone to determine if there were any serious adverse events, changes in medical condition, hospitalizations, or referrals to specialist outpatient clinics that may require a withdrawal from the study. The study doctor reviewed the participant's medical records and determined when there was a need to do so. Participants who were newly diagnosed with a hypertension related condition or complication or met the following exclusion criteria: clinically unstable heart failure, acute kidney injury, glomerulonephritis, liver disease, atrial fibrillation, prescribed warfarin or anti-coagulants, double mastectomy, pregnant, epoxy-resin allergy, referred to specialist outpatient clinic, or hospitalized for complications were withdrawn. Those who had a progression of an existing condition (eg, impaired kidney function) could remain in the study. For study participants who were withdrawn by the study team, a payment of SGD $80 in compensation for forgoing potential payments that the participant might have received had they remained in the study was given. Participants were free to withdraw their consent and discontinue their participation at any time during the intervention, without prejudice or effect on their medical care; however, all data collected until the time of the participants' withdrawal were kept to allow for a comprehensive evaluation.

Outcome Measures

The outcome measures and schedule of collection can be found in Multimedia Appendix 10.

Primary Outcome

The primary outcome was the mean reduction in systolic blood pressure in 6 months. This was to be obtained from the participants' month 6 ambulatory blood pressure monitor results. systolic blood pressure is associated with increased risk of cardiovascular disease [45-47].

Secondary Outcomes

Secondary outcomes were mean reduction in diastolic blood pressure in 6 months, obtained from the participants' month 6 ambulatory blood pressure monitor results; mean cost of financial incentives at month 6, calculated as the total financial incentives earned by Arm 3 participants at the end of the intervention and to be used as part of the cost-effectiveness analysis; mean time taken for the intervention at month 6, calculated as the total number of minutes spent by the clinical research coordinator intervening for the colored flags, adherence calculation, and payment of financial incentives for all study arm participants during the month 6 assessment and to be used as part of the cost-effectiveness analysis; mean adherence to home blood pressure monitoring at month 6; effectiveness of the framing of financial incentives in decreasing nonadherence to blood pressure self-monitoring; and mean adherence to antihypertensive medication (prescribed to be taken most frequently) at month 6.

Diastolic blood pressure may have some associations with future systolic hypertension and with increased risk of cardiovascular disease [47-51].

Exploratory Outcomes

Exploratory outcomes were the proportion of participants who have target blood pressure (defined as less than 130 mmHg/80 mmHg) at month 6; mean change from baseline in European Quality of Life-5 Dimensions-5 Levels [52] score at month 6; mean change from baseline in Brief Illness Perception Questionnaire [53] score, which assesses perceptions of hypertension, at month 6; mean change from baseline in the Global Physical Activity Questionnaire at month 6; mean change from baseline in the Dietary Practices Questionnaires [54] at month 6; mean change from baseline in Healthcare Services Expenditure at month 6; and the Treatment Satisfaction on home blood pressure monitoring, which is a modified version of the Treatment Satisfaction Questionnaire for Medication [55], at month 6.

Sample Size

A key parameter is the systolic blood pressure. To assess this, we computed the sample size to be able to detect differences of 10 mmHg in average systolic blood pressure between study arms at the 5% level with 80% power. To compute the overall sample size, we computed the size of the intervention groups that is required for testing for difference between intervention groups (study arms 2 and 3). After applying a Bonferroni correction (by dividing the test's significance level by 2, which is the number of comparisons that we test in our study for the primary outcome), we found that 68 patients per intervention group is necessary to detect mean differences in systolic blood pressure of 10 mmHg (with 2.5% significance level and 80% power). Given the resulting cumulated sample size for the 2 intervention arms of 136, we then computed the size required for the control group to test the overall effect of the wireless home blood pressure monitoring (with and without financial incentives) with the same effect size, significance level, and power. This computation yielded a size of 45 for the control group. After accounting for 25% attrition in each arm, the resulting sample sizes were 56 for the control group and 84 for each intervention group, resulting in a total of 224 patients. We assumed throughout that the standard deviation of systolic blood pressure is 19 (which is slightly greater than the maximum value reported by a similar size 6-month study of patients with uncontrolled hypertension [56]).

Randomization

Participants were allocated to 1 of 3 study arms by random assignment. Prior to recruitment, randomization numbers was generated by the principal investigator using Stata software (StataCorp LLC) to create an assignment schedule for block-randomization to allocate eligible participants into 1 of the 3 study arms in a ratio of 2:3:3. Randomized stratification was based on whether the patient had diabetes and study site. The block size was not communicated to SingHealth Polyclinics to minimize the predictability of the random sequence.

Furthermore, in order to test a secondary hypothesis (H5), the patients in the home blood pressure monitoring with financial incentives arm were further randomly divided into 2 equal-size groups, 1 per incentive type. The project coordinator and principal investigator then stored the assignment schedule on a secure server at Duke–NUS Medical School. For allocation concealment, the project coordinator and a Duke–NUS Medical School staff external to the study team enclosed the assignments in sequentially numbered, opaque, sealed randomization envelopes. These were handed over to the clinical research coordinator for participant enrollment and assignment.

Allocation Blinding

The clinical research coordinators were not blinded to the group allocation during the study intervention as there was a need for the clinical research coordinators to know the participants' arms to assign study devices to the participants and carry out the intervention accordingly and disburse payouts for the incentive arm participants (Arm 3). The site investigators were also not blinded as they had to explain the remote titration action plan and advise on intervention for the colored protocols (Arm 2 and 3).

Data Management and Monitoring

To maintain confidentiality, all enrolled participants were issued a unique ID based on their randomization number and were referred to via their unique ID thereon. Identifiable data were kept at locked cabinets at Bedok and Marine Parade Polyclinics and only accessible by the SingHealth Polyclinics team. Only deidentified research data were passed to Duke–NUS Medical School, and all data transfers were documented. All keyed in deidentified research data were encrypted, password-protected and stored on a secure server. Blood pressure readings and home blood pressure monitoring adherence data from the mobile app were transmitted automatically to the app via the application programming interface daily. The app did not contain any identifying information, was password protected, and only authorized members of the Duke–NUS Medical School team had access to the website via 2-factor authentication. Investigators have access to the research data collected. All hardcopy research data collected are archived for the next 10 years in compliance with NUS's research data management policies. No Data and Safety Monitoring Board was used for this trial as the study was deemed to be low risk by the investigators as this intervention was modelled after an existing standard of care by the Polyclinics and not involving more than minimal risk to the participants. Compensation was to be considered on a case-by-case basis for unexpected injuries due to nonnegligent causes. This trial was subjected to study review visits and audits to ensure that all investigator-initiated research is conducted effectively and efficiently.

Ethics

This study was approved by the SingHealth Centralised Institutional Review Board E (2016/2026). Amendments to the protocol or other study-related documents were approved by the institutional review board.

Data Analysis

All main analyses were to be based on intent to treat. The mean difference in the systolic blood pressure at 6 months was to be assessed in the context of a linear mixed-effects model with a random effect for subject and fixed effects for baseline mean (the same in both arms) and change in mean at 6 months for each treatment arm (one for each arm). The mixed-effects model allows nonmissing data to be used in analysis without imputation. For estimates of the treatment arm effects to be unbiased, data must be missing-at-random. However, it is possible that the analysis of the pattern of attrition would indicate that additional covariates needed to be included in the mixed-effects models. If data are not normally distributed, appropriate transformations will be attempted before resorting to using nonparametric statistical analysis methods.

Results

Recruitment at Bedok Polyclinic began on January 24, 2018 and at Marine Parade Polyclinic on June 26, 2018. From January 24, 2018 to July 10, 2018, 42 participants (18.75% of the total sample size) were enrolled, and 33 participants completed the 6-month assessment by January 31, 2019. A decision was made to terminate the study prematurely due to unforeseen delays and resulting funding issues. No analysis was carried out due to the lack of sample size and therefore no results are available.

Discussion

This paper reports a protocol for a randomized trial to determine whether a wireless home blood pressure monitoring system, with or without financial incentives, is more effective at reducing blood pressure than a nonwireless home blood pressure monitoring that relies on patient self-report or best practices.

While the 6-month study intervention is sufficient to detect potential blood pressure improvement that is clinically significant, a longer period would be needed to test for the long-term effectiveness of the intervention. There is currently no prior intervention that has the same components as those in our wireless home blood pressure monitoring system.

Unfortunately, due to unforeseen events the study was stopped prematurely. Regardless, as this study raises an interesting set of research questions, this protocol may be of value to other researchers considering similar efforts for blood pressure control or other behavioral targets. Results of such a study would provide evidence on whether a telemonitoring system with or without financial incentives can improve hypertension management, thereby reducing long-term complications and health care cost. By interacting socioeconomic characteristics with the intervention effect, this study may also have provided evidence on the benefit incidence of interventions involving financial incentives. The framing of financial incentives as reward versus health capital, would also have informed the design of future incentive strategies in hypertension management and other chronic diseases. The study would also have added to telemonitoring knowledge on hypertension self-management in patients and remote clinical management of hypertension,

which is increasingly relevant in light of COVID-19 and an increase in the use of telehealth in managing chronic diseases.

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Authors' Contributions

MB conceived and designed the study, acquired funding, and supervised the study. AYLK contributed to the study design and was the site principal investigator. IKYP contributed to the study concept and design. NCT contributed to the acquisition of funding and study design. JB contributed to the acquisition of funding, contributed to study design, and was the co-site principal investigator. JB helped amend the study protocol, provided logistical support, and drafted the manuscript. APMB-A contributed to the study design and provided logistical support. EAF contributed to the study concept, acquisition of funding, and provided supervision.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT E-HEALTH checklist.
[PDF File (Adobe PDF File), 944 KB - resprot_v10i6e27496_app1.pdf]

Multimedia Appendix 2
Participant Information Sheet and Consent Form.
[PDF File (Adobe PDF File), 327 KB - resprot_v10i6e27496_app2.pdf]

Multimedia Appendix 3
Ambulatory Blood Pressure Monitoring.
[PDF File (Adobe PDF File), 280 KB - resprot_v10i6e27496_app3.pdf]

Multimedia Appendix 4
Study timeline for participants.
[PDF File (Adobe PDF File), 232 KB - resprot_v10i6e27496_app4.pdf]

Multimedia Appendix 5
Standard guideline for interpretation of blood pressure readings.
[PDF File (Adobe PDF File), 277 KB - resprot_v10i6e27496_app5.pdf]

Multimedia Appendix 6
Instant home blood pressure monitoring advice.
[PDF File (Adobe PDF File), 946 KB - resprot_v10i6e27496_app6.pdf]

Multimedia Appendix 7
Weekly home blood pressure adherence feedback.
[PDF File (Adobe PDF File), 999 KB - resprot_v10i6e27496_app7.pdf]

Multimedia Appendix 8
The 28-day continuous home blood pressure monitoring assessment.
[PDF File (Adobe PDF File), 534 KB - resprot_v10i6e27496_app8.pdf]

Multimedia Appendix 9
Study payment scheme.
[PDF File (Adobe PDF File), 314 KB - resprot_v10i6e27496_app9.pdf]

Multimedia Appendix 10
Outcome measures and schedule of collection.
[PDF File (Adobe PDF File), 210 KB - resprot_v10i6e27496_app10.pdf]

Multimedia Appendix 11
Peer-review report by the National Medical Research Council (Ministry of Health, Singapore).
[PDF File (Adobe PDF File), 708 KB - resprot_v10i6e27496_app11.pdf]

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Abbreviations

SGD: Singapore dollar
SMS: short message service

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Protocol

Adaptation of the World Health Organization Electronic Mental Health Gap Action Programme Intervention Guide App for Mobile Devices in Nepal and Nigeria: Protocol for a Feasibility Cluster Randomized Controlled Trial

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Abstract

Background: There is a growing global need for scalable approaches to training and supervising primary care workers (PCWs) to deliver mental health services. Over the past decade, the World Health Organization Mental Health Gap Action Programme Intervention Guide (mhGAP-IG) and associated training and implementation guidance have been disseminated to more than 100 countries. On the basis of the opportunities provided by mobile technology, an updated electronic Mental Health Gap Action Programme Intervention Guide (e-mhGAP-IG) is now being developed along with a clinical dashboard and guidance for the use of mobile technology in supervision.

Objective: This study aims to assess the feasibility, acceptability, adoption, and other implementation parameters of the e-mhGAP-IG for diagnosis and management of depression in 2 lower-middle-income countries (Nepal and Nigeria) and to conduct a feasibility cluster randomized controlled trial (cRCT) to evaluate trial procedures for a subsequent fully powered trial comparing

the clinical effectiveness and cost-effectiveness of the e-mhGAP-IG and remote supervision with standard mhGAP-IG implementation.

Methods: A feasibility cRCT will be conducted in Nepal and Nigeria to evaluate the feasibility of the e-mhGAP-IG for use in depression diagnosis and treatment. In each country, an estimated 20 primary health clinics (PHCs) in Nepal and 6 PHCs in Nigeria will be randomized to have their staff trained in e-mhGAP-IG or the paper version of mhGAP-IG v2.0. The PHC will be the unit of clustering. All PCWs within a facility will receive the same training (e-mhGAP-IG vs paper mhGAP-IG). Approximately 2-5 PCWs, depending on staffing, will be recruited per clinic (estimated 20 health workers per arm in Nepal and 15 per arm in Nigeria). The primary outcomes of interest will be the feasibility and acceptability of training, supervision, and care delivery using the e-mhGAP-IG. Secondary implementation outcomes include the adoption of the e-mhGAP-IG and feasibility of trial procedures. The secondary intervention outcome—and the primary outcome for a subsequent fully powered trial—will be the accurate identification of depression by PCWs. Detection rates before and after training will be compared in each arm.

Results: To date, qualitative formative work has been conducted at both sites to prepare for the pilot feasibility cRCT, and the e-mhGAP-IG and remote supervision guidelines have been developed.

Conclusions: The incorporation of mobile digital technology has the potential to improve the scalability of mental health services in primary care and enhance the quality and accuracy of care.

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KEYWORDS

mental health; community mental health; digital technology; primary health care; intervention; eHealth; mHealth; LMIC; remote supervision; training; mobile phone

Introduction

Background

Mental illnesses are common, affecting 1 in every 3 people during their lifetime [1]. Globally, mental illnesses are the leading contributor of years lived with a disability [2]. Despite the prevalence and impact of mental illness, a large difference between true and treated prevalence rates of mental disorders, also known as the mental health treatment gap, exists. It is estimated that more than 80% of people with severe mental illness in low- and middle-income countries (LMICs) receive no treatment [3]. Only 16.5% of people with depression living in LMICs have access to minimally adequate treatment [4]. The consequences of this treatment gap include symptom persistence and deterioration, social exclusion, and long-term disability of people who could be economically productive and socially included. Globally, there is growing recognition of the importance of mental health, as evidenced by its incorporation in the United Nations 2030 Agenda for Sustainable Development and extension of the World Health Organization (WHO) Comprehensive Mental Health Action Plan to 2030 by the World Health Assembly [5].

The limited number of mental health specialists and the concentration of care in hospital settings in urban rather than rural areas limit the availability and accessibility of care [6]. Low treatment rates in LMICs are related to poor demand and supply-side forces. High levels of stigma associated with mental illness manifest in low rates of help seeking among those who would benefit from care [7-10]. The WHO recommends a task-shifting approach to strengthen the generalist workforce and improve access to health care, including mental health care [11]. However, this method requires the availability of evidence-based tools and appropriate training, supervision, and support.

In recent years, there has been an exponential rise in global access to mobile technologies in LMICs. In 2012, there were 287 million unique mobile phone subscribers across sub-Saharan Africa, covering 32% of the population [12]. Moreover, 6 years later, that number rose to 465 million, representing 44% of the population. In Nepal, the number of mobile contracts (27.85 million) surpasses the total population (26.49 million) [13]. The increased application of mobile technology to the health care arena, known as mobile health (mHealth), aims to provide a powerful platform to improve the quality of interventions using a task-shifting approach and reduce the treatment gap. mHealth refers to the use of mobile technology in health interventions and service provision [14]. In a recent WHO survey, 87% of the responding countries reported at least one government-sponsored mHealth program in their country [14]. However, only 14% of countries reported an evaluation of these programs, raising concerns about insufficient evidence of impact.

A systematic review of smartphone use in clinical decision-making by health care professionals identified 7 randomized controlled trials conducted in high-income settings, which demonstrated improved knowledge, diagnosis, treatment decisions, and documentation using mHealth technology [15]. Studies on mHealth tools in LMICs have yielded mixed results [16]. Qualitative data, however, suggest that the intervention facilitated task shifting and improved health workers' morale.

In 2010, the WHO launched the Mental Health Gap Action Programme Intervention Guide (mhGAP-IG) [17], an evidence-based assessment and management guide for mental, neurological, and substance use conditions designed for use by

primary and community health staff in LMICs [18]. The first edition of the mhGAP-IG (v1.0) has been implemented in over 100 countries. An updated version (v2.0) was launched in 2016, with new sections and updated evidence-based guidance [17], along with a first version of a smartphone app available for both Android and iOS devices in 2017. The mhGAP-IG v2.0 consists of 8 modules addressing priority conditions (ie, depression, psychoses, epilepsy, child and adolescent mental and behavioral disorders, dementia, disorders due to substance use, self-harm or suicide, and other significant mental health complaints that impair daily functioning or lead to help seeking). It provides an overview of common presentations for each condition, followed by detailed guidance for assessment, management (including referral to specialist care), and follow-up.

The Emilia (E-mhGAP Intervention Guide in Low- and Middle-Income Countries: Proof-of-Concept for Impact and Acceptability) project seeks to readdress the treatment gap by developing a potentially practical way for primary care workers (PCWs) to diagnose and treat people with mental illness according to evidence-based guidelines.

Aims and Objectives

Emilia aims to test the feasibility of an updated electronic Mental Health Gap Action Programme Intervention Guide (e-mhGAP-IG) and trial procedures for the future conduct of a large-scale trial, which would evaluate differences in depression detection between facilities using the e-mhGAP-IG versus the paper mhGAP-IG. The objectives of this feasibility study, in preparation for a future trial, include the following:

1. To evaluate the feasibility and overall implementability of primary care mental health services using the e-mhGAP-IG for training, supervision, and delivery of care (primary objective).
2. To determine recruitment and retention rates of PCWs and patients.
3. To establish the acceptability and feasibility of assessing PCW and patient outcomes.
4. To assess ethics and safety procedures using adverse event reporting.
5. To describe depression detection rates in primary health clinics (PHCs).
6. To describe depression treatment outcomes in PHCs.

Methods

Settings

The study will take place within the administrative districts of Nepal (Jhapa administrative district) and Nigeria (Ibadan North, Ibadan North West, Ona Ara, and Akinyele local government areas). In each country, a minimum of 6 PHCs will be recruited for the study to represent a range of urban and rural settings.

Nepal is classified as a lower-middle–income country, with an estimated population of 28.1 million [19]. In a recent survey, 16.8% of individuals attending primary care facilities met the criteria for depression [20]. However, only 8.1% had sought care for their mental health [21]. Primary care facilities include PHCs, health posts, urban health centers, community health units, and primary health care outreach clinics. In these facilities, services are delivered by medical officers, health assistants, staff nurses, auxiliary health workers, and auxiliary nurse midwives. However, medical officers and staff nurses are only available in PHCs [22]. The availability of mental health care in the country is limited to services largely provided through hospitals located in the larger cities [22]. The Jhapa administrative district has a total population of 812,650 people. Medical care is provided through 1 zonal hospital, 6 PHCs, 44 health posts, and 6 urban health centers [23]. Specialist outpatient mental health services are located in 2 private hospitals within the district. The mhGAP-IG was adopted by the government of Nepal and implemented in several districts after the major earthquake in 2015. The government has allocated a budget for district-level mental health care services to include the addition of 6 psychotropic drugs to those already freely available within health facilities and the strengthening of community mental health care services [24].

Nigeria is classified as a lower-middle–income country. It is home to the largest national population in Africa (195.9 million as of 2018) [25]. Recent research in the country estimated a 5.5% prevalence of depression [26]. However, similar to other LMICs, 85% of individuals living with a mental disorder receive no treatment [27]. Ibadan metropolis has 11 local government areas and a population of approximately 3.5 million people. The mental health services in Ibadan are primarily provided by 2 large general hospitals. There are 186 PHCs, each serving a population of approximately 10,000 people. The study will be conducted in 2 urban and 2 rural local government areas. PHCs in Nigeria are staffed by nonphysician health workers (nurses, community health officers, and community health extension workers) who provide treatment for common disorders (including depression) presenting in primary care. The country adopted the mhGAP-IG as a national program for expanding mental health services in 2013, and PHCs are among those where providers have received training in the use of the mhGAP-IG. In Ibadan, PCWs are provided with unstructured supervision by a supervisory general practitioner who typically oversees a group of 6-8 PHCs within a local government area.

The use of digital technology in both Nepal and Nigeria has seen exponential growth in recent years, with the trend expected to continue. In Nepal, mobile penetration was 133% in 2018, which is greater than 100% because most Nepalis have multiple mobile phone provider contracts [28]. In the same year, mobile penetration was estimated to be 49% in Nigeria, with a projected increase to 55% by 2025 [29]. A total of 36% of mobile phone connections in Nigeria are linked to a smartphone.

Technology

A 2015 WHO consultation on the 5-year impact of the mhGAP-IG v1.0 highlighted the demand for an e-version. Respondents identified increased utility and coverage of an electronic guide as reasons for its development. An e-version also creates new opportunities for quality improvement (eg, in remote supervision). A year later, a privately developed e-version of the mhGAP-IG for use in Afghanistan was used for 3000 screenings and 600 referrals [30]. Community health workers reported good acceptability of the mobile app. An

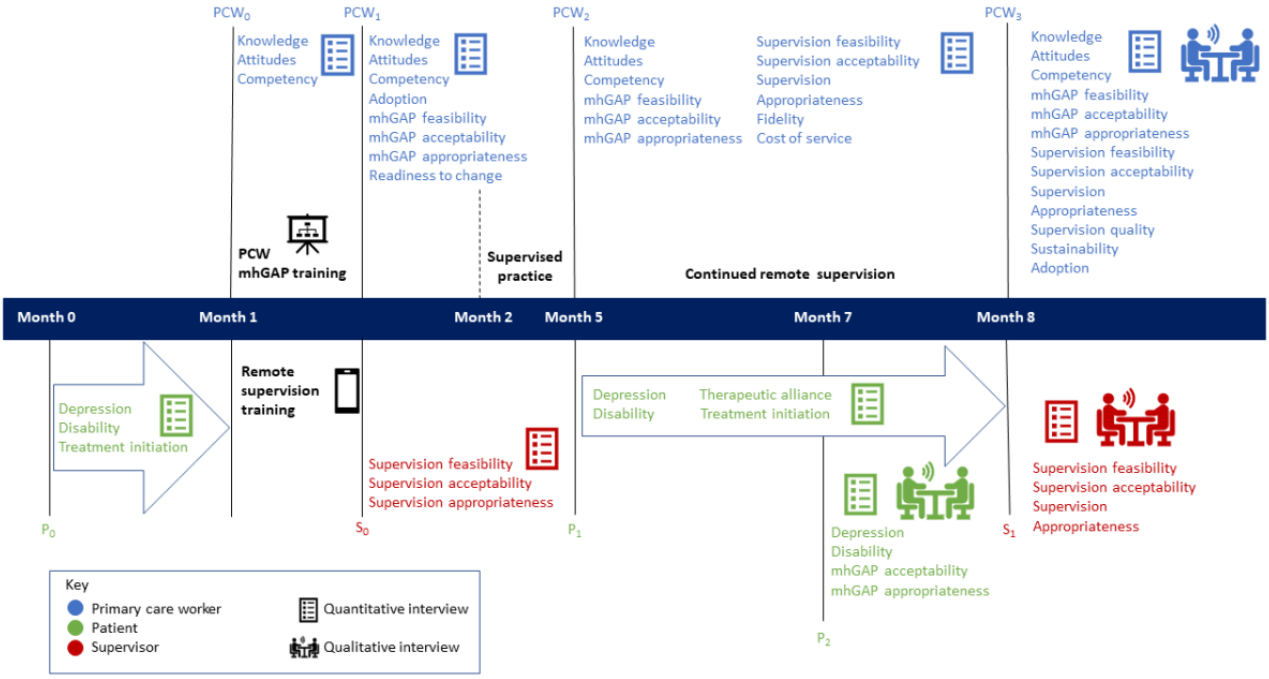
e-version of the mhGAP-IG v2.0 was launched by the WHO in October 2017 for Apple and Android smartphones and tablets.

The Emilia project comprises 3 phases: (1) development of an adapted e-mhGAP-IG, (2) feasibility testing, and (3) knowledge transfer and future work. In phase 1, an updated version of the WHO's electronic intervention guide was developed using a human-centered design approach. Human-centered design is an approach that actively engages stakeholders in the design process using cutting-edge methods to ensure that interventions are optimized for both front-line use and local and national implementation [31]. The approach includes qualitative research with key stakeholders to identify motivations, an iterative process of intervention development and prototyping, and intervention evaluation. The updating of the e-mhGAP-IG included individual and group interviews with PCWs in Nepal and Nigeria to understand the accessibility of technology by health workers, their use patterns, and their preferences for the design of the e-mhGAP-IG. The findings showed that most health workers had access to a personal smartphone, were familiar with the use of various smartphone apps, and valued the idea of an e-version of the mhGAP-IG. Requested features included decision support functions, ability to be used in offline mode, and an easy-to-use design that limited text entry. The formative work also highlighted the importance of recording patient information for review and use in supervision through a clinical dashboard. The resulting updated app features a *reference mode* for training and exploration and a *patient mode* for completing an assessment or management visit with an individual. Health workers can access a brief description of possible conditions through the *Master Chart* (a feature of mhGAP-IG 2.0) and then select modules for further assessment (Multimedia Appendix 1). The mhGAP-IG algorithms are presented in a single-page series of yes or no questions with a *proceed* button, indicating when the end of an algorithm has been reached. Health workers are then presented with an assessment summary, including any additional information to consider, such as whether the individual belongs to a *special population* that may affect treatment decisions. Within the app, health workers can complete additional information for a patient's record, including measures of severity, functioning, and information for follow-up visits. All information is accessible in a clinical dashboard that summarizes key information for each visit as well as aggregate information to help supervisors identify any issues that can be addressed in supervision (eg, overmedication or inaccurate diagnosis). The process of intervention delivery and supervision is described in Multimedia Appendix 2. The e-mhGAP-IG will be available in both English and Nepali. Prototypes of the app have been tested with health workers in Nepal (5 iterations) and Nigeria (4 iterations) who found the app to have an intuitive design that is appropriate and feasible for use in clinical work.

Study Design

A feasibility cluster randomized controlled trial (cRCT) will be conducted to evaluate and compare the implementation outcomes [32] and clinical outcomes of the adapted e-mhGAP-IG v2.0 and the paper version of the mhGAP-IG v2.0. A total of 10 PHCs in each country (Nepal and Nigeria) will be randomized to training, supervision, and care delivery using the paper mhGAP-IG (control arm) or the e-mhGAP-IG (experimental arm), and outcomes of PCWs and patients will be collected over a 9-month period (Figure 1). Data collected through the feasibility study will be used to further refine the intervention (eg, acceptability and feasibility for randomization and recruitment) and power a subsequent cRCT.

Figure 1. Feasibility study patient and provider data collection procedure. mhGAP: Mental Health Gap Action Programme; P_0: patient pre training assessment; P_1: patient baseline health care appointment assessment; P_2: patient 3 months post baseline health care appointment; PCW: primary care worker; PCW_0: primary care worker baseline assessment; PCW_1: primary care worker immediate post training assessment; PCW_2: primary care worker 3 months post training assessment; PCW_3: primary care worker 8 months post training assessment; S_0: Supervisor baseline assessment; S_1: Supervisor 8 months post training assessment.



Participants

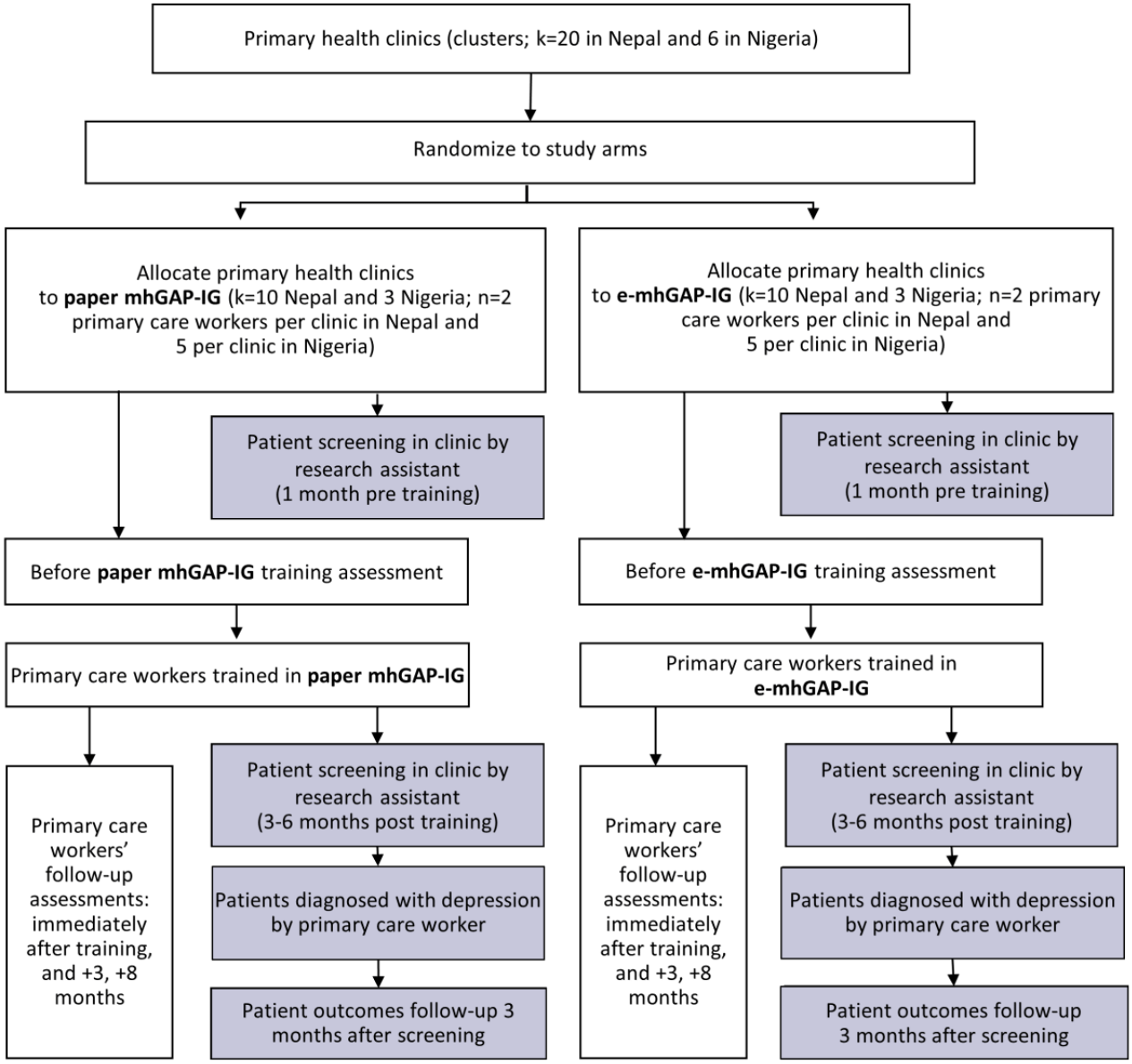
An estimated 20 PHCs in Nepal and 6 PHCs in Nigeria will be identified by local partners. Clinic managers and PCWs will be approached by local research staff with invitations to participate in the study. On the basis of the staffing of PHCs, we estimate that 2-5 PCWs per PHC will participate, equivalent to 40 PCWs in Nepal and 30 PCWs in Nigeria, approximately 15-20 health workers per arm per country (Figure 2).

PCWs will be eligible to participate if they are employed by the PHC or government and have roles and responsibilities related to the use of the mhGAP-IG (eg, direct clinical use or supervision). All relevant PCWs, regardless of individual study participation, will receive training in the mhGAP-IG v2.0 (electronic or paper version) and have ongoing remote support and supervision by health care providers with enhanced mental health knowledge.

Patients presenting to primary care will be enrolled in the study to evaluate their perceptions of services and to obtain descriptive information on detection rates and treatment impact to inform a subsequent fully powered cRCT. There will be 2 periods of patient enrollment: *pre training*, which is before PCWs receive mhGAP-IG training, and *post training*, which is after PCWs have received mhGAP-IG training. For the 1-month before the mhGAP-IG training, a random selection of adults presenting to primary care will be screened by research assistants to determine depression status, which will be compared with documented diagnoses by the PCWs. Similarly, beginning at 3 months post training, a random selection of patients will be screened by research assistants for depression status. This posttraining patient enrollment will last a minimum of 3 months.

On the basis of prior data on primary care service use and screening depression rates, we anticipate being able to screen approximately 50% of adult patients presenting to primary care, with a possibility of screening a higher percentage depending on patient flow in the facility [33]. Therefore, we anticipate screening approximately 200 patients per arm per country per month (ie, 400 patients per country in the 1-month pretraining patient enrollment period and 1200 patients per country in the 3-month posttraining patient enrollment period).

Figure 2. Emilia (E-mhGAP Intervention Guide in Low- and Middle-Income Countries: Proof-of-Concept for Impact and Acceptability) flow chart. e-mhGAP-IG: electronic Mental Health Gap Action Programme Intervention Guide; mhGAP-IG: Mental Health Gap Action Programme Intervention Guide.



Inclusion criteria for patients to be screened include the following:

- Attending PHC for treatment of a new case at recruitment
- Reached the age of adulthood (ie, ≥18 years)
- Fluent in Nepali (Nepal only) or English or Yoruba (Nigeria only).

Adult attendees will be deemed ineligible for the study if they are unable to understand or complete study assessment (eg, individuals with severe learning disability or dementia), unable to provide informed consent, or have a medical emergency requiring immediate intervention.

All patients who meet the eligibility criteria and choose to enroll in the study will then be screened by a research assistant to determine their depression status. Following this screening, patients will be evaluated by a PCW who will make an independent diagnosis without speaking to the research assistant or reviewing the screening results. Administration of screening tools may occur before or after the patient meets the health worker based on the workflow of the clinics. After patients meet the PCWs, a research assistant will review the provider's case notes to document whether or not a depression diagnosis was made.

Study Arms

Intervention Condition

The intervention will consist of (1) availability of the adapted e-mhGAP-IG for use on a clinic tablet, (2) participation in remote supervision and the support module developed in phase 1 for implementation in Nepal and Nigeria, and (3) training to all relevant PCWs and supervisors in the use of the adapted e-mhGAP-IG and clinical dashboard. Health care providers with enhanced mental health knowledge who have attended the training of trainers workshops for the e-mhGAP-IG and remote supervision will act as supervisors for the purpose of the study.

These might include, but are not limited to, psychiatrists, mental health nurses, general physicians, senior PCWs, and counselors.

Control Condition

The control condition will consist of (1) availability of the paper version of the mhGAP-IG v2.0 adapted for use in Nepal and Nigeria, (2) participation in remote supervision and the support module developed in phase 1 for implementation in Nepal and Nigeria, and (3) training to all relevant PCWs and supervisors in the use of the paper version of the mhGAP-IG v2.0 and supervision from distance (Table 1). Trained specialists in the research teams within each study site will act as supervisors for the purpose of the study. Supervisors are intended to be health care providers with enhanced mental health knowledge who have attended the training of trainers workshops for the paper mhGAP-IG v2.0. These might include, but are not limited to, psychiatrists, mental health nurses, general physicians, senior PCWs, and counselors.

Table 1. Feasibility study arm components.

Component	Intervention condition	Control condition
e-mhGAP-IG[a] v2.0	✓	
Paper mhGAP-IG[b] v2.0[c]	✓	✓
Remote supervision and support module	✓	✓
Primary care workers' training in use and administration of the relevant mhGAP-IG v2.0	✓	✓
Primary care workers' training in a clinical dashboard	✓	
Supervisors' training in relevant mhGAP-IG and remote supervision and support	✓	✓
Supervisors' training in a clinical dashboard	✓	

[a]e-mhGAP-IG: electronic Mental Health Gap Action Programme Intervention Guide.

[b]mhGAP-IG: Mental Health Gap Action Programme Intervention Guide.

[c]The paper mhGAP-IG v2.0 will be used in intervention condition training and will be available for use as a resource throughout the study.

Remote Supervision

In both study arms, remote supervision will comprise an initial face-to-face meeting (where possible) and subsequent contact by voice and text messaging to discuss implementation of the mhGAP-IG (paper or e-version) and any case queries. Supervision format (eg, voice calls, video calls, messaging, group, and individual) will be agreed upon by each supervision dyad. Supervisors will be provided with training on how to set up and run supervision remotely using telephone and other common communication platforms such as WhatsApp groups before the start of the study. Training will cover issues such as building rapport, format for running supervision over a telephone, format for clinically supportive WhatsApp groups, and ensuring patient confidentiality when using remote supervision methods. PCWs will receive training on how to make the most of the remote supervision during the mhGAP-IG training. PCWs will have access to project mobile phones to facilitate remote supervision. Both PCWs and supervisors will be provided with data packages.

Randomization and Allocation Concealment

Clinics will be randomized to the control or intervention conditions, with equal number of clinics in either group (1:1). Randomization will be carried out independently (to ensure concealment) by the trial statistician via a computer-generated random sequence before participants are recruited or the intervention is initiated. PCW selection will be performed according to health staffing levels before randomization of clinics to a study arm. Blinding or masking of participants, clinicians, and fieldworkers will not be possible, as it will be clear which conditions clinics or municipalities are assigned to during implementation and data collection. However, the senior and junior trial statisticians who carry out the randomization will not know the characteristics of the clinics being randomized, and the primary statistical analysis will also be blinded to allocation status.

Statistical Power and Sample Size Calculation

The study will take place in 1 government administrative region in Nepal and 4 in Nigeria. We will identify approximately 20 PHCs in Nepal and 6 in Nigeria. In each country, half of the PHCs will be randomly allocated to either the e-version or the paper version of the mhGAP-IG. As the clinics vary in size, we will assess at least two staff members in each clinic, with an estimated 2-5 health workers per facility and an overall enrollment of 40 PCWs in Nepal and 30 PCWs in Nigeria. Regarding patient numbers, on the basis of the sample size for the study by Sangha et al [34] on smartphone app for improving cognition to improve case detection, we will conduct within-arm comparison detection rates if at least 40 patients screen positive on the Patient Health Questionnaire (PHQ-9) in the research assistant interview in the 1-month pretraining period and in the first month of the posttraining patient enrollment period, which begins after 3 months of intensive supervision. This will allow us to detect a within-arm increase in the clinical case identification rate of 43% for the e-mhGAP-IG after the implementation of the e-version with 90% power at the 5% level of significance, assuming an intraclass correlation coefficient of 0.02. For example, with a 10% detection rate pretraining, 2 patients would receive a health worker depression diagnosis out of 20 patients screening positive. After training, the detection rate would increase to 53%, which equates to 11 patients diagnosed by a health worker out of 20 patients screening positive.

Data Collection

Overview

In line with the current best practice in implementation research [32], the research team will evaluate implementation processes and outcomes (eg, acceptability and feasibility) and factors that influence effectiveness implementation (eg, organizational readiness to change) across multiple stakeholder groups, including patients, PCWs, and supervisors, and at different stages of implementation [32,35]. This offers a 360-degree implementation evaluation, which considers the needs and perspectives that typically differ between stakeholder groups and can vary over time. Data collection procedures are outlined in Figure 1 and presented in Multimedia Appendix 3.

Implementation Data

PCWs Data

PCWs will be interviewed by a member of the research team during a 1-week period at each PHC clinic at 4 time points: (1) before mhGAP-IG training, (2) immediately post training, (3) 3 months post training, and (4) 8 months post training (Multimedia Appendix 3). During the research interviews, all PCWs will complete quantitative assessments, assessing 6 variables related to the implementation of the intervention:

1. Implementation readiness: Health workers' resolve and capability to implement the e-mhGAP-IG (ie, readiness to change) will be assessed using the Organizational Readiness for Implementing Change (ORIC) scale [36]. ORIC is a 12-item, theory-based measure assessing health workers' commitment toward and ability to implement change.
2. Acceptability, appropriateness, and feasibility: Acceptability, appropriateness, and feasibility of the mhGAP-IG and remote supervision will be assessed using the Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM), respectively [37]. These brief, 4-item instruments have been developed by implementation scientists and mental health professionals and display good psychometric properties. Cultural and linguistic adaptation and further psychometric evaluation will be undertaken before the deployment of the measures in this study. The appropriateness, feasibility, and acceptability of the mhGAP-IG and remote supervision will also be assessed through qualitative interviews with health workers at the last data collection time point (PCW_3).
3. Fidelity: Patient records and app use, as recorded electronically through the e-mhGAP-IG v2.0, or patient records, as recorded on paper in clinics randomized to provide the paper version mhGAP-IG v2.0 and supervision notes, will be assessed by members of the research team to determine fidelity to the training manuals for the paper mhGAP-IG v2.0 and the adapted e-mhGAP-IG v2.0.
4. Adoption: Health workers' intention to adopt mhGAP-IG will be assessed by using 2 study-specific questions regarding provider-intended use within the study and after the study has ended. Intention to adopt at the provider level will also be assessed through qualitative interviews with health workers.
5. Integration and sustainability: The potential for long-term integration of the mhGAP-IG v2.0 within standard health services will be assessed using the NoMAD (Normalization Measure Development) scale [38,39]. NoMAD is a 23-item instrument that assesses staff perceptions of factors relevant to embedding interventions in health care. NoMAD consists of 4 theoretical constructs: (1) coherence, (2) collective action, (3) cognitive participation, and (4) reflexive monitoring.
6. Operating costs: The time taken to be trained and to use the paper and electronic tools and for remote supervision will be estimated from information collected from staff, and this, combined with information on staff wages, will be used to derive operating costs for the economic modeling.

During the last data collection time point (PCW_3), 15 PCWs in each country will be randomly selected and invited to participate in an additional qualitative interview with a member of the research team to gain further insight into their views on the implementation of the mhGAP-IG v2.0 and remote supervision. We will aim to conduct focus group discussions (FGDs) in the first instance. However, where this is not possible, individual interviews will be conducted. Individual interviews and FGDs will be audio recorded and last no longer than 30 and 60 minutes, respectively. The interviews will be transcribed and anonymized before analysis.

Supervisor Data

mhGAP-IG supervisors will be interviewed by a member of the research team during a 1-week period at 2 time points: (1) immediately post training and (2) 8 months post training (Figure 1). Interviews will focus on perceived acceptability, appropriateness, and feasibility of remote supervision using the quantitative assessments described above (ie, AIM, IAM, and FIM; Multimedia Appendix 3). All supervisors will be invited to participate in a qualitative interview 8 months post training to gain further insight into their experiences of remote supervision. FGDs will be conducted where possible, with the remaining selected participants completing individual interviews. All qualitative interviews will be audio recorded and last between 30 minutes for individual interviews and 60 minutes for FGDs. The interviews will be transcribed and anonymized before analysis.

Patient Data

We estimate screening a minimum of 400 patients at each site during the pretraining enrollment period and 1200 patients in the posttraining enrollment period (starting 3 months after the mhGAP-IG training). In the posttraining period, we will include a subset of patients who have received a health worker depression diagnosis to follow-up for treatment outcomes (Multimedia Appendix 3). We will follow up with them at approximately 3 months after they are screened to measure their treatment outcomes. A subset of patients will also participate in FGDs to assess their perspectives on the acceptability (AIM) and appropriateness (IAM) of the intervention 3 months after their baseline health care appointment.

Outcome Data

PCWs Data

PCWs will be interviewed by a member of the research team during a 1-week period at each PHC clinic at 4 time points: (1) before mhGAP-IG training, (2) immediately post training, (3) 3 months post training, and (4) 8 months post training (Multimedia Appendix 3). During the research interviews, all PCWs will complete quantitative assessments, assessing 5 variables related to the PCW outcomes:

1. mhGAP-IG Knowledge Scale: In the mhGAP-IG training, knowledge is assessed by a standardized set of 30 questions in the multiple-choice question format, the mhGAP-IG Knowledge Scale. These are administered before and after training to measure the change in knowledge.
2. Revised-Depression Attitude Questionnaire (R-DAQ): Previously used in both Nepal and Nigeria, the R-DAQ [40] assesses clinicians' views and understanding of depression. The R-DAQ 22-item scale asks clinicians to rate each item as *strongly disagree*, *disagree*, *neither disagree nor agree*, *agree*, or *strongly agree*. Examples of items include "depression is a disease like any other (eg, asthma, diabetes)," "psychological therapy tends to be unsuccessful with people who are depressed," and "becoming depressed is a natural part of being old."
3. Social Distance Scale (SDS): The SDS was designed by Bogardus [41] to measure the level of acceptability of various types of social relationships between Americans and members of common ethnic groups [42,43]. The modified SDS has been widely used to measure mental health–related stigma and to understand the importance of labels attached to people with former mental illnesses [42,44]. The modified version consists of 12 items that represent social contact with different degrees of distance. The SDS measures the acceptability of different degrees of social distance and thus, by inference, the attitude of the respondent to the person with the condition [45]. The SDS sum score represents the attitude of the respondent toward the condition. The SDS has been used in global mental health research. Among stigma measures, it has been shown to be most strongly associated with health worker competence [46].
4. The Enhancing Assessment of Common Therapeutic Factors (ENACT)-clinician version: The ENACT-clinician version [47] is a measure of therapist competence that has been developed for use in training and supervision across settings varied by culture and access to mental health resources. A version adapted for mhGAP-IG trainings focusing on depression was used, with competencies rated on a 4-point scale from potentially harmful to done well, with good reliability (α=.89). Examples of items include "non-verbal communication, active listening," "assessment of functioning & impact on life," and "explanation and promotion of confidentiality," among others.
5. Perceptions of Supervisory Support Scale (PSS): Supervision quality will be assessed using the PSS [48]. The PSS is a 19-item scale that assesses perceived support. Subscales include emotional support, support for client goal achievement, and professional development support. Each item is rated using a 5-point Likert scale. Additional information about supervision quality will be collected through qualitative interviews with health workers at the last data collection time point.

Patient Data

In the month before mhGAP-IG training, the research team will collect depression diagnosis and treatment initiation data from patient baseline interviews and clinical notes at participating clinics (Multimedia Appendix 3). These data will be used as a baseline assessment of the accuracy of diagnosis and the adequacy of treatment initiation. Patients attending PHC 3-8 months following PCW mhGAP-IG training will be interviewed by a trained member of the research team either immediately before or after their clinic appointment. Quantitative measures will be used to assess depression, disability, intervention acceptability, and therapeutic alliance during individual interviews with a member of the research team as follows:

1. Depression: The PHQ-9 [49] is a self-administered diagnostic instrument for depressive disorders. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for depression are scored as *0* (not at all) to *3* (nearly every day). A PHQ-9 score ≥10 had a sensitivity of 94% and 85% and a specificity of 80% and 99% for major depression in Nepal [50] and Nigeria [51], respectively.
2. Disability: Data on sociodemographic information (sex, age, education, marital status, and work status) will be collected through questions A1-A5 of the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) [52]. The WHODAS 2.0 is a generic assessment instrument assessing health and disability across 6 domains (cognition, mobility, self-care, getting along, life activities, and participation). The research team will use the 12-item interviewer-administered version. The WHODAS 2.0 has been adapted and validated for use in Nepal [53-55] and Nigeria [56].
3. Treatment initiation: Treatment details will be extracted by the research team from patient records to document how diagnosis matches up with treatment and treatment modifications during care.
4. Therapeutic alliance: The ENACT-service user version [47] is a 15-item measure of patient experience of care and perception of therapeutic engagement. Example items include clear explanations, names for health problems, understanding and empathy, and expectations for recovery.
5. Suicidal ideation and behavior: Suicidal ideation and behavior will be assessed, in Nepal only, using suicidality questions adapted from the Composite International Diagnostic Interview suicidality module [57]. This tool has been widely used in Nepal [58]. We will ask participants whether they had thought of taking their own life in the past 12 months. Those who will respond affirmatively to the ideation question will be asked if they had made a plan to take their own life. In Nepal, those who meet the criteria for current suicidal thoughts or those who attempted suicide in the past 3 months will be immediately referred to a trained psychosocial counselor. In Nigeria, patients endorsing the suicidal ideation item from the PHQ-9 will

receive further assessment of suicide risk in line with local protocols.

Confirmation of diagnosis and treatment initiation will be collected from the clinical notes by PCWs. Patients interviewed in the first 3 months of data collection and who screen positive for depression will be invited to participate in a follow-up interview 3 months after their first appointment. The interview will consist of quantitative assessments of depression (PHQ-9), disability (WHODAS 2.0), therapeutic alliance (the ENACT-service user version), and suicide ideation and action Composite International Diagnostic Interview. Treatment details will be extracted by the research team from patient records to document treatment retention.

Measure Translation and Adaptation

All standardized measures, except for the AIM, IAM, FIM, ORIC, NoMAD, and PSS (Nigeria only), have been translated and culturally adapted in Nepal and Nigeria. Psychometrics for translated and validated (when appropriate) measures are provided in the descriptions above. Within each site, where measures have not yet been adapted and validated, the International Test Commission Guidelines for Translating and Adapting Tests [59] will be followed, including cognitive interviewing [60,61] and the assessment of content validity.

Analysis

Implementation Outcome Analysis

Quantitative data will be assessed using generalized linear mixed models, depending on the distribution of the outcome (continuous, binary, and count). Descriptive statistics of the implementation survey data (FIM, AIM, and IAM) will be provided. The association between the primary outcome (changes in the PHQ-9 detection rate) and implementation survey data will be analyzed using linear mixed models at 3 and 8 months post training. A 2-level hierarchical model will be used, and all time points will be included as repeated measures in the model at baseline and at 3 months post training and 8 months post training to improve power and account for clustering of observations at patient and PCW levels. These models use maximum likelihood estimation and thus allow for missing outcome data under the missing at random assumption. Associations between secondary outcomes (eg, knowledge, attitudes, and competency) and implementation survey data will be assessed with a similar methodology for the primary outcomes, using generalized linear mixed models depending on the type of outcome (eg, normal, binary, and count). All analyses will be conducted using STATA V.15.1. (StataCorp).

Qualitative data will be assessed using thematic analyses [62]. Thematic analysis consists of 5 stages: familiarization, generating codes, constructing themes, revising themes, and defining themes [63]. Draft codebooks for each participant group (eg, PCWs, supervisors, and patients) will be developed on an initial subset of transcripts by 2 researchers at each site. Following refinement based on researcher consensus, the final codebooks will be used to code each transcript independently by 2 researchers at each site. Subcategories will be assessed for the number of occurrences across all transcripts and themes and categories relevant to the data identified. The findings will be triangulated with quantitative data on implementation and provider and patient outcomes to assess the feasibility and impact of the e-mhGAP-IG.

PCW and Patient Outcome Analysis

The primary outcome will be the accuracy of the depression diagnosis. The research team will identify a patient as screening positive based on the PHQ-9 result immediately before or after the patient sees the PCW. *Screening positive* will be defined as scoring ≥10 on the PHQ-9. The research team will also assess sensitivity to change, for change in both the PHQ-9 and WHODAS 2.0 scores from baseline and 3 months after initiation of treatment. *Positive diagnosis* will be defined as a clinical diagnosis of depression documented by the health worker in the clinical notes. *Accurate detection* will be defined as PHQ-9≥10 and a health worker depression clinical diagnosis. We will also report findings in terms of the sensitivity and specificity of health worker diagnoses. *Sensitivity* will be defined as the proportion of health worker–diagnosed patients who had PHQ-9 above the cutoff, out of all patients who scored above the PHQ-9 cutoff. *Specificity* will be defined as the proportion of patients who did not receive a health worker depression diagnosis and scored below the PHQ-9 cutoff, out of all patients scoring below the PHQ-9 cutoff.

Features of the cRCT design will be accommodated in all analyses, and an intention-to-treat approach will be used. The principles of analysis will be (1) the PHC-level accuracy outcome is binomial (ie, number of accurate diagnoses out of all diagnoses based on patient-level data), and therefore, a generalized linear mixed model will be used (specifically, a log-binomial regression to obtain probability ratios); (2) accuracy is a cumulative measure, and therefore, there are no repeated measures over time; and (3) missing data can occur at either the health worker or patient level.

Differences in detection rates will be assessed using patient outcome data at 3 months after enrollment, only in depression cases identified in each arm (ie, scoring ≥10 on the PHQ-9), and the health worker clinical diagnosis. A 3-level hierarchical model will be used when all time points will be included as repeated measures in the model to improve power and take into account clustering of the observation at patient and PHC levels. The 3-level linear mixed model will be used to estimate a 95% CI for the comparison of clinical diagnosis and PHQ-9 screening positive rates (as well as a subanalysis with PHQ-9 plus WHODAS 2.0 criteria) within electronic and paper mhGAP-IG versions. Secondary outcomes (eg, knowledge and attitudes) will be assessed within each arm with a similar methodology for the primary outcomes, using generalized linear mixed models depending on the type of outcome (normal, binary, and count). Clinical feasibility will also be triangulated using penetration and costing data.

Health Economic Analysis

We will develop a simulation model to assess the potential cost-effectiveness of the e-mhGAP-IG compared with the paper-based tool. We are not measuring patient outcomes within the study; hence, costs of services and impacts on patients will be taken from other sources. The model will take the form of a

decision tree that maps out key events following the use of either tool and outcomes that are achieved. A simple form of the model will have cases detected or not as key events and whether or not outcomes improve as a result of detection (the latter information coming from previous research). The cost of providing care for people detected will be included as will the reduction in disability-adjusted life years (DALYs) following treatment. Some of the data will be obtained from within the study (costs of using the tools based on staff time and rate of detection of depression), whereas other data (costs of treatment and DALYs) will be obtained from the wider literature and expert opinion. The model will be subject to sensitivity analyses to address the uncertainty of the model parameters. The model will enable us to generate a cost per DALY avoided by using the tool.

Feasibility Criteria for Progression to Full Trial

The primary objective is to evaluate the feasibility and acceptability of the intervention, its implementation, and the trial procedures for the subsequent cRCT. We must establish indicators on what procedures to carry on to the full trial and where modifications should be made to study design or content. The overall feasibility and acceptability will be determined in the intervention arm by the following criteria at the end of the study to determine progression to the full trial:

- Identification of qualitative themes reporting that both PCWs and clients perceive group primary care mental health services as being acceptable, feasible, and appropriate
- Retention of at least 67% (27/40) of PCWs and patients through end line assessments
- Fewer than 15% (15/98) of missing items on outcome measures across all assessments or fewer than 15% (eg, 3/22 items on the R-DAQ) for each questionnaire with more than 10 items) or 50% (eg, 4/9 items on the PHQ-9; for each measure with 10 items or fewer) of missing items on an individual assessment.
- Presence of adverse events among fewer than 10% (4/40) of the participants and any serious adverse events.

In domains where criteria are met, we will retain the procedure for the full trial. In domains where criteria are not met, we will modify the procedures for the full trial, guided by data collected during interviews. The presence of any adverse events and/or serious adverse events will be addressed by the trial team to identify alternative strategies for the full trial and data safety monitoring committee. The number of feasibility and acceptability criteria that are not met will determine the extent of intervention and trial design modification. Ethical approval for this feasibility study was obtained from the following collaborating institutions:

- Psychiatry, Nursing, and Midwifery Research Ethics Committee, King's College London, United Kingdom (May 2020)
- University of Ibadan and University College Hospital Joint Ethics Committee, University of Ibadan, Nigeria (December 2018)
- Nepal Health Research Council for the Transcultural Psychosocial Organization Nepal (October 2020)
- WHO Ethics Review Committee, WHO, Geneva (May 2020).

Results

The Emilia project was funded in July 2018. Formative qualitative studies have been conducted in both countries, with results published from Nepal [64]. Data collection for the pilot feasibility cRCT began in January 2021 and is protected to be completed by March 2022. Activities have been delayed in both countries because of COVID-19.

Discussion

The mhGAP-IG enables greater access to evidence-based mental health care by targeting nonmental health specialists (eg, primary care doctors, nurses, and community health workers) as providers. Despite its use in more than 100 countries, a WHO consultation process identified the paper format to be a hindrance to its uptake, due to the burden on PCWs to carry the guide with them during appointments, and limited availability of mental health specialists to provide support and supervision. The Emilia project aims to address these barriers to scale. The existing WHO-developed electronic mhGAP-IG v2.0 has been adapted and refined for use in Nepal and Nigeria. Through a feasibility cRCT, its impact on detection and treatment initiation for depression, one of the most common mental conditions, will be tested along with stakeholders' perceptions of its implementation and suitability for scale. Although we believe that the availability of the e-mhGAP-IG will improve the demand and usability of the mhGAP-IG, the paper version will still play a vital role in settings where access to electronic technology and/or the internet is limited. The inclusion of a new remote supervision module for the ongoing support of health workers, made available in both trial arms, will allow us to assess its feasibility, appropriateness, and acceptability, in addition to its potential impact on the success of both the paper and electronic mhGAP-IG versions.

This feasibility trial will provide initial evidence of the utility and impact of the e-mhGAP-IG and remote supervision. The study takes advantage of the availability and potential of electronic technology and will advance work to reduce the mental health treatment gap around the world.

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Authors' Contributions

GT, TTS, IB, BAK, MJDJ, LH, OG, NPL, NS, and PMC were involved in designing the study. KC, NC, TD, HL, OG, NPL, LK, PP, and EPG adapted the intervention for electronic use. IB will oversee quantitative data analysis. HL will oversee qualitative data analysis. All authors will be involved in the interpretation of the results. TTS wrote the first draft of this manuscript. All authors have contributed to, read, and approved the final manuscript.

Conflicts of Interest

NS is the director of the London Safety and Training Solutions Ltd, which offers training in patient safety, implementation solutions, and human factors to health care organizations.

Multimedia Appendix 1
Updated electronic Mental Health Gap Action Programme Intervention Guide screenshots.
[PNG File , 376 KB - resprot_v10i6e24115_app1.png]

Multimedia Appendix 2
Description of electronic Mental Health Gap Action Programme Intervention Guide implementation.
[PNG File , 162 KB - resprot_v10i6e24115_app2.png]

Multimedia Appendix 3
Schedule of enrollment, intervention, and assessments.
[DOCX File , 28 KB - resprot_v10i6e24115_app3.docx]

Multimedia Appendix 4
Peer review correspondence from the Medical Research Council (UK).
[PDF File (Adobe PDF File), 254 KB - resprot_v10i6e24115_app4.pdf]

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Abbreviations

AIM: Acceptability of Intervention Measure
ASPIRES: Antibiotic Use Across Surgical Pathways-Investigating, Redesigning, and Evaluating Systems
cRCT: cluster randomized controlled trial
DALY: disability-adjusted life year
e-mhGAP-IG: electronic Mental Health Gap Action Programme Intervention Guide
Emilia: E-mhGAP Intervention Guide in Low- and Middle-Income Countries: Proof-of-Concept for Impact and Acceptability
ENACT: Enhancing Assessment of Common Therapeutic Factors
FGD: focus group discussion
FIM: Feasibility of Intervention Measure
IAM: Intervention Appropriateness Measure
LMIC: low- and middle-income country
mHealth: mobile health
mhGAP-IG: Mental Health Gap Action Programme Intervention Guide
NHS: National Health Service
NIHR: National Institute for Health Research
NoMAD: Normalization Measure Development
ORIC: Organizational Readiness for Implementing Change
PCW: primary care worker

PHC: primary health clinic
PHQ-9: Patient Health Questionnaire
PSS: Perceptions of Supervisory Support Scale
R-DAQ: Revised-Depression Attitude Questionnaire
SDS: Social Distance Scale
WHO: World Health Organization
WHODAS 2.0: World Health Organization Disability Assessment Schedule 2.0

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Protocol

Mobile Tuberculosis Treatment Support Tools to Increase Treatment Success in Patients with Tuberculosis in Argentina: Protocol for a Randomized Controlled Trial

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Abstract

Background: Tuberculosis (TB) is an urgent global health threat and the world's deadliest infectious disease despite being largely curable. A critical challenge is to ensure that patients adhere to the full course of treatment to prevent the continued spread of the disease and development of drug-resistant disease. Mobile health interventions hold promise to provide the required adherence support to improve TB treatment outcomes.

Objective: This study aims to evaluate the effectiveness of the TB treatment support tools (TB-TSTs) intervention on treatment outcomes (success and default) and to assess patient and provider perceptions of the facilitators and barriers to TB-TSTs implementation.

Methods: The TB-TSTs study is an open-label, randomized controlled trial with 2 parallel groups in which 400 adult patients newly diagnosed with TB will be randomly assigned to receive usual care or usual care plus TB-TSTs. Participants will be recruited on a rolling basis from 4 clinical sites in Argentina. The intervention consists of a smartphone progressive web app, a treatment supporter (eg, TB nurse, physician, or social worker), and a direct adherence test strip engineered for home use. Intervention group participants will report treatment progress and interact with a treatment supporter using the app and metabolite urine test strip. The primary outcome will be treatment success. Secondary outcomes will include treatment default rates, self-reported adherence, technology use, and usability. We will assess patients' and providers' perceptions of barriers to implementation and synthesize lessons learned. We hypothesize that the TB-TSTs intervention will be more effective because it allows patients and TB supporters to monitor and address issues in real time and provide tailored support. We will share the results with stakeholders and policy makers.

Results: Enrollment began in November 2020, with a delayed start due to the COVID-19 pandemic, and complete enrollment is expected by approximately July 2022. Data collection and follow-up are expected to be completed 6 months after the last patient is enrolled. Results from the analyses based on the primary end points are expected to be submitted for publication within a year of data collection completion.

Conclusions: To our knowledge, this randomized controlled trial will be the first study to evaluate a patient-centered remote treatment support strategy using a mobile tool and a home-based direct drug metabolite test. The results will provide robust scientific evidence on the effectiveness, implementation, and adoption of mobile health tools. The findings have broader implications

not only for TB adherence but also more generally for chronic disease management and will improve our understanding of how to support patients facing challenging treatment regimens.

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International Registered Report Identifier (IRRID): DERR1-10.2196/28094

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KEYWORDS

tuberculosis; disease management; infectious disease; mHealth; digital health; direct drug metabolite test; mobile phone

Introduction

Background

Tuberculosis (TB) is among the leading causes of death globally, surpassing HIV and malaria, even though most cases are preventable and curable. In 2019, the World Health Organization (WHO) reported a global TB incidence of 10 million, with approximately 1.4 million deaths [1]. To address the global health emergency that TB represents, the WHO End TB Strategy has set goals to reduce deaths and incidence rates by 95% and 90%, respectively, by 2035, relative to 2015 [2]. A critical challenge to meet these targets is to ensure that patients adhere to the full course of treatment to prevent the continued spread of TB and the development of drug-resistant disease. The WHO and others recognize that current strategies to ensure treatment success are insufficient to meet the goal of TB elimination in this century, and new treatment strategies are needed [3-5]. Interest in mobile health (mHealth) or digital health interventions to address these challenges and support patients throughout their treatment is growing, yet rigorous research is needed to evaluate these solutions in diverse settings and varying models of care [6-8].

Of the mHealth approaches under investigation for TB adherence monitoring, drug metabolite testing has been identified as the most promising, ethical, accurate, and least intrusive and stigmatizing strategy compared with other mobile solutions (eg, video observation, medication bottles containing sim card, and ingestible sensors), yet its potential remains largely unexplored [9]. Similarly, mobile apps can provide personalized treatment supervision, increase patients' self-management, and improve patient-provider communication by offering advanced functionalities for patient support and monitoring [10]. However, most apps are consumer facing, whereas health care systems are provider facing; thus, when digital health tools are not connected to systems and human support, they are unlikely to be effective [11]. In systematic reviews of TB-related apps in the marketplace, most apps either targeted health care workers (eg, dosing calculations) or provided general TB information; few of them targeted patients and none supported TB patient engagement in their own care (eg, self-tracking and side effect monitoring) [12,13]. Furthermore, none of them were reported to have been developed and tested for Latinos or Spanish speakers [12].

This protocol builds on preliminary work to develop and refine a patient-centered tuberculosis treatment support tools (TB-TSTs) based on patient and expert feedback through focus groups, field testing, and pilot testing (K23NR017210, primary investigator: Iribarren) and to test the TB-TSTs (R01AI147129, multiple primary investigators: Iribarren, Rubinstein). In our work with patients undergoing active treatment, we identified priority components of the mobile app, such as the need for reliable TB education, medication reminders, interactivity with a treatment supporter, treatment and side effect tracking, and social networking [14]. Further modifications were completed to integrate patient recommendations of, for example, simplifying reporting steps, improving treatment progress visualization, and developing a test strip that was easier to use. The refined TB-TSTs app has the following main functionalities: (1) TB disease and treatment education, (2) treatment adherence tracking (both by self-reporting and direct metabolite test strip images), (3) tracking self-reported potential treatment side effects, (4) interactive messaging with a treatment supporter, and (5) anonymous discussion forum to connect patients with others in treatment. This trial will be conducted in Argentina where TB treatment success rates continue to be low, the default (incomplete treatment) rates are high, patients commonly receive self-administered treatment, and strong research collaborations have been established [15]. The findings will be presented and discussed with key stakeholders and policy makers to support leaders who may expand and adapt mHealth tools to meet the needs of their communities. Guided by strong theoretical frameworks [16,17] and integrating direct adherence monitoring and personalized feedback and support, this work has the potential to improve TB treatment outcomes and have a sustainable public health impact. The findings have broader implications and will improve our understanding of how to support patients in challenging treatment regimens for both communicable and noncommunicable diseases.

Objective

The aims of this study are to (1) evaluate the impact of the TB-TSTs on treatment outcomes (success and default rates) compared with usual care and (2) assess patient and provider perceptions of the facilitators and barriers to implementation of the TB-TSTs and synthesize lessons learned.

We *hypothesize* that managing drug-sensitive pulmonary TB in adults using TB-TSTs intervention will result in improved treatment outcomes and patient satisfaction with care.

Methods

Trial Design

The TB-TSTs trial is a 2-arm, unblinded, pragmatic, randomized trial in which 400 participants with a confirmed diagnosis of drug-susceptible pulmonary TB initiating treatment will be

randomized 1:1 into 2 parallel groups. We will follow up with patients through their full treatment course (6 months) and compare the TB-TSTs intervention with usual care. The unit of randomization will be individual patients seen at hospitals where they receive TB care by self-administered treatment. The objective of this study is to evaluate the effectiveness of the TB-TSTs intervention for improving treatment outcomes for patients (as measured by increased treatment success and reduced defaults) and as a tool to support health care professionals to more easily manage TB cases. A protocol outlining the methods of this trial was registered at ClinicalTrials.gov (NCT04221789) [18]. The trial and interventions are described in accordance with the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) guidelines for reporting mobile randomized controlled trials [19].

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Boards of the Ministry of Health of the province of Buenos Aires (ACTA-2019-15552860-GDEBA-CECMSALGP) and the University of Washington institution review board Committee in Seattle, United States (STUDY00007533).

Theoretical Framework for Intervention Development

The information, motivation, and behavior change model was used for behavior change content and educational material development and to guide coding of qualitative focus group data during intervention development [20-22]. The intervention is guided by the theory domains through multiple mediators, including education, cues to action and skill building, and personal and social motivation elements (eg, behavioral incentives). For example, education related to strategies to remember to take medication daily corresponds to *self-efficacy behavior skills* to incorporate behavior into daily life. Education related to disease transmission and medication side effects corresponds to *adherence information*.

Eligibility Criteria

Individuals are eligible if they are 18 years or older, newly diagnosed with drug-susceptible TB, have regular access to a smartphone, and are able to operate the phone or have someone to assist. It is estimated that by the end of 2021, 73% of Argentina's population will have smartphones and smartphone access will continue to increase over the next 5 years [23]. Participants will be excluded if they are severely ill (ie, requiring hospitalization), reside in the same household with another study participant, or are confirmed to have drug resistance. Individuals without access to a smartphone or those who reside in areas without cellular network coverage will be excluded. Screened patients who do not meet study eligibility will have specific screening data (including sex, age, and reason for exclusion) entered into the study database to examine reasons for exclusion and feasibility of enrollment criteria.

Case definition—is defined as TB confirmed by positive results on a sputum smear test or diagnosis of pulmonary TB based on radiological findings and clinical signs and symptoms but with negative results on sputum smear test. The diagnosis may be confirmed by other methods, such as nucleic acid amplification (polymerase chain reaction), or enzyme-linked immunosorbent assay.

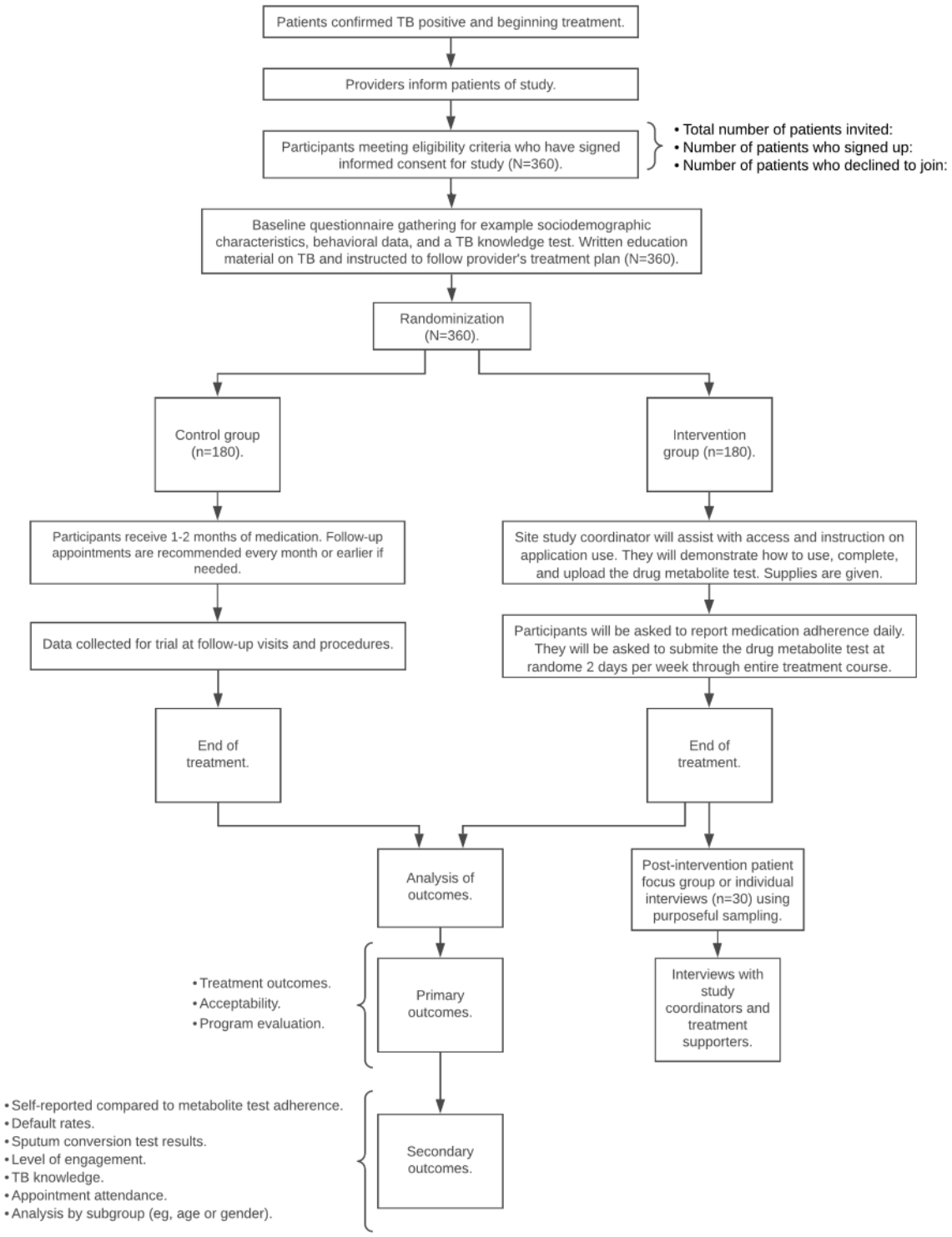
Study Settings

The study will be conducted in the capital and the province of Buenos Aires, Argentina, where more than 65% of the annual TB cases in the country are diagnosed and treated. Most patients are at respiratory specialized public hospitals where they receive treatment by self-administration. We selected 4 public hospitals with varying geographical catchments in high TB burden areas defined by established criteria from Argentina's National Tuberculosis Program (NTP). The study sites together treat approximately 1400 patients with TB annually. Reports from the NTP for the last 5 years and our cohort study showed that more than 60% of patients with TB were managed in public hospitals and 65% of them received treatment by self-administration. Of these, 85% were of low socioeconomic status, 50% were unemployed, 25% were smokers, and 20% reported alcohol or drug use [24].

Participant Recruitment

Patients will be enrolled on an ongoing basis, and the research team will invite every eligible patient to participate until the required sample size is achieved. The research team at each site will present the study to newly diagnosed patients as they are routed to register and receive treatment. Eligibility will be assessed by a trained clinical staff member who will then describe the study to the eligible patient face to face and answer any study-related questions. Patients interested in participating in the study will be required to provide informed consent, after which they will complete a baseline study survey that will include sociodemographic characteristics, behavioral data, self-management measures, and a TB knowledge test. A recruitment log will be maintained to document screened patients and reasons for declining participation (if willing to share reason). The primary recruitment strategy is to screen all patients who are diagnosed at the study sites within the first week of their treatment. We estimate that a total of 20-25 individuals per month will be enrolled by the research team. The COVID-19 pandemic has affected care seeking and the diagnosis of TB [25,26]. We anticipate that participant enrollment will take approximately 2 years. All participants will receive the standard TB education, including TB treatment, potential side effects, and need for treatment adherence. They will then be randomized into one of the two groups. The recruitment flow is shown in Figure 1.

Figure 1. Recruitment flow diagram. TB: tuberculosis.



Randomization Procedures

We will randomize participants sequentially with a ratio of 1:1 allocation to receive either usual care or usual care plus TB-TSTs. A random allocation sequence will be generated using a randomization software. We will use randomly permuted blocks of different sizes between 6 and 10 and stratified by hospital to ensure that the numbers are balanced by center and group. Each block will contain equal proportions of the control and intervention groups. The randomization sequence will be uploaded to REDCap (Research Electronic Data Capture) for treatment allocation concealment by the department of data management at the Institute for Clinical Effectiveness and Healthcare Policy. Once a patient signs the consent form, they will meet with the treatment supporter who will access the REDCap randomization module to access the assigned randomization.

Blinding

Owing to the nature of the intervention, blinding to the group allocation is not possible for participants after assignment to the study arm. The research staff allocating participants to study arms during randomization will be blinded to the sequence to minimize the likelihood that research staff will be able to predict the next study arm assignment. Clinicians will not be made aware of the group allocation unless their patient informs them. Site coordinators, who will collect the monthly standard NTP follow-up information (eg, return date to pick up medication and data from the follow-up visits) and final treatment outcomes will be blinded to the group allocation of the participants. Study investigators will be blinded to the allocation and preliminary analysis before the end of the study. Only the trial statistician will be unblinded to the analysis.

Interventions

Overview

Regardless of the study arm, participants will receive standard instructions, NTP educational material, and brochures. TB treatment is provided free of charge in the public health system. The standard of care includes routine clinical and laboratory tests. Treatment of drug-susceptible TB consists of a 6-month regimen consisting of a 2-month *intensive* phase of 4 drugs (rifampicin, isoniazid, pyrazinamide, and ethambutol or streptomycin) followed by a 4-month *continuation* phase with isoniazid and rifampin daily [27]. Where available, medications are provided in a combined pill with 3 or all 4 drugs.

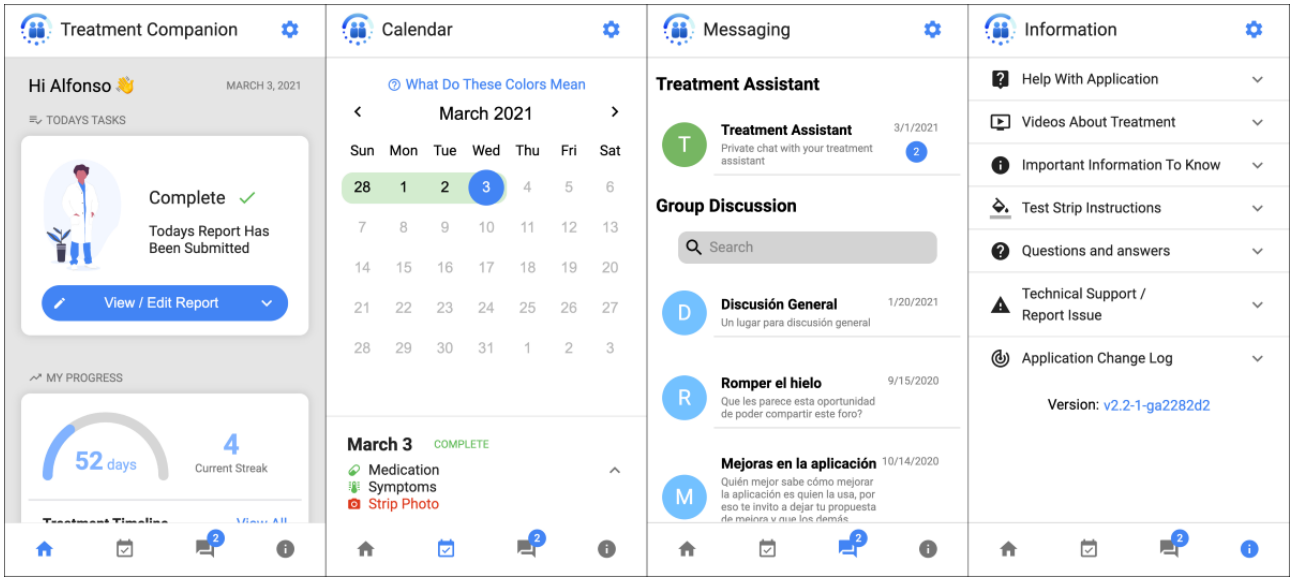
Control

At the study sites, self-administration of treatment is usual care. In general, patients receive a 1- to 2-month supply of medication and are asked to return monthly for follow-up appointments, or earlier if they experience problems. Patients in the control group will be followed up for routine visits according to the NTP guidelines. The research staff will collect data on the participants' follow-up visits and procedures.

Intervention

TB-TSTs patient app version 2.0+ is a progressive web app that includes the following functions: (1) *TB disease and treatment education*, which is provided in written and video form and will be sent weekly as brief messages that correspond to the treatment phase; (2) *treatment progress tracking*, which includes both daily self-reporting and direct metabolite test adherence with the corresponding calendar and treatment progress indicator; (3) *potential treatment side effects reporting*, after which the treatment supporter will reach out for further assessment; (4) *interactive messaging with a treatment supporter* to ask questions and help resolve issues; (5) *medication and appointment reminder setting*; and (6) *anonymous discussions* to connect patients with others in treatment (a request by prior patients; Figure 2).

Figure 2. Patient app features.



Participants will be asked at random 1 to 2 days per week to complete a direct drug metabolite home-based urine test and upload an image of the test in the app. The test is a paper-based colorimetric test that is based on classic chemistry (the Arkansas method) that changes the color of the strip to purple when a drug metabolite of isoniazid (isonicotinic acid hydrazide; INH) is present in urine [28-30]. INH, one of the main first-line TB drugs, is considered an ideal target and good biomarker for daily adherence monitoring because its metabolites are detectable in urine for approximately 24 hours [31]. INH is often combined with other TB drugs in the same pill. Therefore, testing for INH metabolites in urine is an indicator that the combined pill was ingested within the last 24 hours. The test is quickly dipped (1-2 s) in a collected sample of urine and allowed to run for 15-20 minutes. The daily reports and test image will sync automatically to the treatment supporter interface.

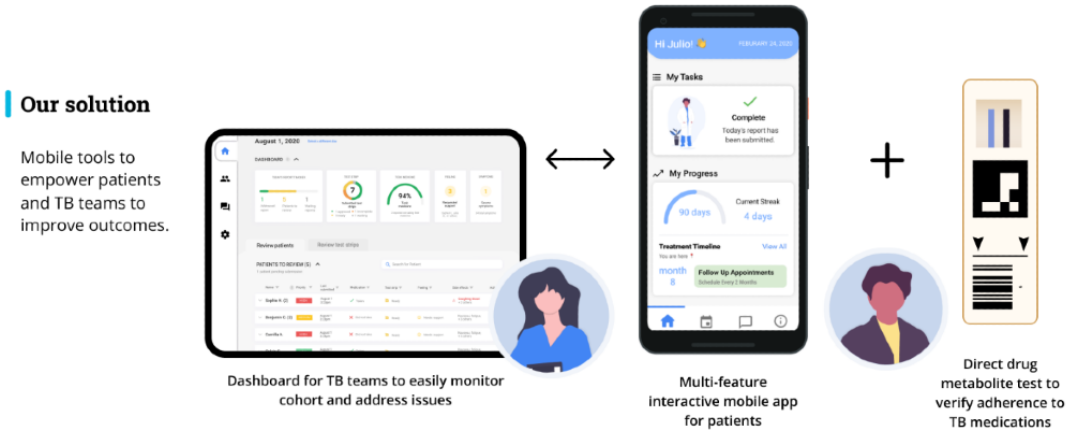
At each study site, a member of the TB team (eg, a TB specialized nurse or social worker) will serve as the treatment supporter and log in to the secured TB-TSTs system via a tablet or laptop to review daily reports and test results. The treatment supporter will thus be able to track missed doses and/or reported side effects and follow up within the app with appropriate support or advice using actions specified in the study standard

operating procedures. The treatment supporter will log contacting participants, determine the results of the test strip, and monitor the discussion board for group questions or concerns.

Treatment Supporter

The treatment supporter will be trained on app and provider portal use, research goals, and protocols by the primary investigators and collaborating regional TB program team members. The main function of the treatment supporter is to oversee daily reports and help address participant questions and challenges. The treatment supporter facilitates a communication route to mitigate unforeseen events. Overall, the role is supportive to participants to create a sense of companionship and trusted guidance to improve commitment to treatment responsibilities. Figure 3 provides an overview of the TB-TSTs intervention.

Figure 3. Intervention overview. TB: tuberculosis.



Procedures

Overview

TB-TSTs group participants will be assisted with gaining access to the app and will receive verbal and written instructions as well as a one-on-one demonstration of app features by the site research team member. They will also receive verbal and written instructions on how to complete the paper-based drug metabolite test and upload an image into the app (instructions also within the app). Participants in the intervention group will be informed that interaction with the treatment supporter through the app is provided within a clinic-based system during office hours and that any emergencies must be directed through standard routes.

Access to the App

Access is granted by the treatment supporter who enters the patient's details to generate a one-time user password that they can use to set up the participant's account. This code will be given directly to a patient or sent via WhatsApp (Facebook, Inc) along with a link to the web application. The treatment supporter will guide the participant through each step of the app's installation, explain the use of the app, and demonstrate how to perform a complete report. At the first visit to the web application, they will be prompted to install it on their home screen for easier access. After installation, the app functions like any other app on a mobile phone. When a patient first logs in to the app, they will be prompted to change their password and complete an onboarding survey where we gather some of their preferences. Passwords can be updated, and new temporary passwords are provided if the password is forgotten.

Compensation for Expenses

Patients in the intervention arm will be asked to complete an exit survey and interview (described in the following section). We will pay for 1 GB of data per month to cover data use from the app.

Study Outcomes

The primary outcome will be treatment success based on WHO definitions [27]. Treatment outcomes are defined as success (cure or completion of regimen), default, transferred out, deceased, or lost to follow-up. Secondary outcomes will include self-reported adherence compared with direct adherence test results (self and direct adherence), technology use measured by actual use of the app, and technology usability measured by the Health Information Technology Usability Evaluation Scale [32].

Power and Sample Size

The trial is powered on the primary outcome measure of treatment success. Argentina's WHO TB country report indicates that treatment success rates have ranged from 44% to 66% over the past 10 years [33]. These rates include cases that were lost to follow-up. For those with known outcomes, Argentina's NTP and our previous cohort study estimated that the treatment success rate among patients under self-administered treatment was approximately 70%, with a default rate of 20% [34]. To detect a success rate of at least 85% in the experimental group with 90% power, the calculated sample size is 360 individuals (180 subjects per arm). Assuming an attrition rate of 10%, we would require a minimum final sample size of approximately 400 (200 per group). All calculations are based on a 2-sided test with α=.05 level.

Statistical Methods

All analyses will be based on intention to treat in their respective intervention categories. Two-tailed tests (both chi-squared and *t* tests) will be used for dichotomous or categorical and continuous variables, respectively, to assess group assignment

differences. One-tailed tests will be used to evaluate the primary outcomes. Standard descriptive statistics of frequency, central tendency, and dispersion will be used to describe each sample. A *P* value less than .05 will be set to detect a statistically significant difference for all analyses. We will compare group baseline characteristics, including age, sex, education, income, comorbidity, travel time to center, medication regimen adherence, and baseline TB knowledge. The primary end points will be evaluated using the Chi-square test. Although we do not expect group differences, logistic regression analysis will be used to adjust for potential confounders if necessary. Statistical analyses will be performed using STATA version 16. Table 1 provides an overview of the variables, hypotheses, operationalization, data collection, and measurement points.

Table 1. Overview of variables, hypotheses, operationalization, and data collection.

Outcome or variable	Hypothesis	Outcome measure	Analysis	Measurement point			
				Screening (T0)	Baseline (T1)	2 months (T2)	6 months (T3)
Primary outcomes							
Treatment outcomes	Intervention> control; intervention<control	Treatment success (%); other outcomes (eg, failed, default, or died)	Chi-square test				✓
Acceptability[a]	N/A[b]	MARS[c] scale (Likert scale), interviews	Descriptive or qualitative				✓
Program evaluation[a]	N/A	Feasibility, ease of use, recommendation	Descriptive or qualitative				✓
Secondary outcomes							
Drug metabolite test[a,d]	N/A	Self-reported compared with test results	N/A			✓	✓
Default rate	Intervention<control	Abandon treatment for 2 months or more	Chi-square test				✓
Sputum conversion	N/A	At 2, 4, and 6 months	GEE[e]		✓	✓	✓
Global Health PROMIS[f] SFv1.1	Intervention>control	CDE[g] outcome for self-management	One-tailed *t* test	✓			✓
Level of engagement[a,d]	N/A	Daily use, message, question counts	Descriptive	✓	✓	✓	✓
Appointment attendance	Intervention>control	Proportion	Chi-square test		✓	✓	✓
Subgroup analyses			Chi-square test				
Sex	Female>male	N/A	N/A				
Age	Older>younger	N/A	N/A				
Mobile phone access type	Personal>shared	N/A	N/A				
Time to clinic	Less and greater than 30 minutes	N/A	N/A				

[a]Data collected from the intervention group only.

[b]N/A: not applicable.

[c]MARS: Mobile App Rating Scale.

[d]Data collected throughout trial.

[e]GEE: generalized estimating equation.

[f]PROMIS: patient-reported outcomes measurement information system.

[g]CDE: common data element.

Methods for App Data Management

Overview

All data generated in the app will be sent securely over the network to a virtual machine hosted on site at the University of Washington. The virtual machine is administered by a team of health care information technology experts and requires authentication as a limited subset of users for administrative access. End users interact with a web app, which securely communicates with an application programming interface hosted on the server. The application programming interface processes user input and then stores it in a suitable database (PostgreSQL database or file server).

Data Viewing

To view patient reports, study treatment supporters will log in to a separate portion of the app, where they have access to the reports of only the patients registered at their site. Access control is implemented at the server level to ensure that only the appropriate actors have access to patient data. For example, a patient cannot access other patients' information and a coordinator can only see the patients they directly supervise.

Data Exporting

If data need to be exported from the system, they can be queried from the database and reshaped to meet the requirements of its use. Photos can be exported as a zipped folder and do not have any personally identifiable information directly attached to them.

Considerations for this app included interoperability, support of local and remote health data storage, user-friendly data visualization, and modular development for extensible future technologies.

Methods for Postintervention Interviews or Focus Groups

Overview

Following the intervention, we will conduct 3 focus groups of 8-10 people randomized to the TB-TSTs group and 2 focus groups with TB treatment supporters and TB team members to assess their experience using the TB-TST and its accompanying case management platform. Individual interviews will be conducted with those unable to attend focus group sessions. We will assess patients' and providers' perceptions pertaining to the facilitators and barriers to implementation of the TB-TSTs intervention and synthesize lessons learned.

Sample

We will attempt to include participants who abandoned treatment, those who had difficulties, and those who completed treatment successfully. Conducting 2-3 focus groups has been found to capture about 80% of themes on a topic using a semistructured guide [35].

Procedures

The focus groups will be 60-90 minutes in length. Following completion of the informed consent process, all focus group sessions will be audio recorded. The focus group guides will be informed by the Mobile App Rating Scale to assess *acceptability* (perceived usefulness and ease of use) [36]. The Mobile App Rating Scale has been shown to be a highly reliable tool for assessing app quality [36-38]. The scale includes 3 sections and a modifiable app-specific section. Questions include identifying challenges and bottlenecks, if the intervention meets needs, satisfaction with care, confidentiality concerns, and postintervention perceptions and recommendations. We will use a sociotechnical perspective that considers the structure process outcome to understand, for example, issues of workflow and altered practice and delivery of service and evaluation [39]. From a human-centered design standpoint, we will assess, for example, accessibility concerns, awkward flows for actions, confusing features, and user interface issues to identify the need for optimization and improvement.

Participants will be compensated the equivalent of US $20 in Argentinean pesos for their time participating in an interview or focus group.

Analysis

The focus group transcripts will be transcribed verbatim for coding [40]. The transcripts will be entered into a qualitative data management software, such as NVivo, to organize and facilitate analysis. We will iteratively code using thematic and descriptive qualitative methods [41,42]. Specifically, we will use an inductive approach that provides a systematic set of procedures for analyzing and deriving reliable and valid findings from qualitative data [43]. The following steps will be used for analysis: (1) preparation of raw data files—clean data; (2) close reading of text to gain an understanding of the issues discussed by the participants; (3) creation of categories (codes): identify and define categories, themes, and subthemes; (4) reconcile overlapping coding and revise coding scheme; (5) continuing revision and refinement of coding scheme: within each category, search for subtopics, including contradictory points of view and insights and selected appropriate quotes that convey the themes; and (6) apply the final coding scheme to the full data set and assess intercoder reliability.

The transcripts will be independently coded by 2 team members. The coding team will meet regularly to discuss the categories of themes and synthesize interpretations across the team. During the application of the final coding scheme, we will assess if we are applying the coding in the same way and resolve discrepancies between coders by discussing until a consensus is achieved. We will code the transcripts in the native language and translate exemplar Spanish quotes to English after coding for the final presentation. The findings will be organized into main categories of actionable change for further iterative intervention modification, considerations for broader application (or not), barriers and facilitators, and lessons learned.

Data Management

Data collection forms will be developed using REDCap, a secure, web-based app with interactive data capture checks designed to support data capture for research studies, providing an intuitive interface, audit trails, and automated export.

Results

Overview

We will present the primary and secondary findings of this study. The main findings will include treatment outcomes based on the WHO definitions and results of the intervention use, such as rates of self-reported adherence versus confirmation of adherence based on the test strip results, app use, and participant usability assessments. We will present patients' and providers' perceptions pertaining to the facilitators and barriers to implementation of the TB-TST intervention and synthesis of the lessons learned.

The study was approved by 2 institutional review boards and the ethics committees at each of the participating recruitment sites. Enrollment into the randomized controlled trial began in November 2020. Enrollment is expected to be completed by the end of 2022. Follow-up will continue for 6 months after the final participant is enrolled. Postintervention surveys will be carried out as soon as possible following the participant's time in the study. Focus group sessions will begin after one-third of the participants have completed treatment. Data collection is expected to be completed 9 months after the last participant is enrolled. Results from the analyses based on the primary end points are expected to be submitted for publication within a year of data collection completion.

The findings will be presented and discussed with key stakeholders (patients, TB teams, and regional and national TB program officers). The study team will present findings to the health care professionals at recruitment sites that are open to the community to disseminate findings and encourage feedback and involvement for widespread dissemination and use and further tailoring to meet the local needs. We aim to build the capacity of leaders who may expand and adapt mHealth tools to meet the needs of their communities.

Trial Status

Initiation of the TB-TST trial was delayed because of the COVID-19 pandemic and country lockdowns. Recruitment began in November 2020 at the first of the 4 sites.

Discussion

We will discuss the main primary and secondary findings of this study.

Rationale

TB remains an urgent global health threat and one of the world's deadliest infectious diseases (above HIV). Nonadherence to treatment is a known cause of poor individual and societal outcomes, including prolonged infectivity, relapse, increased morbidity and mortality, and the development of drug resistance [44-46]. The spread of TB is exacerbated by a myriad of challenges to patients such as the lengthy treatment course, social stigma, fear, discrimination, poverty, lack of knowledge about the disease and its treatment, medication side effects, and lack of support [45,47,48]. Furthermore, growing rates of drug resistance threaten to reverse the progress made by TB eradication efforts to date [15]. It is estimated that by 2050, drug-resistant TB alone could kill as many as 2.5 million people per year and cost the global economy up to US $16.7 trillion [49]. Drug-resistant TB is more contagious, costly, and deadly. In the United States, the estimated cost to treat one case of multidrug-resistant TB is US $243,000 compared with US $46,000 for drug-susceptible TB [50]. Health care systems are burdened by the volume of patients, the HIV epidemic, lack of resources, and lack of advanced monitoring and tracking technology [51,52]. As a result, prevention of the spread of the disease and development of resistance is a global public health priority [3]. To achieve this, health care systems must ensure the completion of treatment.

The incomplete application of effective control measures has resulted in incidence and death rates associated with TB being either stagnant or decreasing more slowly than expected [53]. The current recommended target rate for treatment success is 90% for all identified cases [3]. The WHO Americas region has the lowest treatment success rate (75%), one of the highest rates of patients who are lost to follow-up, and a high percentage of deaths because of TB compared with other WHO regions [54]. In Argentina, treatment success rates have been one of the lowest in the region, from 44% to 66% since being tracked, and there have been consistently high rates of treatment default (abandoning treatment for a minimum of 2 months) of about 30% [33,34]. In addition, it is one of the 5 countries in the Americas with a high number of estimated multidrug-resistant TB cases [15]. Therefore, Argentina is one of the countries in which the health care system needs to implement more effective TB treatment adherence strategies.

Currently, there is a lack of feasible, acceptable, and effective strategies to directly monitor treatment adherence and provide timely support for patients undergoing self-administered treatment. The current strategies are recognized as insufficient to meet the goal of TB elimination in this century [3,4]. The mHealth approaches for TB treatment adherence monitoring being tested include *indirect* patient-facilitated or device-facilitated monitoring (eg, self-reporting, medication bottles containing sim card, and video observed therapy) [55,56] and *direct* monitoring through embedded sensors [57] or drug metabolite testing [28,58]. Concerns regarding the privacy, accuracy, and costs of these interventions have been raised [9]. For example, although direct video monitoring may avoid issues of stigmatization, patients can feign ingestion. Drug metabolite testing is potentially superior to video observed therapy because it requires actual ingestion of the drug and has been identified as the most promising, ethical, accurate, and least intrusive and stigmatizing of these mobile strategies, yet its potential remains largely unexplored [9]. Preliminary reports outside of the peer-reviewed literature highlight the potential for drug metabolite testing [59]; however, there is a need for further development of the technology and rigorous research to assess its impact on treatment outcomes.

In response to the challenges of implementing directly observed therapy, current developments in treatment management involve the utilization of digital health (eg, eHealth, mHealth, and connected health) technology, such as the use of cellular phones, tablets, smartphones, and other wireless devices, to explore more efficient and effective ways to ensure that patients

complete their treatment [6]. For example, apps can facilitate real-time adherence monitoring or side effect tracking, on-demand or tailored education, and bidirectional communication with health care teams [10]. In a systematic review of TB-related apps in the marketplace, most of the apps targeted health care workers (eg, dosing calculations and treatment recommendations) or provided general TB information [12]. Few apps have been developed for use by patients, and none have been developed to support TB patient engagement in their own care (eg, reminders, side effects monitoring, or interaction with their health care providers), thus limiting the potential of these apps to facilitate patient-centered care. Given that more than 95% of the global population is living in an area that is covered by a mobile cellular network and mobile phone and smartphone ownership is rapidly rising, maximizing mobile tools for treatment support holds promise to heighten patients' engagement in care and improve adherence, monitoring, communication, and delivery of evidence-based interventions [6,9,60]. However, more evidence is needed to develop, adapt, and validate these tools under diverse conditions and models of care [6,7].

This protocol describes the design and methods of a randomized controlled trial assessing the effectiveness of using TB-TSTs to improve TB treatment success rates in high TB burden setting in Argentina. This study leverages the accessible features of a mobile phone app, a direct drug metabolite test, and interactive remote support by a treatment supporter. To our knowledge, this study is the first to design a TB patient-centered mobile app using an iterative user-centered design, which has been shown to improve the quality, functionality, and engagement with patient-facing health apps. We will utilize real-time data collection and provide participants with feedback on their adherence performance in graphic and text forms. The intervention will provide bidirectional messaging, which includes personalization based on participants' responses and results (eg, side effects and adherence reporting). Unidirectional, *push* messages can provide reminders or nudges for patients to take a more active role in their management; however, the bidirectionality may maximize the intervention potential.

The proposed study is innovative for several reasons. First, the patient-facing and treatment supporter–facing app facilitates interactivity and timely personalized support throughout the course of treatment to address problems or potential side effects. Second, the reengineering of a paper-based test for home use for detecting a drug metabolite in the urine and mobile phone image capture of the results together allow for novel real-time direct adherence monitoring. The test confirms medication ingestion within approximately the previous 24 hours, thus avoiding the poor accuracy of self-reporting. This may improve a treatment supporter's ability to provide personalized or precision feedback to promote positive health behaviors and to ensure treatment adherence. Self-reporting or other surveillance methods are considered less accurate, increase stigmatization, or are intrusive to the patient [9]. Third, collecting repeated and longitudinal data on TB medication side effects by phone, throughout the treatment course, is novel in Argentina and may lead to new insights on side effects and treatment adherence over time. Finally, building the app and provider interface in a modular fashion using open-source software and open standards allows for future integration into health care systems (eg, eHealth records and surveillance systems) and future functionality expansion based on end user needs. A mobile optimized web app allows it to be used on any patient smartphone rather than relying on one operating system or phone type.

Limitations

It is likely that patients will need assistance in navigating the app tool or other components, such as a test strip outside of the initial education upon enrollment. Additional instructions on how to use the tool have been developed, in video and written form, to support users. An onboarding session was developed to walk participants through the steps to use the app at first use, and it can be accessed later for review. The short videos demonstrate how to submit the daily report and include step-by-step instructions on how to conduct the metabolite test and upload a photo to the app. A third video provides an overview of other app features such as accessing education, setting appointment date reminders, individualized notification system for medication or appointments, and accessing messaging and discussion forums.

It is possible that participants may have inconsistent access to Wi-Fi or lose mobile phone services, which could delay reporting. An offline reporting feature was developed to support offline reporting and upload once a cellular network or Wi-Fi connection is re-established. There is also the potential for participants to lose or change their phones. To address this, we will document their WhatsApp number to reach out to participants if they fail to report for an extended period. If app access is lost, a link will be resent, allowing participants to log in with their previously set up username and password. In the case of a lost password, the treatment coordinator can provide a temporary password for the patient to create a new password. If participants forget to report, they will be allowed to report retroactively for the previous 3 days. Users will also be able to provide an explanation on reporting variances. If an image of the drug test strip is taken too soon, it may appear as a false negative and conflict with self-reported adherence. The treatment supporters may reach out to the participants to assess how the test was conducted.

Harms or Unintended Effects

Research staff will monitor and take note of privacy breaches, technical problems, or unintended effects. This may include qualitative feedback from participants or observations from staff or researchers on intervention shortcomings or why people do not use the intervention as intended. The research staff will also monitor and document unintended positive effects, which can include qualitative feedback on the strengths of the system.

Conclusions

The TB-TSTs trial is a pragmatic trial to test a novel, scalable approach to optimize TB treatment adherence and completion. According to the National Institute of Health, "the dynamic nature of adherence underscores the need to improve routine monitoring of individual's adherence to recommended healthcare regimens, and to re-examine or develop new

interventions to support adherence over the course of care" [61]. The significance of this study is at least threefold. First, it will be the first randomized controlled trial to use a home-based direct metabolite adherence test in combination with an interactive, multifeatured patient-centered app and treatment support platform. Second, the intervention has been tailored to the local setting and for Spanish speakers, for which there is a dearth of evidence. Third, we will assess the impact of the TB-TSTs and the potential for scaling the technology if the results suggest that it is effective. The success of TB-TSTs could inform us of the opportunities for treatment adherence and symptom management for various populations with complex care needs. Our long-term goal is to revolutionize patient monitoring, improve patient-provider communication, and promote self-management of treatment by optimizing and designing convenient and acceptable digital adherence tools that are tailored to their settings, in this case, Spanish speakers in Argentina.

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Conflicts of Interest

Some of the authors are developers (SI, KG, and OAAV) and evaluators (SI, HM, CC, HT, and FR) of the software.

Multimedia Appendix 1
Awarded grant peer-review report from NIH-NIAID [redacted].
[PDF File (Adobe PDF File), 141 KB - resprot_v10i6e28094_app1.pdf]

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Abbreviations

CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
INH: isonicotinic acid hydrazide
mHealth: mobile health
NTP: National Tuberculosis Program
REDCap: Research Electronic Data Capture
TB: tuberculosis
TB-TST: tuberculosis treatment support tool
WHO: World Health Organization

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Protocol

A Digital Gaming Intervention to Improve HIV Testing for Adolescents and Young Adults: Protocol for Development and a Pilot Randomized Controlled Trial

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Abstract

Background: Two strategies of the US Ending the HIV Epidemic initiative are early diagnosis of infections via widespread testing and prevention of new infections using pre-exposure prophylaxis (PrEP). These strategies are particularly important for adolescents and young adults (AYAs) who are disproportionately affected by HIV, particularly if they identify as Black and/or lesbian, gay, bisexual, transgender, queer or questioning, and others (LGBTQ+). This study will develop and test an interactive life-simulation game in which players can enact real-life behaviors and receive their HIV risk profile to improve HIV testing and PrEP access among AYAs aged 13-24 years in Washington, DC.

Objective: This mixed methods study aims to determine the acceptability of an interactive, enhanced life-simulation game prototype among AYAs, conduct a pilot test of the gaming intervention among a small cohort of AYAs to ensure game usability and acceptability, and evaluate the efficacy of the game in a randomized controlled study with AYAs at risk for HIV in Washington, DC.

Methods: This research protocol will be conducted in 3 phases. A formative phase will involve surveys and focus groups (n=64) with AYAs living in the DC area. These focus groups will allow researchers to understand youth preferences for game enhancement. The second phase will consist of a pilot test (n=10) of the gaming intervention. This pilot test will allow researchers to modify the game based on formative results and test the planned recruitment and data collection strategy with intended end users. The third phase will consist of a randomized controlled study among 300 AYAs to examine the efficacy of the life-simulation game compared with app-based HIV educational materials on HIV and PrEP in changing HIV testing, knowledge, risk behaviors, and PrEP access. Participants will have unlimited access to either the life-simulation game or the educational app for 3 months from the time of enrollment. Study assessments will occur at enrollment and at 1, 3, and 6 months post enrollment via e-surveys. At 6 months, a subset of intervention participants (n=25) will participate in in-depth *exit* interviews regarding their experience being in the study.

Results: Institutional review board approval was received on February 5, 2020. This project is currently recruiting participants for the formative phase.

Conclusions: This interactive life-simulation intervention aims to increase HIV testing and PrEP access among AYAs in the DC area. In this intervention, players can enact real-life behaviors and receive their HIV risk profile to promote HIV testing and PrEP seeking. Such an intervention has great potential to improve knowledge of HIV and PrEP among AYAs, increase motivation

and self-efficacy related to HIV testing and PrEP use, and decrease individual and structural barriers that often preclude engagement in HIV prevention services.

Trial Registration: ClinicalTrials.gov NCT04917575; https://clinicaltrials.gov/ct2/show/NCT04917575

International Registered Report Identifier (IRRID): PRR1-10.2196/29792

(JMIR Res Protoc 2021;10(6):e29792) doi:10.2196/29792

KEYWORDS

HIV testing; pre-exposure prophylaxis (PrEP); youth; mobile phone

Introduction

Background

The goals of the US National HIV AIDS Strategy, Ending the HIV Epidemic initiative, and the HIV care continuum to reduce new HIV infections by intensifying prevention efforts where HIV is most heavily concentrated [1-3] are particularly important for adolescents and young adults (AYAs) aged 13-24 years who are disproportionately impacted by HIV. In 2018, AYAs accounted for 21% of new HIV infections, and young men who have sex with men (YMSM) and transgender women who identified as Black or Latinx were most severely affected [4]. In Washington, DC, a geographic hotspot for HIV [3], AYAs accounted for 21% of new diagnoses in 2019 [5]. Furthermore, Black youth and YMSM in DC accounted for 75% and 60% of new HIV diagnoses among youth in 2019, respectively [6]. Thus, creative strategies to support risk assessment, prevent HIV infection, encourage routine HIV testing, and link AYAs to care are increasingly paramount.

Barriers to HIV testing among youth include difficulty identifying and accessing HIV testing sites, low health literacy and beliefs that HIV remains a severe and fatal disease, and lack of self-perceived risk for HIV [7-12]. Aside from HIV testing, the use of other HIV prevention interventions, such as pre-exposure prophylaxis (PrEP), has been limited among AYAs. Hence, there is a need to improve youth understanding of HIV, how to prevent it, and behaviors that put one at risk for infection and to provide them with resources to access HIV testing and PrEP, in a youth-friendly and nonjudgmental manner [8,13,14]. A review of HIV testing interventions focused on increasing adolescents' intentions to obtain HIV testing found that facilitators of testing include understanding testing as an essential part of accessing early treatment, helping youth think about future health, and learning how to effectively communicate with their sexual partners [12]. Furthermore, with the US Food and Drug Administration expansion of PrEP to adolescents and the US Preventive Services Task Force Grade A recommendation for PrEP, options for HIV prevention interventions for AYAs have expanded [15-17].

Despite the fact that AYAs are more receptive to HIV information when it is provided in an entertaining format [12,18] and when the material comes from a peer [19-21] or is shared over social media, interventions to promote HIV testing among AYAs have been limited. Digital game–based interventions are a potential strategy to increase HIV testing among AYAs as they overcome traditional barriers faced by this group [22] and can educate while simultaneously motivating AYAs [23]. In addition, paradata, or information related to the process of data collection, can be used to assess the levels of intervention exposure and can assist in further tailoring interventions to individual AYAs. Paradata can potentially inform which elements of HIV interventions are most useful, should be modified, or removed to increase an intervention's efficacy and can assist in tailoring game-based interventions in a timely and cost-effective manner [24].

Theoretical Framework for Intervention

We will use social cognitive theory (SCT) and the health belief model (HBM) to ground our intervention development. SCT provides a framework relevant to both health behaviors and interventions and has been widely used in HIV interventional studies [24-27]. We hypothesize that the game intervention will positively influence youth self-efficacy, risk perceptions, and knowledge of HIV prevention as well as influence AYAs' social support. The HBM proposes that health behaviors are influenced by a person's perceived susceptibility and seriousness of a disease and the benefits of acting to reduce that risk [28]. HBM has been used to assess HIV testing uptake among various populations, including AYAs [29-32]. We expect that as AYAs navigate and experience the various game scenarios, encounter persons of different HIV risk, and learn about HIV and associated risks, the game will increase HIV risk perception, increase HIV and PrEP knowledge, and improve self-efficacy with respect to sexual relationships and HIV prevention, that is, seeking HIV testing, PrEP, or reducing risky sexual behaviors.

Aims and Objectives

This mixed methods study will enhance a life-simulation game intervention for AYAs at risk for HIV in the Washington, DC, metropolitan area. The game will be informed by findings from the focus groups with 64 AYAs. We will then conduct a pilot test with 10 AYAs and a randomized controlled trial (RCT) with 300 AYAs. To evaluate the efficacy of the life-simulation game compared with app-based HIV educational materials on HIV and PrEP in changing HIV testing, knowledge, risk behaviors, and PrEP access, RCT participants will have unlimited access to either the game or the educational app for 3 months from the time of enrollment. Electronic study assessments will occur at enrollment and at 1, 3, and 6 months post enrollment. At 6 months, a subset of intervention participants (n=25) will participate in in-depth *exit* interviews regarding their experience being in the study.

Methods

Participants

AYAs will be eligible for enrollment in each phase of the study based on the following criteria: (1) ages 13-24 years; (2) English speaking; (3) sexually active; (4) HIV-negative status; (5) residing in DC, Maryland, or Virginia; and (6) able to provide informed consent or assent. AYAs participating in the second and third phases will also need to have a mobile phone that they are willing to use for the study. We are limiting the study to AYAs aged 13-24 years because they account for a significant proportion of new HIV cases in Washington, DC, and doing so will allow for the development of a life-simulation gaming intervention that is targeted, acceptable, and engaging for this specific population. We plan to enroll a sample representative of diverse racial and ethnic and sexual behaviors.

Description of Intervention Content

The life-simulation game prototype for smartphones (iOS and Android), tablets, and the web was developed in a phase 1 Small Business Innovation Research study [33] and shows an AYAs' HIV risk based on their sexual choices in the game. Several areas for modification were identified in the phase 1 study, including the incorporation of a customizable avatar; the development of additional activities, locations, and dating scenarios; incorporation of data analytics features to collect game and paradata; and access to a PrEP provider locator. The incorporation of these modifications has resulted in an enhanced life-simulation game that will be further refined throughout the course of the study (Figure 1). Players can create their in-game *self* using a system that unifies all forms of racial and gender expression into a single avatar, allowing both cisgender and unique transgender and nonbinary characters customized to the player's specifications. Our previous data suggest that increasing in-game self-expression can result in player identification with their onscreen character, concern for their character's HIV risk profile, and interest in HIV testing and prevention. The player's character can seek to date same-sex partners, opposite-sex partners, both, or neither (Figure 2). The game features in-depth dialog for players to explore social interactions for both dating and platonic relationships. Fresh branches of storylines are opened up or shut down based on the player's choices. The game directly links both rewards and penalties to the player's choices, which establishes credibility with players that the game is not arbitrary but displays real-life consequences for all their actions. This credibility is necessary for the consequences of their sexual choices to be meaningful and impactful. When the player's flirtations succeed, a screen appears with their chosen partner and a range of sexual choices based on the sex of the player and their partner [33]. For each sexual act selected, the player is prompted to decide whether to use condoms. When the player clicks *Let's Get It On*, the player hears romantic music and fireworks burst onto the screen to imply sexual activity, with no graphic content displayed.

After the implied sexual activity, the music abruptly stops, and the player sees the estimated HIV risk their character just incurred (Figure 3). The player is then offered an opportunity to locate low-cost or free HIV testing sites near them by inputting their ZIP code or giving the game permission to read their phone's location. Data from the US Centers for Disease Control and Prevention testing locator appear with details on where to get tested locally (Figure 4). Although AYAs do not see their HIV risk immediately after a real-life sexual encounter, AYAs in this game are directly confronted by the reality of the risk their character incurs. Our phase 2 study will test whether this system helps reinforce the connection between sex and risk, thereby improving HIV testing.

Figure 1. Draft avatar editor system showing a sample character that can transition from masculine to feminine gender expression.

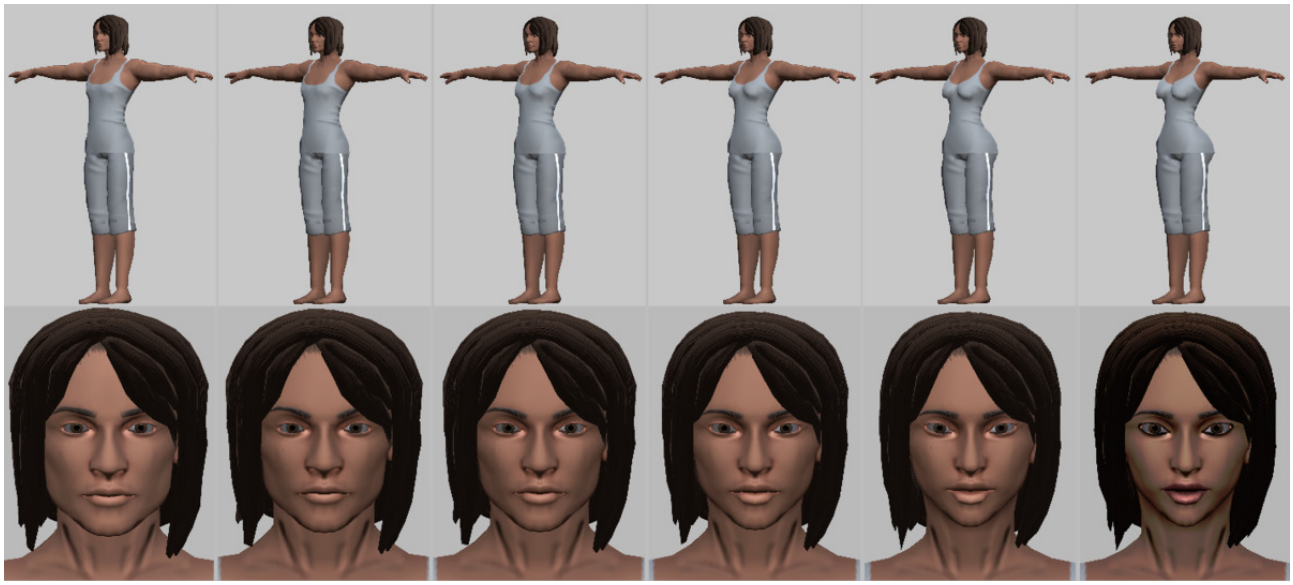


Figure 2. Draft scene of opposite sex and same sex flirtation.

Figure 3. Draft HIV risk screen adapted from the Centers for Disease Control and Prevention risk estimator tool.

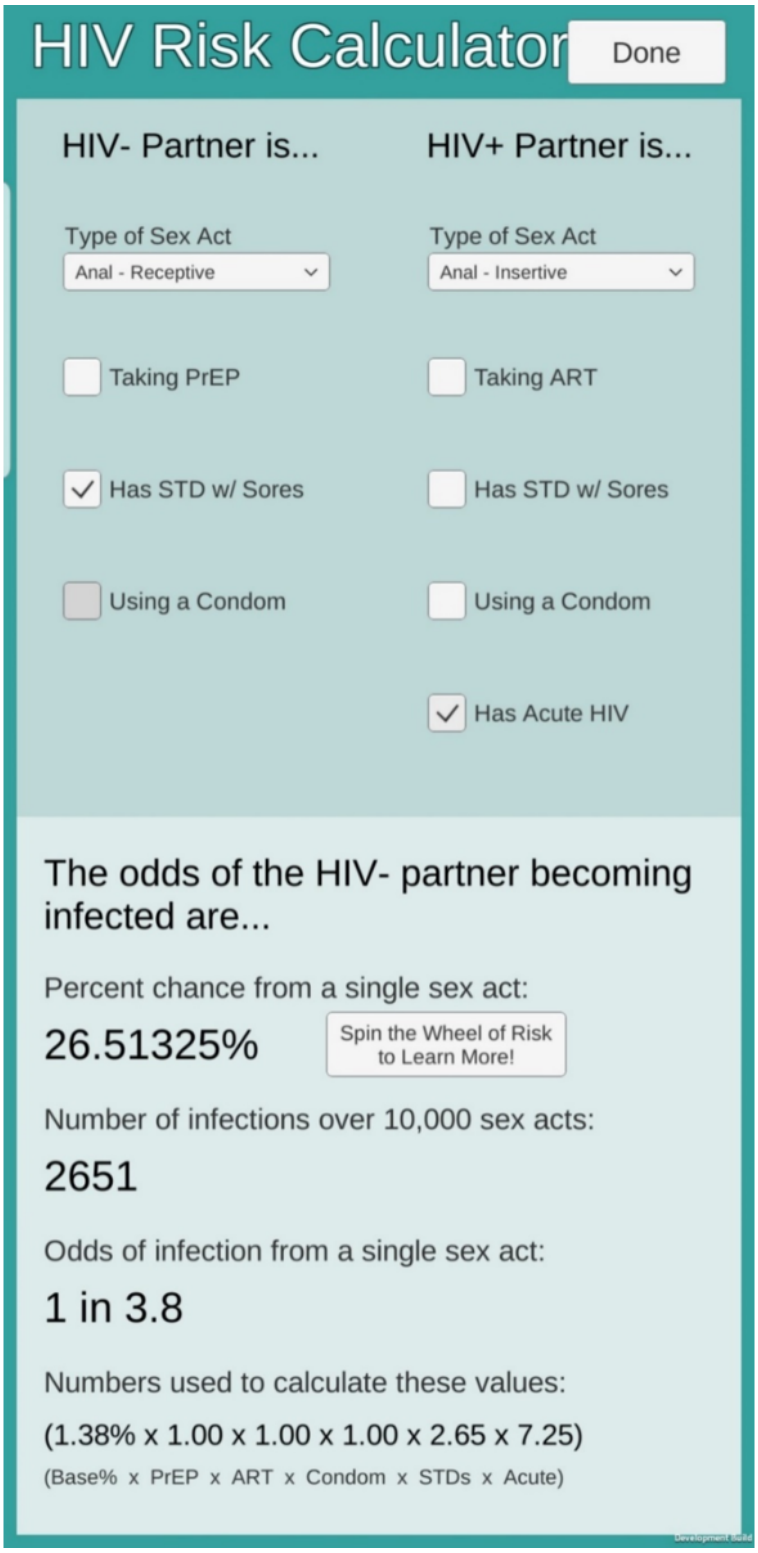
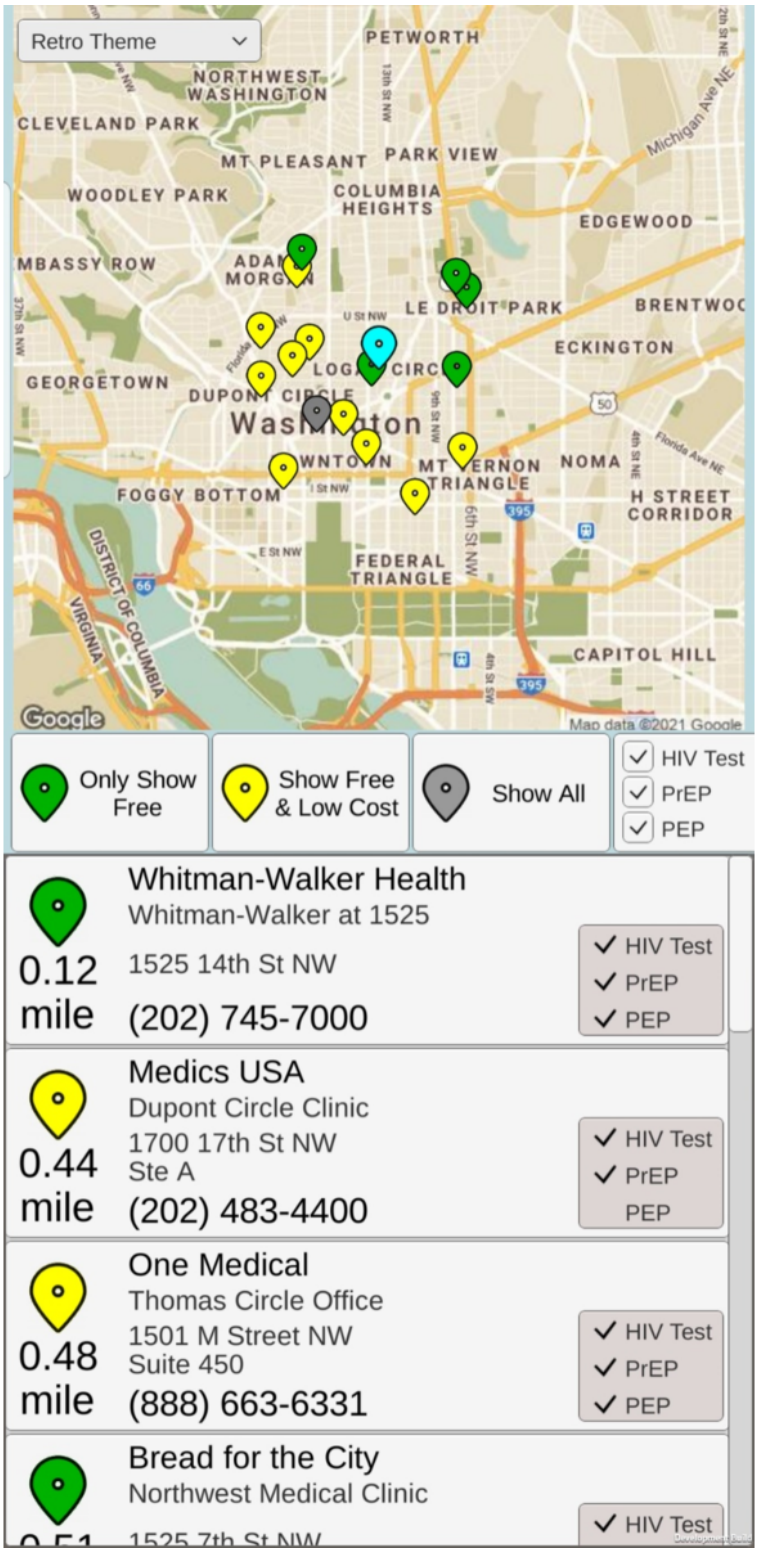


Figure 4. HIV prevention services locator based on publicly available the Centers for Disease Control and Prevention locators.



Formative Focus Groups

Focus groups will occur in 2 rounds (n=32 each) and will be conducted by ADC, DG, and BW, who have experience with qualitative research used to develop behavioral interventions. Focus group participants will be recruited via advertisements placed on various social media sites (eg, Facebook, Snapchat, and Instagram). Interested participants will be directed to a web-based eligibility screener in the REDCap (Research Electronic Data Capture) platform, a secure Health Insurance Portability and Accountability Act (HIPAA)–compliant web application designed exclusively to support data capture for research studies [34], to determine their age, gender, sexual behaviors and orientation, and state of residence. Eligibility will also be confirmed by the project staff via phone. Those eligible and interested will be sent a link to survey in REDCap, with the consent and assent forms embedded, meant to collect information on youth sociodemographics, use of games and

social media, knowledge of HIV and PrEP, sexual risk behaviors, and experiences with HIV testing and PrEP use. Eligible and interested participants will also provide information on the date and time of the focus. Focus groups will be stratified by sexual orientation (heterosexual vs lesbian, gay, bisexual, transgender, queer or questioning, and others [LGBTQ+]), and age (13-17 years vs 18-24 years). Before the focus groups, the research staff will review the consent and assent forms with participants and obtain verbal consent and assent before proceeding with the focus group.

Focus group questions cover the following topics: HIV and PrEP knowledge, perceptions and experiences regarding HIV testing, current use of and access to gaming technology (eg, use of smartphones, game consoles), perceptions regarding game enhancements and their potential role in increasing HIV testing and access to PrEP, perceptions about the role of social media and its influence on HIV testing behaviors, and opinions regarding effective recruitment approaches through social media. The enhanced life-simulation game will be demonstrated to participants, and feedback will be elicited regarding the acceptability and relevance of characters, texts, actions, and graphics, as they relate to race, culture, and structural factors. Following the focus group, participants will be sent the link to a survey in REDCap to assess their change in knowledge of HIV and PrEP as well as their satisfaction with the game prototype.

All focus groups will be audio recorded, and a verbatim transcription is professionally produced. The resulting text file will be entered into the qualitative data analysis software Atlas.ti 7.0 (ATLAS.ti Scientific Software Development GmbH) and analyzed using an a priori and open coding process aimed at identifying relevant themes and categories to inform the development of the game modifications for round 2 focus group testing as well as the final game prototype in the pilot test. Key decisions will include potential differences by age and sexual orientation, the types of games, art styles, social features, type or frequency of in-game bonuses, and responses of different kinds of in-game virtual rewards for actions such as demonstrating knowledge of HIV risks and virally spreading the game to peers. Game modifications will be made based on the initial focus group feedback (n=32), after which the second group of participants (n=32) will be recruited and shown the revised game. Survey data will be cleaned, downloaded, and exported into Excel or SAS files, and descriptive statistics will be analyzed. Pre- and postgame knowledge levels will be calculated; however, because of the small sample size, no statistical testing will be performed.

Pilot Test

Finalization of Game Prototype

If it is determined that AYA in the formative focus group does not like the enhanced life-simulation game, additional modifications will be made. Once the look and feel have been finalized, the game production team will implement v2.0, creating base code, audio, and 3D art or animation using the Unity *middleware* engine.

User Field Testing

Pilot test participants will be recruited via advertisements placed on various social media sites. Interested participants will be directed to a web-based eligibility screener in REDCap. Participant eligibility will be confirmed by the project staff via phone. Eligible participants will provide electronic consent and assent and complete the baseline survey electronically via a HIPAA-compliant participant management database. Participants will then be sent the gaming app electronically to download on their phone and will have unlimited access for 1 month. User pilot testing will allow project staff to identify any unanticipated issues with game log-ins, navigation, functionality, paradata collection, or other unforeseen technical issues. During user testing, game use as well as HIV testing and PrEP locator use will be monitored and paradata will be accessed for a 1-month period.

We will also pilot the use of the HIPAA-compliant participant management database for participant screening, survey collection, and data management and troubleshoot for any issues with phone connectivity, data caching, paradata collection, or other potential issues. Baseline data on HIV testing and knowledge will be collected to preliminarily describe the anticipated characteristics of our web-based sample. Measures of game satisfaction [35], usability [36], and a modified version of the motivation, attitude, knowledge, and engagement instrument [37] will also be piloted to determine how well the game addresses HIV knowledge and testing. At the end of the 1-month period, brief surveys and in-depth interviews (IDIs) will be conducted with the 10 pilot participants to elicit features of the games that worked well and identify those that might prohibit full use of the intervention.

Survey data will be cleaned, downloaded, and exported into Excel or SAS files. Given the small sample size and objectives of this study, quantitative analysis will be primarily descriptive to measure usability, acceptability, and satisfaction as well as to confirm baseline characteristics and behaviors of our intended study population. All interviews will be audio recorded, and verbatim transcription professionally produced. The resulting text file will be entered into the qualitative data analysis software Atlas.ti 7.0 and analyzed using an a priori and open coding process aimed at identifying potential barriers and facilitators to use. Critical and essential modifications will be made to the game, paradata, and HIPAA-compliant data management platforms before the RCT.

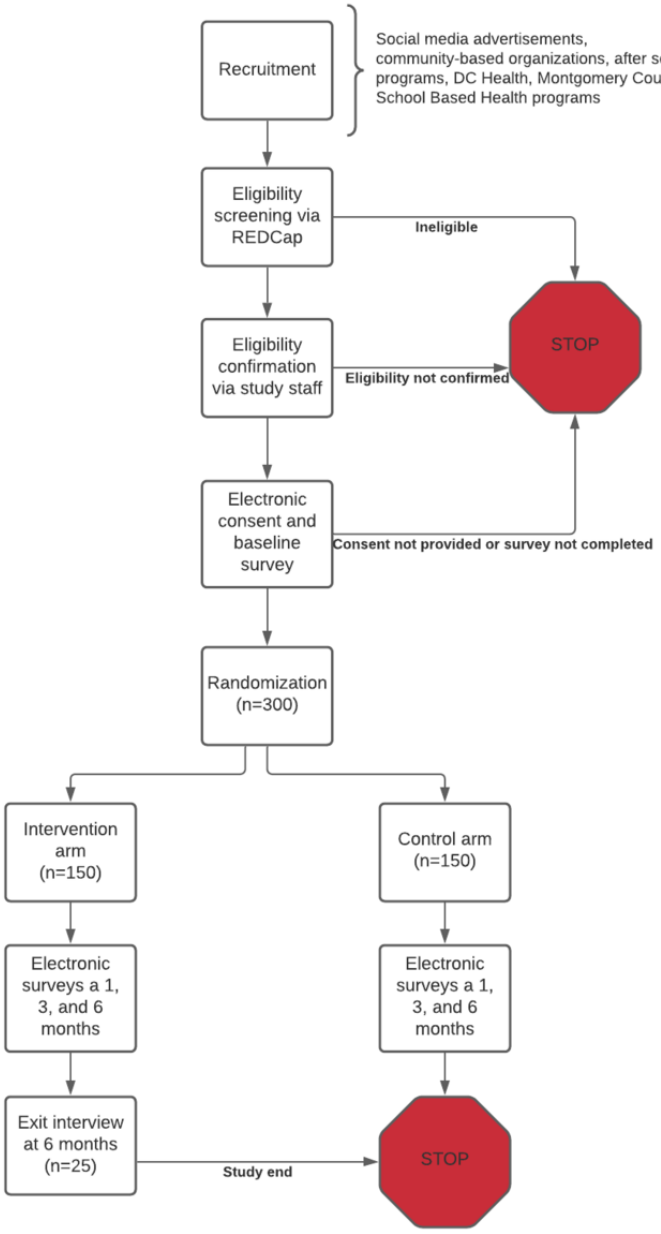
Randomized Controlled Trial

Overview

We will evaluate the impact of the life-simulation game compared with app-based HIV educational materials in an RCT with 300 AYAs. To enroll a sample representative of diverse racial or ethnic and sexual behaviors as well as a sample of non–clinic-attending AYAs, recruitment will occur primarily through social media. We will place targeted advertisements toward YMSM and Black and Hispanic AYAs on social media sites, such as Facebook, Instagram, and Snapchat. In addition, we will provide recruitment materials with quick response codes to the DC Health and Montgomery county school-based health

programs. Interested AYAs will click on an advertisement and be directed to a web-based eligibility screener to determine their age, gender, sexual behaviors and orientation, state of residence, and availability of a reliable cell phone. The eligibility of the participants will be confirmed by the project staff via phone. Eligible participants will then provide electronic consent and complete the baseline survey electronically. Participants will be randomized using the block randomization method designed to ensure groups of equal sample sizes (1:1). Participants will be randomized in blocks of 6, stratified by age (13-17 years and 18-24 years) and sexual behavior (LGBTQ+ vs heterosexual), using a random number generator for assignment. Randomization will occur through the HIPAA-compliant participant management database platform. We will compare conditions on HIV testing, knowledge, risk behaviors, and PrEP access at enrollment and at 1, 3, and 6 months post enrollment via electronic survey assessments. At 6 months, a subset of intervention participants (n=25) will participate in in-depth *exit* interviews regarding their experience being in the study. A schematic of the study design is shown in Figure 5.

Figure 5. Aim 3 study flow diagram. DC: District of Columbia; REDCap: Research Electronic Data Capture.



Intervention Delivery

Intervention participants will have access to the full revised study game for 3 months from the time of enrollment and will be able to play the game and have up to 30 hours of content available. To sustain interest and engagement over the study period and maximize potential efficacy, new downloadable game content will be available every 4 weeks post enrollment through the 3-month follow-up.

Control Condition

Before rolling out the RCT, we will develop an app that will include basic information on HIV (eg, routes of transmission, data on the epidemiology of HIV among youth, prevention information, and information on HIV testing and PrEP) as well

as a link to the HIV risk estimator and HIV testing and PrEP locators. Participants assigned to the control arm will receive a link to download this informational app containing this content and will have unlimited access to the app for a 3-month period.

Measures

Electronic surveys via REDCap will be used to assess the behavior at baseline and at 1, 3, and 6 months post enrollment, as it is confidential and allows for complex branching or skip patterns [34]. Participants will be emailed the REDCap surveys 7 days before their designated completion date, on their completion date, and 7 days after their completion date if not completed. Standard items will be administered to gather demographic data (including age, educational level, sexual orientation, socioeconomic status, race, and ethnicity). Surveys will collect information on the following validated domains: HIV- and PrEP-related knowledge; self-reported sexual and HIV risk behaviors; self-perceived risk for HIV; perceived norms; barriers to HIV testing; reported HIV testing and PrEP uptake; behavioral intentions including intent to test for HIV; seeking PrEP; and reducing risky behaviors, self-efficacy, and game use, interest, acceptability, and usability.

At 6 months, a purposely selected subset of intervention participants (n=25) will participate in IDIs regarding their experience being in the study. The IDIs will be conducted by trained qualitative interviewers and will follow semistructured interview guides. The IDIs will assess the extent to which app components facilitate or inhibit HIV testing. Central to the IDIs will be understanding the participants' use of the app. To obtain a range of perspectives, we will seek feedback from participants stratified by sexual behaviors (heterosexual vs LGBTQ+), age group (13-17 years vs 18-24 years), whether they sought and received HIV testing, and levels of game play and locator use based on the paradata (none, low-moderate, and high use).

Outcomes

Primary Outcomes

The primary outcome measure for the study is HIV testing. This will be measured as self-reported HIV testing in the past 6 months. For all participants who report testing, we will attempt to validate reported testing by eliciting a description of the HIV testing process and requesting that a secure photo of their test results be sent to study staff to minimize social desirability bias. We will compare self-reported HIV testing between the 2 groups at 6 months.

Secondary Outcomes

As self-reported measures tend to overestimate HIV testing and given the age range of our participants and potential structural barriers to the receipt of HIV testing among AYAs (eg, parental knowledge of testing, lack of transportation, inconvenient clinic times), a secondary outcome will be intent to test for HIV. The intent to test will be assessed using a validated 6-point Likert scale [38], shown to be predictive of future testing behavior, with responses ranging from *very unlikely* to *extremely likely* to test in response to the question. "how likely are you to get tested in the next 6 months?" We will dichotomize this score into *extremely likely* versus other. Other secondary outcomes will use previously published questions and validated scales (Table 1) and include changes in (1) HIV knowledge [39]; (2) risk perception [40] and behaviors (eg, condomless sex); (3) PrEP knowledge [41,42], screening [41,42], and uptake (also verified with a photograph of a pill bottle or prescription); (4) risk estimator scores and locator (HIV and PrEP) use; and (5) game acceptability [35] and usability [36], including frequency and duration of use, and reasons for continued or discontinued use.

Table 1. Measures planned for each phase.

Domain	Assessment time		
	Focus group	Pilot test	RCT[a]
Primary outcome			
HIV testing			
Tested during intervention period[b]	✓[c]	✓	✓
Interval and frequency of test	✓	✓	✓
Reason for test [43]	✓	✓	✓
Perceived benefit of HIV testing	✓	✓	✓
Secondary outcomes			
Behavioral intentions			✓
Intent to test [38]			✓
Intent to seek PrEP[d] [41]	✓		✓
Intent to reduce risky behaviors [44]			✓
HIV knowledge [39]	✓	✓	✓
Perceived susceptibility to HIV [40]			✓
Risk assessment			
Sexual behaviors	✓	✓	✓
Ever STD[e] diagnoses	✓	✓	✓
Alcohol and illicit drug use [45]	✓	✓	✓
Perceived norms [46]			✓
PrEP			✓
Knowledge and screening [41,42]	✓		✓
Use or uptake			✓
Self-efficacy or likelihood of action			
Ability to negotiate condom use [29]	✓		✓
Encourage partners or friends or peers to get HIV testing	✓		✓
Game and paradata			
Game downloads		✓	✓
Frequency and duration of game play		✓	✓
Game satisfaction [35]		✓	✓
Usability [36]		✓	✓
Teaching approach [37]		✓	✓
CDC[f] Risk Estimator scores		✓	✓
Number of linkages to HIV testing locator		✓	✓
Number of linkages to PrEP locator		✓	✓
Recommend app to friend or share on social media		✓	✓
Modifying factors			
Demographics	✓	✓	✓
Use of social media and gaming	✓	✓	✓
Exposure to health or sex education programs	✓	✓	✓
Perceived barriers to HIV testing	✓		✓

[a]RCT: randomized controlled trial.

[b]Verification of HIV testing and pre-exposure prophylaxis uptake will be conducted through photos and in-depth interviews.

[c]The tick mark indicates that the measure will be assessed during that specific phase of the study.

[d]PrEP: pre-exposure prophylaxis.

[e]STD: sexually transmitted disease.

[f]CDC: Centers for Disease Control and Prevention.

Statistical Analysis

In our pilot study [33], we found that approximately 10% of sexually active AYAs reported being tested for HIV in the past 4-6 months. A sample of approximately 300 subjects (150 per arm) would achieve >80% power to detect a moderate effect corresponding to a difference of at least 13 percentage points (equivalent to a relative risk of 2.3 assuming a 10% prevalence of HIV testing in the past 4-6 months in the control group) in HIV testing between the intervention and control groups after 6 months using a two-sided test at a 5% significance level and assuming a 16% attrition rate after 6 months. All data will be inspected for inaccurate input (eg, out-of-range values, implausible means, and variation). We will first summarize the outcome measures descriptively overall and within each intervention arm at each time point. We will make every effort to obtain all data. Any patterns of missingness will be investigated and reported. Sensitivity analyses, including rerunning analyses with imputed values for missing data, will be conducted to assess the impact of missingness on the study findings.

All primary analyses will be conducted using an intent-to-treat approach. The primary analysis will focus on differences between the treatment and control groups at the 6-month follow-up visit using a chi-square test for independence (the outcome will be taken as having had an affirmative response on the outcome measure during the 6-month study period). We will also investigate the differences between the rates of HIV testing in the treatment and control groups, stratifying by age (13-17 years vs 18-24 years) and sexual orientation (LGBTQ+ vs heterosexual identity). We will perform a longitudinal analysis on the repeated measures from each subject using logistic mixed effects models with a subject-specific random intercept. In each model, we will include time as a 4-level categorical predictor (with baseline serving as the reference level) as well as a treatment indicator and time-by-treatment interaction. We will jointly test the interaction coefficients to determine if the effect of treatment varies over time. If the effect is found to vary over time, we will test the intervention effect at each time point and characterize the difference between the treatment and control groups using risk differences and their corresponding 95% CIs. If no evidence of a time-by-treatment interaction is present, we will refit the logistic model without the interaction terms and provide the overall intervention effect and its corresponding 95% CI.

Furthermore, we will provide a descriptive analysis of each secondary outcome overall and within each intervention arm at each time point. Secondary outcomes will also be compared between the treatment and control groups using one-tailed *t* tests for continuous measures and chi-square tests for categorical measures. The corresponding group differences (in mean scores or proportions) and their 95% CIs will be reported. Within the intervention group, we will investigate game use changes over time and whether there exists a dose-response relationship between various game use indicators (eg, amount of time playing the game) and the various survey responses, including HIV testing, intent to test for HIV, PrEP uptake, and intent to seek PrEP as well as the other secondary outcomes. Qualitative data from IDIs will be transcribed and involve thematic coding using Atlas.ti version 7.0 to identify themes regarding intervention delivery and acceptability.

Incentives

For their participation in the formative focus groups, AYAs will receive a US $30 gift card and an additional US $10 gift card for a peer recruited who participates in the focus group. For their participation in the pilot test, AYAs will receive US $80 gift cards (US $20 for the baseline survey, US $30 for the 1-month survey, and US $30 for the IDI). For their participation in the RCT, AYAs will receive up to US $150 in gift cards (US $30 for the baseline survey, US $25 for the 1-month survey, US $25 for the 3-month survey, US$40 for the 6-month surveys, and US $30 for the IDI).

Ethical Considerations

To protect participants from potential loss of confidentiality, the following measures will be taken: informed consent and assent will be required for participation in the focus groups, pilot testing, and intervention. Each study participant will be assigned a pseudonym to participate in the focus groups, and interviews and surveys will be labeled with a study ID. Participants will be informed that individual results will not be shared, and only aggregate results will be disclosed at study completion. Summary statistical data stratified by age, race, or other categories may be released. However, if the total information will allow identification of the exact person or persons the information will not be released.

All study-related materials will only be accessible to the research staff. All data collection will take place with HIPAA-compliant software (ie, WebEx and REDCap). All study personnel have completed training and received certification in Human Subjects Research Protection (Collaborative Institutional Training Initiative Program) and HIPAA regulations and will continue to renew this training in compliance with institutional review board policies. We will adapt measures successful in other studies to reduce the risk of potential breaches by using passwords, not sending any sensitive information, and eliciting AYAs' preferred method of communication and receipt of study information (eg, surveys and incentives).

Results

The study was funded on April 2, 2020. The protocol has been reviewed and approved by the George Washington Institutional Review Board (NCR191708) on February 5, 2020 and was

registered on ClinicalTrials.gov (NCT04917575). Data collection for the formative phase is projected to begin in June 2021.

Discussion

Review

The life-simulation gaming intervention aims to increase HIV testing and PrEP access among AYAs by reducing individual and structural barriers. Through digital content aligned with SCT and the HBM, the intervention attempts to positively influence youth self-efficacy, risk perceptions, and knowledge of HIV prevention as well as influence AYAs' social support.

Limitations and Anticipated Challenges

There are several potential challenges to the success of our trial. First, if it is determined that AYAs in the formative focus groups do not like the proposed enhancements, we will modify the game accordingly. Second, for all 3 phases, we plan to intentionally recruit AYAs who are not regular clinic attendees and rely primarily on social media recruitment. If this proves challenging, we will consider expanding recruitment to local community-based organizations that are not HIV focused and consider recruiting from after-school programs or events geared toward AYAs. Third, although web-based recruitment is ideal to identify our population of interest, there is a risk of fraud, and we plan to have staff verify the eligibility of potential participants. Finally, AYAs' gaming preferences change far faster than the pace of research. Avatar clothes and other in-game items may no longer be popular during the game's release. The software architecture is designed to be modular and flexible to allow many elements to be altered both before and after release. To ensure adequate game content to keep AYAs engaged during the study period, as per industry standards, we will build in frequent releases of new game content.

Conclusions

As the number of new HIV infections among AYA continues to grow, innovative methods to scale up HIV prevention for this population are required. The results of this study will be useful for understanding the extent to which a digital game can increase HIV testing and PrEP access among AYAs. If effective, we will work with the local health departments, health clinics, and school-based clinics to make the game available to their students and patients. We will also look into making the game and locators relevant and available to AYAs living in areas of the United States with some of the highest rates of HIV infection, such as the Southern United States.

Conflicts of Interest

DG, a principal investigator on the grant, has a stake in Media Rez consistent with the policy on Small Business Innovation Research.

Multimedia Appendix 1
Peer-review report by the Center for Scientific Review Special Emphasis Panel, Small Business: Disease Prevention and Management, Risk Reduction and Health Behavior Change (National Institutes of Health).
[PDF File (Adobe PDF File), 173 KB - resprot_v10i6e29792_app1.pdf]

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Abbreviations

AYA: adolescents and young adults
HBM: health belief model
HIPAA: Health Insurance Portability and Accountability Act
IDI: in-depth interview
LGBTQ+: lesbian, gay, bisexual, transgender, queer or questioning, and others
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SCT: social cognitive theory
YMSM: young men who have sex with men

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Protocol

Physical Activity Together for People With Multiple Sclerosis and Their Care Partners: Protocol for a Feasibility Randomized Controlled Trial of a Dyadic Intervention

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Abstract

Background: Physical activity (PA) is beneficial for all people; however, people affected by multiple sclerosis (MS) find regular PA challenging. These people may include individuals with advanced disabilities and their care partners.

Objective: The objective of this study is to determine the feasibility of a dyadic PA intervention for people with advanced MS and their care partners.

Methods: This study is a randomized controlled feasibility trial of a 12-week intervention, with 1:1 allocation into an immediate intervention condition or delayed control condition. A target of 20 people with MS–care partner dyads will be included. The outcomes will be indicators of process, resources, management, and scientific feasibility. Participant satisfaction with the intervention components will be evaluated using a satisfaction survey. The subjective experience of participation in the study will be explored using semistructured interviews.

Results: The project is funded by the Consortium of Multiple Sclerosis Centers. This protocol was approved by the Ottawa Hospital Research Ethics Board (20190329-01H) and the University of Ottawa Research Ethics Board (H-09-19-4886). The study protocol was registered with ClinicalTrials.gov in February 2020. The findings of this feasibility trial will be disseminated through presentations at community events to engage the MS population in the interpretation of our results and in the next steps. The results will also be published in peer-reviewed journals and presented to the scientific community at national and international MS conferences.

Conclusions: The data collected from this feasibility trial will be used to refine the intervention and materials in preparation for a pilot randomized controlled trial.

Trial Registration: ClinicalTrials.gov NCT04267185; https://clinicaltrials.gov/ct2/show/NCT04267185.

International Registered Report Identifier (IRRID): PRR1-10.2196/18410

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KEYWORDS

multiple sclerosis; advanced disability; care partners; physical activity; dyadic intervention; feasibility randomized controlled trial

Introduction

Background

Multiple sclerosis (MS) is a neurodegenerative disease characterized by a variable course and largely unpredictable exacerbations leading to progressive disability [1]. Within 15-20 years of disease onset, it is estimated that approximately 50% of people with MS will require a walking aid (eg, cane) to walk about 100 m with or without rest (ie, Expanded Disability Status Scale [2] score≥6) [3]. Approximately 40%-80% of people with MS with walking impairment report a need for support from informal care partners to engage in everyday activities and to participate in aspects of daily life that are important and meaningful to them [4-6]. Care partners are relatives, family members, or friends who provide a broad spectrum of assistance, ranging from help in activities of daily living to emotional support for people with MS [7]. Although there are positive aspects of MS caregiving [8], the negative effect on care partners' own well-being is often great. MS care partners report poorer quality of life than the general population [9]. These MS care partners also experience a higher level of activity limitations, more emergency department visits, and hospitalizations than care partners of people with other chronic diseases [10]. Together, this evidence suggests that MS has life-altering consequences for people with MS and their care partners and points to an opportunity to identify strategies to improve the health of *both* partners to the benefit of each individual and the dyad (ie, partnership).

Physical activity (PA) is a health-promoting behavior in the general population and an emerging strategy for managing MS [11]. Researchers have reported that PA interventions that incorporate behavioral strategies (eg, goal setting) can increase PA levels and improve symptomatic and participatory outcomes among people with mild-to-moderate MS [12,13]. Emerging evidence from other chronic disease contexts (eg, dementia) suggests that dyadic behavioral PA interventions (ie, targeting *both* care recipients and care partners) can increase PA levels, improve physical and psychological health, and improve exercise adherence for both individuals [14,15]. Other researchers have reported a reduction in stress and improvement in coping skills among care partners of people with dementia after dyadic PA interventions [16,17]. Despite the promise of dyadic PA interventions, no studies to date have capitalized on the potential benefits of including both people with advanced MS and their care partners together as *active participants* in a dyadic behavioral PA intervention. We contend that a dyadic behavioral PA intervention could improve the well-being of people with MS and could help care partners maintain their roles for longer periods with lower health risks.

Within the literature specific to people with MS, there is limited research on behavioral PA interventions that can be widely disseminated for people with advanced MS who experience mobility and transportation limitations [18] and require high levels of caregiving support [19]. Dyadic health researchers have also been challenged to integrate telerehabilitation into intervention design to provide more sustainable and widely disseminated behavioral interventions for dyads with chronic health conditions [20]. Telephone delivery is one of the most widely available telerehabilitation modalities and holds distinct promise for its potential for adoption by public health systems and organizations (eg, MS Societies) that routinely provide telephone support for people with chronic health conditions [21,22]. In particular, group-based teleconferencing offers the added benefit of social modeling, social support, and opportunities for vicarious learning experiences [23,24]. Collectively, existing evidence suggests that telephone-based PA interventions have the potential to increase PA and improve the health of people with MS and their care partners.

Objectives

The objective of this study is to conduct the first randomized controlled trial (RCT) to determine the feasibility of a dyadic behavioral PA intervention—Physical Activity Together for People With Multiple Sclerosis (PAT-MS) and their care partners. Specifically, we will explore the 4 primary areas of focus of feasibility studies (ie, process, resources, management, and scientific feasibility) [25,26] recommended for PA studies involving people with MS [27].

Methods

Study Design

This protocol has been written following both the Standard Protocol Items: Recommendations for Interventional Trials and Consolidated Standards of Reporting Trials guidelines [28,29] (Multimedia Appendix 1). We will conduct a single site, assessor-blinded, parallel group, randomized controlled feasibility trial using a 1:1 allocation into an immediate intervention condition or a delayed intervention condition. A delayed intervention condition was deemed appropriate for PAT-MS based on the decision framework for appropriate control conditions for behavioral intervention trials [30,31].

Participants

Sample Size

As a feasibility trial, this study will provide robust estimates of the likely rates of recruitment and retention as well as estimates of the variability of the proposed scientific outcomes to inform a well-designed pilot RCT. With these considerations in mind, our goal is to recruit 10 people with MS–care partner dyads per condition within a 6-month recruitment window, consistent with sample size guidelines for feasibility trials [32] and previously published exercise trials for people with advanced MS [33]. Enrolling 10 dyads per condition will account for approximately 15% attrition rate, as recommended for feasibility trials [34].

Recruitment and Enrolment

Potential participants will be provided with a study information sheet at the local MS clinic and asked for consent to be contacted by the research team. A research coordinator will then contact interested participants by phone to discuss the study and conduct eligibility screening.

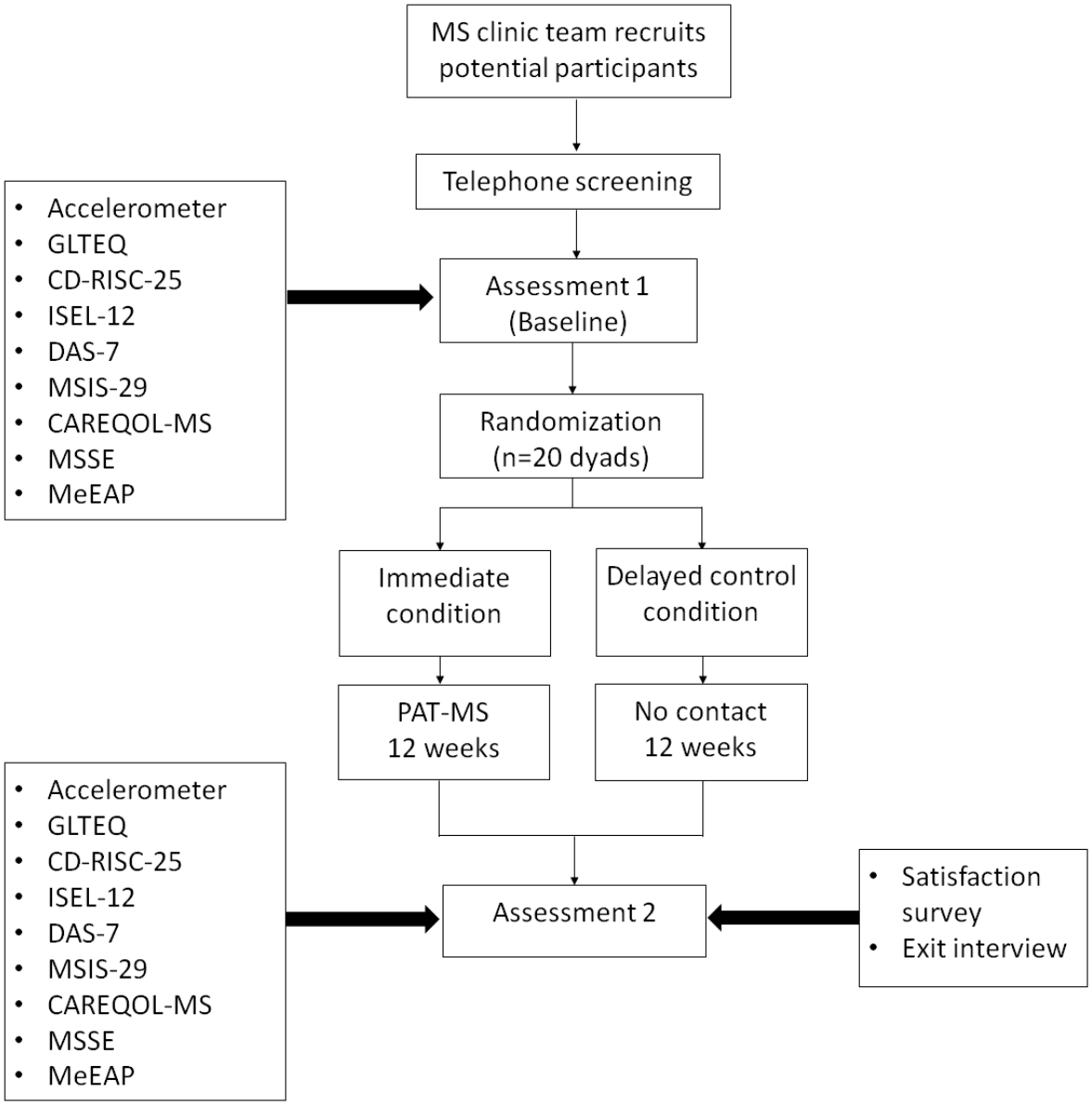
The inclusion criteria for people with MS are as follows: (1) a neurologist-confirmed MS diagnosis and stable course of disease-modifying therapies over the past 6 months, (2) an Expanded Disability Status Scale score between 6.0 and 6.5 based on a neurostatus-certified assessor examination, (3) relapse free in the past 30 days, and (4) having a care partner (ie, relative or close friend) who provides ≥1 hour per day of unpaid assistance or help. Additional inclusion criteria for both people with MS and care partners are as follows: (1) ≥18 years of age, (2) currently inactive (ie, purposeful exercise ≤2 days per week for 30 min), and (3) asymptomatic (ie, no major signs or symptoms of acute or uncontrolled cardiovascular, metabolic, or renal disease) based on the Get Active Questionnaire. The exclusion criteria for both people with MS and care partners are (1) presence of other neurological conditions and (2) inability to communicate in English.

Study Procedures

Figure 1 presents the flow of participants throughout the study. All eligible participants will be scheduled for a baseline assessment (T1) for the provision of informed consent and collection of baseline data (scientific feasibility outcomes) at a university research laboratory. People with MS and their care partners will complete the measures in separate rooms to ensure privacy and confidentiality during the data collection process. Outcome measures will be collected by treatment-blinded assessors who are experienced with the administration of the proposed measures. In the 7 days following the baseline assessment, both people with MS and their care partners will be asked to wear an accelerometer during all waking hours. The accelerometer will be placed in a pouch on an elastic belt worn around the waist, with the device placed on the nondominant hip. Prestamped, preaddressed envelopes will be provided for the return of the accelerometer. Randomization will occur after baseline data collection.

The randomization sequence will be generated by an independent biostatistician using 1:1 permutated block randomization. Variable-sized blocks will be used to ensure approximately equal numbers in the 2 trial conditions. Participants will then complete the immediate intervention condition or the delayed intervention condition (ie, maintenance of usual activities) for 12 weeks. The same scientific feasibility outcomes as the baseline will be repeated immediately after the intervention (T2). We anticipate that each assessment session will last for approximately 2 hours. At the completion of the intervention, participants will also be asked to complete a satisfaction survey and an individual exit interview to assess their satisfaction with specific intervention components (ie, intervention content, interventionist, and delivery method) and their subjective experiences of participation in all aspects of PAT-MS, respectively. People with MS and their care partners will complete the same surveys. We anticipate that the survey will take approximately 15 minutes to complete. Individual exit interviews will be conducted over the phone by a member of the research team and will last for approximately 30 minutes. The same interview guide will be used for people with MS and their care partners. Participants in the delayed intervention condition will receive the intervention after the postintervention assessment (T2). We will follow the same intervention delivery procedures for the delayed condition as for the immediate intervention condition.

Figure 1. Flow of participants through the study. CAREQOL-MS: Caregiver Quality of Life in Multiple Sclerosis Scale; CD-RISC-10: Connor-Davison Resilience Scale; DAS-7: Short-form Dyadic Adjustment Scale; GLTEQ: Godin Leisure-Time Exercise Questionnaire; ISEL-12: Interpersonal Support Evaluation List-12; MeEAP: Measure of Experiential Aspects of Participation; MS: multiple sclerosis; MSIS-29: Multiple Sclerosis Impact Scale-29; MSSE: Multiple Sclerosis Self-Efficacy Scale; PAT-MS: Physical Activity Together for People With Multiple Sclerosis.



Intervention

PAT-MS is a dyadic behavioral PA intervention approach that incorporates a toolbox of evidence-based strategies adapted from previous trials on promoting PA in care partners of people with Alzheimer disease [35,36], a comprehensive program of research [20,37-39], and input from people with MS and care partners. PAT-MS is grounded in the theory of dyadic illness management [40]. Behavior change techniques [41] that target key theoretical constructs from the social cognitive theory [42] and self-determination theory [43] are included to facilitate behavior change. The social cognitive theory and self-determination theory have proven effective for increasing PA in the general population [44] and among people with MS [45-47]. Table 1 provides a summary of the content and main behavior change techniques [41] that will be targeted across the six teleconference sessions. In brief, the intervention includes the following main components:

- Education: Participants will be provided with a PAT-MS manual that includes information on PA and introduces the concepts of shared appraisal of disease impact and dyadic coping. The benefits of shared participation in PA as a coping strategy to optimize well-being at the individual and dyadic levels will be discussed.
- Guidance from a trained interventionist: Participants will be provided with specific verbal and written guidance to improve their confidence in engaging in PA behavior. Given that PA interventions are more effective when combined with behavior change techniques [48], PAT-MS will include

techniques commonly used in dyadic health interventions for persons with chronic neurological conditions and their care partners [20]. These techniques include, but are not limited to, goal setting and review, problem solving and action planning, behavioral practice, and instruction from a credible source.

- Social support: Participants will be provided practical, emotional, and informational social support during the intervention (eg, links to community programs for continued PA participation and opportunities to engage with and learn from other group members).

Intervention Structure and Delivery

People with MS–care partner dyads will receive six group teleconferencing sessions (approximately 60 min each) every other week for a period of 12 weeks (Table 1). Each session is structured to include a review of material from the previous week, teaching content, group discussions, and explanation of practice activities to be completed before the next session. The group sessions will be interspersed with brief (approximately 15 min each) one-on-one support telephone calls in the weeks in which the group sessions do not occur. The intervention schedule will provide regular contact with the research team but will recognize the time commitment of the participants. We will seek to have 2-3 dyads on each teleconference call to manage the call more easily and to monitor the intervention process. The group-based teleconference format will provide opportunities for social modeling, social support, and vicarious learning experiences [23,24], which in turn will support behavior change, consistent with the theoretical foundations of PAT-MS [42,43]. Makeup sessions will be offered to those who miss teleconference sessions. The intervention will be delivered by a trained interventionist who will be provided with a structured manual for intervention delivery. Compliance to the protocol by the interventionist will be monitored using a checklist, weekly review meetings, and episodic monitoring of the teleconference sessions according to the guidelines of Bellg [49].

Outcomes

The outcomes will relate to process, resources, management, and scientific feasibility, as outlined below.

Process Outcomes

Process outcomes will include assessing recruitment rates (ie, response of participants to recruitment strategies, number of potential participants who remain interested in the study after information and screening, and reasons for refusal to participate).

Resource Outcomes

Resource outcomes will include assessing the rates of participant compliance (ie, number of practice activities, teleconference sessions, and one-on-one phone calls completed), attrition (ie, percentage of participants who drop out of the study and reasons for dropping out), suitability of eligibility criteria (ie, percentage of interested participants who meet the inclusion criteria and reasons for exclusion), and total cost of intervention delivery (ie, cost of equipment, personnel, and participant remuneration).

Management Outcomes

Management outcomes will include assessing staff time (ie, staff preparation and training time, call time, attempted call time, and report-taking time), use of technical support (ie, number of equipment-related data collection problems and number of technical support calls made by staff and/or participants), intervention fidelity (ie, interventionist's compliance to the protocol), and efficiency and accuracy of data collection and entry (ie, data completeness and time to collect, enter, and check data).

Scientific Outcomes

These will include assessing safety, treatment effect, participant satisfaction with intervention components (ie, intervention content, interventionist, and delivery method), and subjective experience of participating in the intervention.

Safety

Safety will involve reporting of adverse events (AEs). AEs are defined as any unfavorable change in health experienced by a participant during the trial period [50]. Each AE will be rated based on severity (grade 1 [mild] through 5 [death]), expectedness, and potential relation to study participation (ie, not related, possibly related, or definitely related) using the National Institutes of Health terminology and classification scheme [50]. AEs will be reported as the overall rate, severity, and characteristics of the AEs.

Table 1. Timing, content, and main behavior change techniques in Physical Activity Together for People With Multiple Sclerosis.

Timing, description, and overview of session content	Code for behavior change techniques included in each session	Main behavior change techniques included in each session
Week 1		
Teleconference 1		
Getting started	2.3	Self-monitoring of behavior
Ground rules for the teleconference sessions	3.3	Social support (emotional)
Understanding the basics of physical activity	4.1	Instruction on how to perform the behavior
How much physical activity do you need?	5.1	Information about health consequences
Is it safe for you to participate in physical activity?	5.4	Monitoring of emotional consequences
Setting up a physical activity program	9.1	Credible source
Recording your baseline physical activity	N/A[a]	N/A
Explanation of practice activity	N/A	N/A
Week 2		
Phone call 1		
Monitoring and providing individualized support, advice, and encouragement	1.2	Problem solving
Promoting accountability, maintaining motivation, and troubleshooting	3.2	Social support (practical)
N/A	9.1	Credible source
Week 3		
Teleconference 2		
Dyadic coping	1.1	Goal setting (behavior)
Review material from last session	1.2	Problem solving
Understanding dyadic coping	3.3	Social support (emotional)
Setting physical activity goals	4.1	Instruction on how to perform the behavior
Setting goals in PAT-MS[b] physical activity log	8.1	Behavioral practice
Explanation of practice activity	9.1	Credible source
Week 4		
Phone call 2		
Monitoring and providing individualized support, advice, and encouragement	1.2	Problem solving
Promoting accountability, maintaining motivation, and troubleshooting	3.2	Social support (practical)
N/A	9.1	Credible source
N/A	10.4	Social reward
Week 5		
Teleconference 3		
Action planning	1.2	Problem solving
Review material from last session	1.4	Action planning
What can physical activity do for people with multiple sclerosis?	1.5	Review behavior goals
What can physical activity do for support partners?	1.6	Discrepancy between current behavior and goal

Timing, description, and overview of session content	Code for behavior change techniques included in each session	Main behavior change techniques included in each session
Developing an action plan for meeting physical activity goals	2.3	Self-monitoring of behavior
Explanation of practice activity	5.1	Information about health consequences
N/A	8.1	Behavioral practice
N/A	8.7	Graded tasks
N/A	9.1	Credible source
N/A	10.4	Social reward
Week 6		
Phone call 3		
Monitoring and providing individualized support, advice, and encouragement	1.2	Problem solving
Promoting accountability, maintaining motivation, and troubleshooting	3.2	Social support (practical)
N/A	9.1	Credible source
N/A	10.4	Social reward
Week 7		
Teleconference 4		
Staying motivated	1.2	Problem solving
Review material from last session	1.5	Review behavior goals
Understanding motivation	1.6	Discrepancy between current behavior and goal
Staying motivated to increase your physical activity	2.3	Self-monitoring of behavior
Explanation of practice activity	7.1	Prompts or cues
N/A	8.1	Behavioral practice
N/A	8.7	Graded tasks
N/A	9.1	Credible source
N/A	10.4	Social reward
Week 8		
Phone call 4		
Monitoring and providing individualized support, advice, and encouragement	1.2	Problem solving
Promoting accountability and troubleshooting	3.2	Social support (practical)
N/A	9.1	Credible source
N/A	10.4	Social reward
Week 9		
Teleconference 5		
Building support	1.1	Goal setting (behavior)
Review material from last session	1.2	Problem solving
Building a strong support system	1.5	Review behavior goals
Types of social support	1.6	Discrepancy between current behavior and goal
Explanation of practice activity	2.3	Self-monitoring of behavior
N/A	8.1	Behavioral practice
N/A	8.7	Graded tasks

Timing, description, and overview of session content	Code for behavior change techniques included in each session	Main behavior change techniques included in each session
N/A	9.1	Credible source
N/A	10.4	Social reward
Week 10		
Phone call 5		
Monitoring and providing individualized support, advice, and encouragement	1.2	Problem solving
Promoting accountability and troubleshooting	3.2	Social support (practical)
N/A	9.1	Credible source
N/A		Social reward
Week 11		
Teleconference 6		
Final tips	1.1	Goal setting (behavior)
Review material from last session	1.2	Problem solving
Making physical activity a life-long habit	1.5	Review behavior goals
Closing comments	9.1	Credible source
N/A	9.3	Comparative imagining of future outcomes
N/A	10.4	Social reward
Week 12		
Phone call 6		
Monitoring and providing individualized support, advice, and encouragement	1.2	Problem solving
Promoting accountability and troubleshooting	3.2	Social support (practical)
N/A	9.1	Credible source
N/A	10.4	Social reward

[a]N/A: not applicable.

[b]PAT-MS: Physical Activity Together for People With Multiple Sclerosis.

Treatment Effect

This will involve assessing changes in the following outcomes between T1 (baseline) and T2 (12 weeks): accelerometer-measured PA, self-reported PA, resilience, social support, dyadic relationship quality, quality of life, MS self-efficacy, experiential aspects of participation, and coping. Table 2 provides a summary of the treatment outcomes and psychometric properties of the outcome measures included in the study.

Table 2. Treatment effect outcomes, outcome measures, and psychometric properties.

Outcome, outcome measure and psychometric properties	Reliability and validity statistics	Intraclass correlation coefficient
Change in accelerometer-measured PA[a] (ie, minutes of sedentary, light, and moderate-to-vigorous activity)		
ActiGraph model GT3X-BT accelerometer [51]		
Validity	r_s=0.61, 95% CI 0.47-0.71	N/A[b]
Test-retest reliability	r_s=0.49, 95% CI 0.40-0.57	0.84, 95% CI 0.81-0.87
Change in self-reported PA (ie, total PA minutes)		
Godin Leisure-Time Exercise Questionnaire [52-54]		
Convergent validity	*r*=0.38-0.7; *P*<.01	N/A
Divergent validity	*r*=−0.32 to −0.45; *P*<.01	N/A
Test-retest reliability	*k* coefficient=0.40, 95% CI 0.21-0.60	0.74, 95% CI 0.69-0.78
Change in resilience		
Connor-Davison Resilience Scale [55,56]		
Internal consistency	Cronbach α=.89	N/A
Test-retest reliability	N/A	0.87
Convergent validity	*r*=0.83; *P*<.001	N/A
Change in social support		
Interpersonal Support Evaluation List-12 [57,58]		
Internal consistency	Cronbach α=.82	N/A
Convergent validity	*r*=0.33-0.40; *P*<.001	N/A
Change in dyadic relationship quality		
Short-form Dyadic Adjustment Scale [59,60]		
Internal consistency	Cronbach α=.78	N/A
Construct validity	*r*=0.38-0.72; *P*<.01	N/A
Change in quality of life among people with MS[c]		
Multiple Sclerosis Impact Scale-29 [61,62]		
Reliability	Cronbach α≥.89 for all subscales	N/A
Convergent validity	r_s≥0.57; *P*<.001	N/A
Change in quality of life among MS care partners		
Caregiver Quality of Life in Multiple Sclerosis Scale [63]		
Internal consistency	Cronbach α≥.75 for all subscales	N/A
Test-retest reliability	Weighted *k*≥0.46	N/A
Construct validity	N/A	0.96; *P*<.001
Change in MS self-efficacy		
Multiple Sclerosis Self-Efficacy Scale [64]		
Internal consistency	Cronbach α=.81	N/A
Test-retest reliability	*r*=0.81; *P*<.001	N/A
Construct validity	r_s≥0.55; *P*<.01	N/A
Change in experiential aspects of participation		
Measure of Experiential Aspects of Participation [65]		

Outcome, outcome measure and psychometric properties	Reliability and validity statistics	Intraclass correlation coefficient
Internal consistency	Cronbach α≥.95 for all subscales	N/A
Convergent validity	N/A	≥0.62; *P*<.001 for all subscales
Change in coping among MS care partners		
Coping with Multiple Sclerosis Caregiving Inventory [66]		
Internal consistency	Cronbach α≥.57 for all subscales	N/A

[a]PA: physical activity.

[b]N/A: not applicable.

[c]MS: multiple sclerosis.

Satisfaction With Intervention Components—Content, Interventionist, and Delivery Method

This will be assessed in both people with MS and care partners using a satisfaction survey developed for this study. Items will be scored using a 5-point Likert-type scale, with higher scores reflecting greater satisfaction.

Subjective Experience of Participation in All Aspects of PAT-MS

This will be explored in both people with MS and care partners using a semistructured exit interview. Suggestions for intervention improvement and participants' willingness and concerns regarding future participation in PA will also be explored.

Data Management and Analysis

Quantitative Data Analysis

Data management and analysis will be performed using IBM SPSS Statistics for Windows (IBM Corp). Descriptive statistics, including means and SDs (continuous variables) and frequencies and proportions (categorical variables), will be used to summarize all demographic and feasibility data. Within-subject changes and effect sizes for improvement in scientific outcomes from T1 to T2 will be calculated using Cohen *d* separately for people with MS and care partners and by condition (immediate vs delayed control).

Qualitative Data Analysis

All audiorecorded interviews will be transcribed and anonymized before the analysis. The qualitative analysis will be underpinned by a social constructivism paradigm [67], which will allow exploration of the meaning and understanding of the experiences of our participants relative to participation in PAT-MS. The systematic six-phase process of thematic analysis as described by Braun and Clark [68] will be undertaken. The rigor of the qualitative analysis will be maximized through a range of strategies recommended by Smith and McGannon [69].

Determining Progression to a Definitive Trial

Progression to a pilot RCT will be considered if minimum success criteria are achieved in key feasibility metrics or if we can identify strategies for overcoming any identified challenges in these areas [70]. These criteria were selected based on the guidelines for prospectively defining progression to future evaluative studies [71,72]. The criteria include the following:

- A minimum of 50% of the intended 20 dyads are recruited within a 6-month recruitment window
- A minimum of 70% participant compliance
- Study satisfaction ≥4/5 on the satisfaction survey
- Less than 10% of participants report a serious AE
- Less than 20% participant attrition.

Ethics Approval and Consent to Participate

This protocol was approved by the Ottawa Hospital Research Ethics Board (20190329-01H) and the University of Ottawa Research Ethics Board (H-09-19-4886). The trial is conducted in compliance with the Declaration of Helsinki. Informed written consent will be obtained from all the participants.

Results

The project is funded by the Consortium of Multiple Sclerosis Centers. This protocol was approved by the Ottawa Hospital Research Ethics Board (20190329-01H) and the University of Ottawa Research Ethics Board (H-09-19-4886). The study protocol was registered with ClinicalTrials.gov (NCT04267185) in February 2020. The findings of this feasibility trial will be disseminated through presentations at community events to engage the MS population in the interpretation of our results and in the next steps. The results will also be published in peer-reviewed journals and presented to the scientific community at national and international MS conferences.

Discussion

Principal Findings

Several direct outcomes are anticipated from this trial. First, the delivery of this trial will provide important insights for the research team on the practicality of running a future pilot trial, if the proposed intervention is feasible. Second, this trial will provide key information on the feasibility of PAT-MS, including estimates of recruitment, compliance, and attrition. It will also enable us to assess the acceptability of the intervention from the participants' perspective. Finally, conducting this work will lead to the development of a manualized research protocol for

PAT-MS. This manual will include the recruitment and selection criteria, details about the intervention and training of intervention staff, recommendations for managing study logistics, and possible challenges and strategies for overcoming them. The development of this manual will facilitate the delivery of future efficacy and effectiveness trials, including those using a multicenter approach. In addition, it will ensure the fidelity of the intervention and its long-term delivery in community, health care, or other multiservice settings.

Strengths and Limitations

The PAT-MS intervention is unique in several ways. PAT-MS uses a novel approach that combines both people with MS and their care partners together as active and collaborative participants in the intervention. There are potential synergistic benefits of this intervention on the health of each partner individually and on the dyad (ie, partnership). In addition, the focus on people with advanced MS disability is novel, as few interventions target this segment of the MS population. This MS cohort requires accessible strategies for disease management and requires high levels of caregiving support. Finally, the use of a telerehabilitation offers a cost-effective strategy for widespread long-term dissemination and is one of the preferred delivery formats for PA interventions among people with MS [73].

When executing the proposed trial, foreseeable challenges are compliance and attrition, which may be related to disease symptoms, comorbidities, or changes in medications. Care partners who are often working outside of the home, in addition to their caregiving role, may perceive participating in the intervention as a dyad to be burdensome, rather than beneficial. We have incorporated various methods into the study design to maximize retention and compliance: (1) flexibility in assessment sessions and phone call times; (2) follow-up by telephone and makeup session options; (3) offsetting participation costs through remuneration, toll-free calling, and reserved parking for testing visits; (4) including intervention content on the potential benefits of regular PA participation and how participants can safely engage in PA; and (5) incorporating behavior change techniques and using group-based delivery to reinforce social support, social modeling, and vicarious learning. Another potential challenge is the fidelity of the intervention. To promote the standard application of the intervention, an interventionist manual will be provided and incorporated into the interventionist's training.

Conclusions

This is the first study to examine the feasibility of the PAT-MS intervention. PAT-MS offers people with MS who have advanced disability and their care partners an opportunity to achieve important health and well-being benefits associated with PA participation. The findings from this study will be relevant in informing future dyadic health promotion research in MS.

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Authors' Contributions

AF designed the study and drafted the manuscript. AELC and LAP contributed to the study design and provided feedback at all stages of its development and writing of this protocol. MLF and MSF contributed to the design of the study protocol. All authors critically reviewed the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors consent to the publication of this protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT (Consolidated Standards of Reporting Trials) checklist.
[PDF File (Adobe PDF File), 321 KB - resprot_v10i6e18410_app1.pdf]

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Abbreviations

AE: adverse event
MS: multiple sclerosis
PA: physical activity
PAT-MS: Physical Activity Together for People With Multiple Sclerosis
RCT: randomized controlled trial

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Protocol

Optimizing Oral Targeted Anticancer Therapies Study for Patients With Solid Cancer: Protocol for a Randomized Controlled Medication Adherence Program Along With Systematic Collection and Modeling of Pharmacokinetic and Pharmacodynamic Data

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Abstract

Background: The strengthening or substitution of intravenous cytotoxic chemotherapy cycles by oral targeted anticancer therapies, such as protein kinase inhibitors (PKIs), has provided impressive clinical benefits and autonomy as well as a better quality of life for patients with cancer. Despite these advances, adverse event management at home and medication adherence remain challenging. In addition, PKI plasma concentrations vary significantly among patients with cancer receiving the same dosage, which could explain part of the observed variability in the therapeutic response.

Objective: The aim of this optimizing oral targeted anticancer therapies (OpTAT) study is to optimize and individualize targeted anticancer treatments to improve patient care and self-monitoring through an interprofessional medication adherence program (IMAP) combined with measurement PKI plasma concentrations.

Methods: The OpTAT study has two parts: (1) a 1:1 randomized medication adherence program, in which the intervention consists of regular motivational interviewing sessions between the patient and the pharmacist, along with the delivery of PKIs in electronic monitors, and (2) a systematic collection of blood samples and clinical and biological data for combined pharmacokinetic and pharmacodynamic analysis. On the basis of the electronic monitor data, medication adherence will be compared between groups following the three operational definitions: implementation of treatment during the persistent period, persistence with treatment and longitudinal adherence. The implementation will be described using generalized estimating equation models. The persistence of PKI use will be represented using a Kaplan-Meier survival curve. Longitudinal adherence is defined as the product

of persistence and implementation. PKI pharmacokinetics will be studied using a population approach. The relationship between drug exposure and efficacy outcomes will be explored using Cox regression analysis of progression-free survival. The relationship between drug exposure and toxicity will be analyzed using a pharmacokinetic-pharmacodynamic model and by logistic regression analysis. Receiver operating characteristic analyses will be applied to evaluate the best exposure threshold associated with clinical benefits.

Results: The first patient was included in May 2015. As of June 2021, 262 patients had participated in at least one part of the study: 250 patients gave at least one blood sample, and 130 participated in the adherence study. Data collection is in process, and the final data analysis is planned to be performed in 2022.

Conclusions: The OpTAT study will inform us about the effectiveness of the IMAP program in patients with solid cancers treated with PKIs. It will also shed light on PKI pharmacokinetic and pharmacodynamic properties, with the aim of learning how to adapt the PKI dosage at the individual patient level to increase PKI clinical suitability. The IMAP program will enable interprofessional teams to learn about patients' needs and to consider their concerns about their PKI self-management, considering the patient as an active partner.

Trial Registration: ClinicalTrials.gov NCT04484064; https://clinicaltrials.gov/ct2/show/NCT04484064.

International Registered Report Identifier (IRRID): DERR1-10.2196/30090

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KEYWORDS

neoplasms; medication adherence; oral anticancer therapies; interprofessional program; adherence electronic measure; pharmacokinetics; pharmacodynamics; NONMEM; motivational interviewing

Introduction

Background

On the basis of the Global Cancer Observatory estimates, cancer was responsible for almost 10 million deaths globally in 2020 [1], making it a leading cause of death [2]. In Switzerland, more than 40,000 new patients are diagnosed with cancer each year [3]; however, the mortality rate of many cancers is decreasing, mainly because of the implementation of both screening programs and novel targeted and immune-related therapies [4].

For 15 years, the strengthening or alternatively the substitution of intravenous cytotoxic chemotherapy cycles by oral, sometimes long-term, targeted anticancer therapies has offered impressive clinical benefit and autonomy as well as a better quality of life for patients with cancer. Targeted cancer therapies involve protein kinase inhibitors (PKIs) and inhibitors of growth factor receptors, which are used to treat a variety of cancers, including gastrointestinal stromal tumors; kidney, thyroid, colorectal, lung, and breast cancers; melanoma; and sarcomas. Although treatment failure and poor tolerance are common in clinical practice, they cannot all be attributed to solid tumor multidrug resistance, as they can also be triggered by suboptimal medication adherence or inadequate drug plasma concentrations.

Suboptimal medication adherence is one of the causes of cancer progression and higher costs for health systems [5-7]. Thus, supporting patient drug self-management is key to achieving the best clinical outcome. In the past decade, interventional studies have focused mainly on patients with breast cancer treated with hormonal treatments and patients with chronic myeloid leukemia using imatinib. Evaluations of interventions to support PKI adherence in other solid cancers are scarce. In a systematic review, adherence to oral anticancer therapies was estimated to vary between 46% and 100% [8]. This review addressed adherence to various classes of oral anticancer therapies using various measures of adherence among patients with solid cancers, multiple myeloma, and chronic leukemia. Adherence estimation is not often reliable, as it is frequently evaluated through a moderate-quality methodology using subjective self-report questionnaires [9-11]. The link between longitudinal medication adherence, clinical factors, quality of life, survival, and cancer progression has been underinvestigated in the literature [12].

Since 1995, a routine interprofessional medication adherence program (IMAP) has been implemented at the University Community Pharmacy of the Center for Primary Care and Public Health Unisanté (Lausanne, Switzerland) to support drug self-management in patients with chronic illness [13]. Before initiating the optimizing oral targeted anticancer therapies (OpTAT) study, we conducted a feasibility study in which the included patients were mostly diagnosed with gastrointestinal stromal tumors or breast cancer. Adherence was estimated for several classes of oral anticancer therapies (capecitabine, letrozole, exemestane, imatinib, sunitinib, and temozolomide). We showed that patients with cancer agreed to participate and adopted the program; 12-month persistence was estimated at 85%, and the 12-month implementation rate was 97% in persistent patients [14].

Oral PKIs are licensed at a fixed dose despite the variable plasma concentrations observed in real-life situations [15,16]. This substantial interpatient pharmacokinetic variability may be explained by demographic (eg, age, body weight, and sex) and environmental factors (eg, concomitant medication and smoking), relevant physiopathological conditions (eg, organ failure and albumin levels) [17,18], genetic polymorphisms of metabolic enzymes or drug transporters, and patient behavior (eg, medication adherence) [12]. The characterization of pharmacokinetic variability is essential in oncology, given the risk of under- or overexposure, which may contribute to insufficient efficacy or undesirable toxicity in patients with cancer, respectively. Moreover, considerable efforts remain to

be undertaken to characterize the correlation between drug plasma concentrations and the therapeutic response of most PKIs and to define the therapeutic targets associated with clinical benefits in the context of therapeutic drug monitoring [19].

Objectives

The global aims of the OpTAT study are to establish the necessary knowledge to build rational monitoring strategies through medication adherence monitoring and patient-adjusted dosage in real-life conditions, which should contribute to optimizing the therapeutic benefit of PKIs, in order to improve outpatient cancer care.

The primary objectives are to better characterize the prospective and longitudinal patterns of PKI adherence in patients participating in a medication adherence program versus a control group and to identify key driver-modifiable adherence factors.

The secondary objectives are to quantify interpatient variability, identify sources of variability in serum PKI levels, and characterize the relationships between the serum concentration, the therapeutic response and the toxicity of these treatments in a population of patients with solid cancer.

The hypothesis states that the medication adherence program will increase PKI implementation and persistence before the treatment is stopped for any reasons beyond the patient's control or therapeutic change compared with the control group. Moreover, it is hypothesized that interpatient variability in PKI plasma concentrations plays a fundamental role in the heterogeneity of the therapeutic response and may play a role in PKI adherence.

Methods

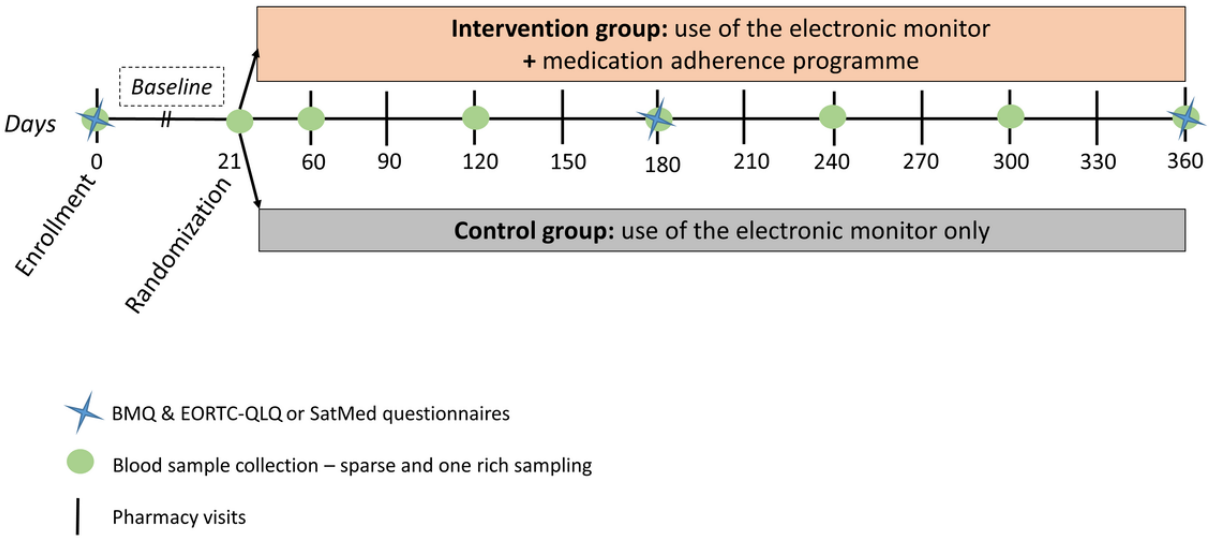
Ethical Considerations

The local ethics committee (Vaud, Switzerland) approved the OpTAT study in April 2015. Since then, two amendments have been accepted in July 2017 and October 2020. The study will be conducted in accordance with the current version of the Declaration of Helsinki and international good clinical practice principles. The protocol was peer-reviewed by five experts in April 2017 (Multimedia Appendix 1), leading to the founding of the study by the Swiss Cancer Research Foundation. This protocol was written according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Multimedia Appendix 2) [20].

Trial Design

This monocentric prospective study comprises two parts: (1) an open randomized controlled medication adherence study and (2) an observational pharmacokinetic and pharmacodynamic study. This design (Figure 1) explores whether medication adherence evolves differently in each group and explores the interplay between adherence and PKI pharmacokinetic parameters.

Figure 1. Design of the optimizing oral targeted anticancer therapies study. BMQ: Belief about Medicines Questionnaire; EORTC-QLQ: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; SatMed: Treatment Satisfaction with Medicines Questionnaire.



Enrollment of Participants

This translational study will be conducted at the Medical Oncology Service of the Department of Oncology of the Lausanne University Hospital (CHUV) outpatient clinic (Lausanne, Switzerland) in collaboration with the Community Pharmacy of the Center for Primary Care and Public Health Unisanté (Lausanne, Switzerland) and the Center for Research and Innovation in Clinical Pharmacy Sciences (CHUV).

Adult patients aged >18 years who were treated with a PKI for solid tumors and followed at the CHUV were eligible to

participate in this study. Participants with an inability to make decisions, with cognitive disorders, under tutelage, or not fluent in French or English or without the aid of an interpreter will be excluded from the study. Patients will be excluded solely from the medication adherence part of the study if they do not self-manage oral anticancer treatment (ie, nursing homes and home care services) or if they are already enrolled in an interventional study. If one PKI is switched to another PKI during the study, the patient will continue to participate in the study. However, if the PKI treatment is stopped or changed to a non-PKI anticancer treatment, the participant exits the OpTAT study; but, the data collected are kept for analysis.

The OpTAT study is voluntary, and patients will need to sign an informed consent form to participate in the medication adherence study, the pharmacokinetic and pharmacodynamic study, or both. The recruitment of participants began in May 2015. It ended in March 2021 for the medication adherence part but is ongoing until December 2021 for the pharmacokinetics part.

Oncologists were asked to refer eligible patients to a pharmacist PhD student or to the research staff from the Center of Experimental Therapeutics (CHUV), who will present the informed consent form to the patient after the medical visit. The participants will follow their treatment as usual, and no changes in the usual medical procedure will be made. No payment or compensation will be provided to the patients or to the oncologists as the patients are being seen as part of their routine follow-up clinical care.

Randomized Controlled Medication Adherence Study

Instruments: Use of the Electronic Monitors MEMS and Questionnaires in Both Groups

All patients participating in the medication adherence study will use an electronic monitor (MEMS and MEMS AS, AARDEX Group) for 12 months or until PKI is stopped. The electronic monitor registers the date and time of each opening, and a liquid-crystal display monitor on top of the cap indicates the number of daily openings to the patient. All patients included in the study will be asked to complete two validated questionnaires at three timepoints: inclusion, 6 months postinclusion, and at the end of the study. The first questionnaire is the *Belief about Medicines Questionnaire*, which assesses the patient's cognitive representation of medication [21]. The second is the *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire* (version 3.0), which assesses the quality of life of patients with cancer [22]. During the initial months of the study implementation, the patients with cancer filled out the *Treatment Satisfaction with Medicines Questionnaire* [23]; however, it was switched to the *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire*, as the latter was more adapted to patients treated with a PKI. The questionnaires were translated and validated in French, with satisfactory psychometric properties [24-26].

Repeated Medication Adherence Interviews and Feedback (Intervention Group)

Patients included in the intervention group will visit the routine IMAP of the pharmacy of Unisanté. They will attend 15- to 30-minute medication adherence interviews, which will take place after each clinical appointment over 12 months. On the basis of the information-motivation-behavior model embedded in sociocognitive theory [27], the pharmacist will explore in depth the home drug self-management skills, side effect management, motivation, self-efficacy, and consider cofactors such as depression, anxiety, and drug or alcohol addiction. Patients' beliefs about PKIs will be explored, and information about the PKI will be delivered and discussed at each visit. Determinants of and gaps in medication adherence will be discussed with the pharmacist in an empathetic and nonjudgmental way using motivational interviewing skills.

The electronic monitor data will be uploaded to MEDAMIGO software (MEMS and MEMS AS), which generates graphs of electronic monitor daily openings. Feedback on adherence to PKI therapy, based on the information generated by the electronic monitor, will be provided to and discussed with the patient. Interprofessionality is a cornerstone of the program, and pharmacists will summarize the intervention in a semistructured report sent to the oncologist after each intervention. During the COVID-19 pandemic, motivational interviews will be conducted by phone calls with patients considered by clinicians to be at a high risk of SARS-CoV-2 infection. All pharmacists who perform the medication adherence intervention must have attended specific training to lead motivational interviews (two full-day medication adherence initial training and continuous education based on the debriefing of a motivational interview with a patient every 12-18 months) [13].

Control Group

Patients included in the control group will use an electronic monitor but will be considered standard-of-care patients as they will not receive any medication adherence intervention. The electronic monitor opening data of the control group will be concealed from the patients, pharmacy team, clinicians, and investigators until the end of the study. If an oncologist expressively asks for adherence data because of stringent and urgent clinical matters, the patient will be excluded from the OpTAT study and referred to the routine medication adherence program of the Community Pharmacy of the Center for Primary Care and Public Health Unisanté.

Assignment of the Intervention

The collection of adherence data patterns in both groups at baseline is crucial to check whether adherence patterns are homogeneous between the groups before the intervention starts. In both groups, patients will use an electronic monitor for at least 21 days before randomization. At the end of the baseline period, the patients will be randomized 1:1 to either attend the medication adherence program (intervention group) or be part of the standard of care (control group; Figure 1). The randomization lists will stratify participants according to their cancer type and the time elapsed between PKI initiation and the

time of inclusion (less or more than 30 days). The randomization sheet lists 1 (intervention group) or 0 (control group) and will be provided by an independent researcher from the Unisanté Research Support Unit. The randomization list established by Excel (version 2016, Microsoft) will be based on variable size block randomization to prevent predictability and ensure a balanced allocation to each group. After randomization, the patient, research team, pharmacy, and clinical team will all be aware of the assigned group.

Observational Pharmacokinetic and Pharmacodynamic Study

A total of 10 mL of peripheral blood samples will be collected for up to a maximum of 8 samples per patient or until PKI is stopped at an unselected time after the last PKI intake. The blood samples will be centrifuged, the plasma will be frozen and stored until PKI levels are measured, and the dry pellet will be analyzed for the exploration of genetic variants involved in PKI pharmacokinetics. Moreover, for patients who accept, 6 × 5 mL blood samples will be collected over a maximum of 12 hours during one visit to the hospital. Specific information on pharmacokinetic data will be collected at each blood draw, and all relevant clinical and biological information will be obtained from the medical files of the patients (detailed in the *Collection and Management of Data* section).

Outcomes

Primary Outcomes: Randomized Controlled Medication Adherence Study

The primary outcome was global adherence, defined as the percentage of days with correct medication use of each subject. The sample size was calculated to ensure sufficient power to test the difference in the mean logit global adherence between groups (see the *Sample Size* section). Medication adherence will also be compared between groups following the three operational definitions defined by the EMERGE (European Society for Patient Adherence, Compliance, and Persistence Medication Adherence Reporting Guideline) guidelines: implementation of treatment during the persistent period (daily management of oral targeted anticancer drugs), persistence with treatment (the distribution of times between enrollment and discontinuation), and longitudinal adherence (the product of persistence and implementation) [14,28,29].

Secondary Outcomes: Pharmacokinetic and Pharmacodynamic Data

The plasma concentrations of the PKI and active metabolites, if appropriate, will be measured using validated methods of liquid chromatography-tandem mass spectrometry for each blood sample collected [30,31]. Internal standards will be used to optimize the analytical accuracy and precision of the method, essentially by abrogating the influence of matrix effects and inherent variability in the extraction procedure. The pharmacokinetic variables quantifying PKI exposure will then be calculated from population-based individual Bayesian pharmacokinetic parameters and expressed as the area under the curve and trough drug concentrations (minimum drug concentration) [32]. The efficacy of anticancer drugs will be expressed as progression-free survival, which is the time interval between PKI initiation and the date of tumor progression, defined according to the standardized criteria *Response Evaluation Criteria In Solid Tumors* [33], or death from any cause. If a patient is event-free (progression or death), the time will be censored at the last follow-up visit, the end of the study follow-up, or treatment discontinuation. The response to treatment will be assessed according to local standards, usually every 3 months, using a computed tomography scan or positron emission tomography scan. In addition, an overall survival analysis will be undertaken in an exploratory manner. The toxicity of PKI will be assessed according to the National Cancer Institute–Common Terminology Criteria for Adverse Events [34].

Sample Size

Randomized Controlled Medication Adherence Study

We assumed that the mean longitudinal adherence will remain stable at 95% in the intervention group during the follow-up period, whereas it would decrease from 95% to 80% in the control group during the 340 days from randomization to the end of follow-up. We also assumed an SD for the logit of longitudinal adherence of 1.8, for both groups and at all timepoints. This corresponds to 95% individual adherence in the intervals 10%-99.3% and 35%-99.9% in the control and intervention groups, respectively, at the end of follow-up. A sample size calculation was performed to simulate individual series of daily medication (1=at least the correct number of daily openings of the electronic monitor; 0=fewer daily openings than prescribed) according to the above parameters to consider both the interindividual variability (SD 1.8) and the intraindividual variability (the measurement error). Considering that the number of measures of a subject will be 340 and assuming a 10% dropout in the middle of the year, 120 patients must be included in the study (60 in each group) to reach a power of 80% with a .05 significance level when comparing the mean of the logit of global adherence between groups using a two-tailed Student *t* test. Differences are considered statistically significant if $P<.05$.

Pharmacokinetic and Pharmacodynamic Study

It has been empirically determined that at least 50 patients with several samples per PKI are necessary to characterize drug pharmacokinetics and variability.

Collection and Management of Data

In collaboration with the investigators, the community pharmacy of Unisanté will manage the PKI adherence data, and the Center of Experimental Therapeutics will manage the blood samples as well as the clinical, biological, and sociodemographic data. The schedule of enrollment, intervention, and assessments is shown in Multimedia Appendix 3. Sociodemographic and relevant clinical and biological information regarding the evaluation of the disease will be obtained from the administrative and electronic patient medical records (Soarian, Cerner). The data will be registered prospectively in the REDCap (Research Electronic Data Capture; Vanderbilt University) platform, a secure web application for research data collection, providing a unique study identification number for each patient. To ensure confidentiality and data quality, only principal investigators will have access to this file. After the

analysis, the database will be registered in the secured data repository of the University of Geneva (Yareta). Patient blood samples will be stored in the Center of Experimental Therapeutics, and the health data will be stored in the data warehouse of the CHUV for a maximum of 15 years after the end of the study before destruction.

Data Analyses

Medication Adherence Analysis

Adherence to PKI will be assessed using electronic monitor, calculated pill counts, and patient reports. Medication behavior will be described with a binary variable (1=at least the correct number of daily openings of the electronic monitor; 0=fewer daily openings than prescribed) in each group. This coding method is commonly used; however, this code cannot discriminate overadherence, which is considered in the same way as optimal adherence. The implementation will be described in each group using generalized estimating equation models; persistence with PKI (ie, adherence until PKI discontinuation) will be represented using a Kaplan-Meier survival curve [14]. Global adherence will be estimated in each group with the proportion of patients with correct medication taking, defined as ≥95% days with correct dosing during days 1 to 360, compared between groups using a chi-square test. As ≥95% days with the correct dosing threshold is an assumption, we will perform sensitivity analysis with other thresholds such as 90%, 85%, and 80%. Multivariate logistic regression models will be used to evaluate whether any detected effect of the intervention remained after adjusting for potential sociodemographic or clinical confounders. As a secondary analysis, the difference in medication taking will be explored across genders.

A systematic computerized term search in the adherence reports of the intervention group will be performed to identify the most frequent variables affecting PKI adherence, and a regression model will be used to discover their association with adherence [35].

Sociodemographic data and quality of life and beliefs about medication of patients who refused to participate and completed both questionnaires versus those who accepted to participate in the adherence study will be compared at baseline. For patients included in the adherence study, the results of the questionnaires will be compared at randomization, 6 months, and at the end of the study. Changes in *Belief about Medicines Questionnaire* and *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire* or the *Treatment Satisfaction with Medicines Questionnaire* will be described longitudinally for the included patients and transversely per group at 6 and 12 months. Medians and IQRs or proportions will be used as appropriate. Nonparametric tests (eg, Mann-Whitney-Wilcoxon) or Fisher exact test of two proportions will be used to test the differences between groups.

Ultimately, the adherence patterns and their relationship with drug exposure and clinical response will be evaluated in an exploratory analysis.

To minimize interpretation bias, the statistician will not be aware of the group assignments during the analysis. The data will be analyzed in an intention-to-treat manner. All statistical analyses will be performed using the R statistical package (version 3.6, The R Foundation for Statistical Computing) [36].

Population Pharmacokinetic Analysis

Population pharmacokinetic analyses will be performed using nonlinear mixed regression models with the software program NONMEM (Icon Development Solutions). This approach allows for the characterization of the average pharmacokinetic profile of PKI from data pooled over all sampled individuals and the quantification of inter- and intraindividual variability. This approach allows us to analyze sparse (few drug concentrations per patient) and unbalanced data. The built models integrate active metabolites when appropriate. The impact of potential sources of variability will be evaluated using linear and nonlinear functions.

Relationships Between PKI Exposure, Efficacy, and Toxicity

The correlation between PKI exposure and efficacy will be explored using Cox regression analysis of progression-free survival. The correlation between PKI exposure and toxicity will be explored by pharmacokinetic and pharmacodynamic models using the software program NONMEM or by logistic regression analysis. Receiver operating characteristic analyses will be used to evaluate the best exposure threshold to predict clinical outcomes and performance (in terms of area under the receiver operating characteristics curve and sensitivity and specificity).

Missing Data

Missing data will not be imputed but will be clearly identified and considered during the analysis process (nature and frequency) and described in the publication.

Patient and Public Involvement

Patients or the public will not be involved in the design, conduct, reporting, or dissemination plans of this research. The participants will be informed about the study results after the final publication using lay language.

Results

The first patient was included in May 2015. Until June 2021, 262 patients have participated in at least one part of the study (250 patients have given at least one blood sample, and 130 have been included in the adherence study). In June 2021, 51 patients treated with palbociclib have provided at least one blood sample, and the adherence study currently includes 43 participants with breast cancer, which corresponds to most of the included participants. Moreover, so far, at least one blood sample has been collected from patients treated with 31 different PKIs and their combination (Multimedia Appendix 4).

Data collection is in process, and the final analysis will be performed in 2022. The results of the study will be submitted to local, national, and international conferences and to peer-reviewed open access journals for publication.

Discussion

Strength of the Study

The OpTAT study is based on a mixed methodology involving a randomized controlled medication adherence study, along with pharmacokinetic and pharmacodynamic data collection. The methodology is robust, as adherence data will be assessed through electronic monitoring, often considered the gold standard, in both the intervention and control groups. Participants randomized to the intervention group will be included in a routine medication adherence program (IMAP) that has previously been shown to lead to significant improvements in terms of medication adherence; clinical outcomes; and retention in care of other chronically ill patients, such as those with HIV [13,14,37-39]. Moreover, the association between longitudinal adherence and clinical data as well as quality of life and beliefs about medicines through questionnaires will be explored, and the literature in this area is scarce.

The second strength of this study is the pharmacokinetic analysis of a wide range of PKIs. PKIs are marketed under a single regimen according to *the one dosage fits all patients* paradigm, which may be an important source of side effects that are potentially detrimental to the continuation of the course of the treatment and patient adherence. Hence, our ultimate and cutting-edge development is to combine an analysis of PKI adherence, pharmacokinetics, and pharmacodynamics.

Limitations of the Study

This study has some limitations. First, the adherence data will be collected over 12 months, a time frame during which several stops and breaks in the treatment regimen can occur. This will be a challenge for data analysis; however, the adherence team and the statistician, who will perform the analysis, have already dealt with this kind of data and are experts in this field [14]. Second, we expect some variability in the frequency of adherence visits among participants. Indeed, the adherence interviews are scheduled after each patient's clinical appointment, and the frequency can vary from a quarterly to a monthly visit depending on the organization of the clinic and the severity of the patient's disease. Third, the use of an electronic monitor can introduce a Hawthorne effect during the first 6 weeks of the study, which disappears afterward [40]. This effect is explained by the fact that patients who know they are being observed may improve their usual medication behavior. The impact of this effect will be explored in the analysis. Fourth, the number of blood samples may not be sufficient to initiate a population pharmacokinetic analysis for each monitored PKI. All limitations will be considered while analyzing the results and will be detailed in the final publication.

Conclusions

The OpTAT study will strengthen knowledge on the effectiveness of the routine IMAP medication adherence program in patients with solid cancers treated with PKIs. The IMAP will enable interprofessional teams to learn about patients' needs and concerns about their PKI self-management. The study will also shed light on PKI pharmacokinetics and its relationship with pharmacodynamic properties, with the aim of adapting dosage regimens at the individual patient level, increasing the clinical suitability of PKIs.

Adherence combined with pharmacokinetic data will inform pharmacists and clinicians on how to support patients during the entire course of their PKI treatment and how to manage adaptations of treatment efficiently, with the patient as an informed partner.

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Authors' Contributions

CB and EC wrote the manuscript. All coauthors reviewed and approved the manuscript. IL reviewed the statistical aspects of the protocol. CC, MPS, EC, CB, DW, LD, and NW contributed to the development of the study protocol. A Digklia, KZ, A Diciolla, VC, AS, ALV, A Dolcan, A Sarivalasis, AL, HB, AO, SP, and DW identified and followed the patients clinically. MPS, EC, CB, and JDC organized the implementation of the study within the medication adherence program (IMAP) at the pharmacy of Unisanté.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review reports from the Scientific Office of the Swiss Cancer League/Swiss Cancer Research.
[PDF File (Adobe PDF File), 2624 KB - resprot_v10i6e30090_app1.pdf]

Multimedia Appendix 2
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist completed for the optimizing oral targeted anticancer therapies protocol.
[PDF File (Adobe PDF File), 170 KB - resprot_v10i6e30090_app2.pdf]

Multimedia Appendix 3
Schedule of enrollment, intervention, and assessments of the optimizing oral targeted anticancer therapies study.
[DOCX File , 15 KB - resprot_v10i6e30090_app3.docx]

Multimedia Appendix 4
Protein kinase inhibitors and their combination included in the optimizing oral targeted anticancer therapies study.
[DOCX File , 13 KB - resprot_v10i6e30090_app4.docx]

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Abbreviations

CHUV: Lausanne University Hospital
EMERGE: European Society for Patient Adherence, Compliance, and Persistence Medication Adherence Reporting Guideline
IMAP: Interprofessional medication adherence program
OpTAT: Optimizing oral targeted anticancer therapies
PKI: Protein kinase inhibitor
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Factors Influencing the Adoption of Contact Tracing Applications: Protocol for a Systematic Review

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Abstract

Background: Following the onset of the COVID-19 pandemic, digital contact tracing apps have become prevalent worldwide in a coordinated effort to curb the spread of COVID-19. However, their uptake has been low and slow due to privacy concerns, the lack of trust and motivational affordances, and their minimalist design.

Objective: The objective of this article is to present a protocol for a systematic review of the main factors, including facilitators and barriers, that influence the adoption of contact tracing apps.

Methods: We searched seven databases, namely, Scopus, CINAHL, PubMed (MEDLINE), IEEE Xplore Digital Library, Association for Computing Machinery (ACM) Digital Library, Web of Science, and Google Scholar, for relevant publications between October 30, 2020, and January 31, 2021. Three authors were involved in removing duplicates, screening, and selection of relevant articles according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-analysis Protocols) guidelines.

Results: Altogether, we retrieved 777 articles from the seven databases. As of May 14, 2021, we have completed the screening process and arrived at 13 eligible articles to be included in the systematic review. We hope to elicit, summarize, and report the main findings in the systematic review article by the end of August 2021. We expect to uncover facilitators and barriers related to app utility, data security, ease of use, and persuasive design that are deemed important to adoption of contact tracing apps.

Conclusions: The findings of the systematic review will help researchers to uncover the gaps in the adoption of contact tracing apps, and decision makers and designers to focus on the principal adoption factors necessary to create better and more effective contact tracing apps.

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KEYWORDS

contact tracing app; technology acceptance; user perception; adoption; COVID-19; review; perception; barrier; challenge; effective; usability

Introduction

Rationale

Digital contact tracing apps have become prevalent worldwide due to the COVID-19 pandemic, which began in the first quarter of 2020. Specifically, these apps have been developed to fast-track the identification and self-isolation of individuals exposed to SARS-CoV-2, the coronavirus known to cause COVID-19, by being in close contact with infected persons. Several factors hinder the uptake of contact tracing apps, as is suggested in the gray and academic literature; these include privacy concerns, lack of trust, and poor persuasive design [1]. Moreover, there is limited understanding of the overall factors that influence user acceptance and adoption of such apps. According to Thorneloe et al [2], "There is a dearth of evidence [especially based on systematic reviews] regarding the barriers and facilitators to uptake and engagement with COVID-19 digital contact tracing applications." There are several systematic reviews from the early stages of the pandemic, but they are unrelated to technology acceptance. Specifically, some systematic reviews, such as those by Braithwaite et al [3], Davalbhakta et al [4], and Juneau et al [5], did not address motivators and barriers to adoption of contact tracing apps. Hence, a systematic review of the existing literature is necessary to understand users' perceptions, including the factors that facilitate their adoption of contact tracing apps, barriers and challenges to contact tracing app adoption, measures undertaken to tackle existing challenges, and the moderating effect of demographic or human factors. The findings of such a systematic review will uncover available opportunities to improve the design, adoption, and effectiveness of contact tracing apps in future iterations. Given the concerns and intense debate about COVID-19 contact tracing apps among governments, media, the research community, and the wider population across the globe, we surmise that privacy concern, trust, and data security will play a significant role in the adoption of contact tracing apps [6-8]. In addition, we envisage the impact of persuasive design (eg, reward and self-monitoring) on contact tracing app adoption [9]. A number of digital health researchers [10,11] have advocated the need to redesign contact tracing apps as persuasive technologies to improve their motivational appeal and overall user experience. Hence, we surmise that the incorporation of persuasive features into contact tracing apps has the potential of improving their uptake among potential users. Thus, a systematic review will reveal how relevant these empirical constructs (related to trust, privacy, security, and persuasive design) are to the adoption of contact tracing apps within and across different demographics globally.

Objectives

This protocol, which follows the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-analysis Protocols) guidelines [12], serves as a basis for our ongoing systematic review, which sets out to identify empirical studies conducted on the acceptance and adoption of contact tracing apps since the onset of the COVID-19 pandemic. The systematic review aims to synthesize and present the empirical studies' findings to contact tracing app stakeholders, including researchers, designers, and policymakers to improve the design of future contact tracing app iterations. Particularly, the systematic review aims to answer the following research questions (RQs):

- RQ1: What are the key facilitators and barriers that are associated with the adoption of contact tracing apps?
- RQ2: What motivational strategies are being implemented to increase the adoption of contact tracing apps?
- RQ3: What are the adoption rates of contact tracing apps among their target audiences?

Methods

Eligibility Criteria

For inclusion in the systematic review, the work must be a user study (quantitative, qualitative, or both) evaluating the facilitators and barriers associated with contact tracing app adoption and particular outcomes such as the intention to download, install, or use the app. The evaluation of contact tracing app must be conducted among participants from any countries around the world aged 18 years and above. These user studies must have been conducted within the period of the COVID-19 pandemic, meaning studies conducted earlier than 2020 were not considered. Moreover, the studies must be about the acceptance and adoption of contact tracing apps; that is, they can be either an evaluation of a hypothetical (described) contact tracing app or a prototype. Above all, all articles must be in English and peer reviewed. Articles that do not meet these criteria, for example, those that do not discuss facilitators and/or barriers to contact tracing app adoption, do not evaluate the adoption of contact tracing apps among participants, are not about COVID-19 contact tracing apps, are part of the gray literature, or are not written in English, will be excluded from the systematic review.

Information Sources

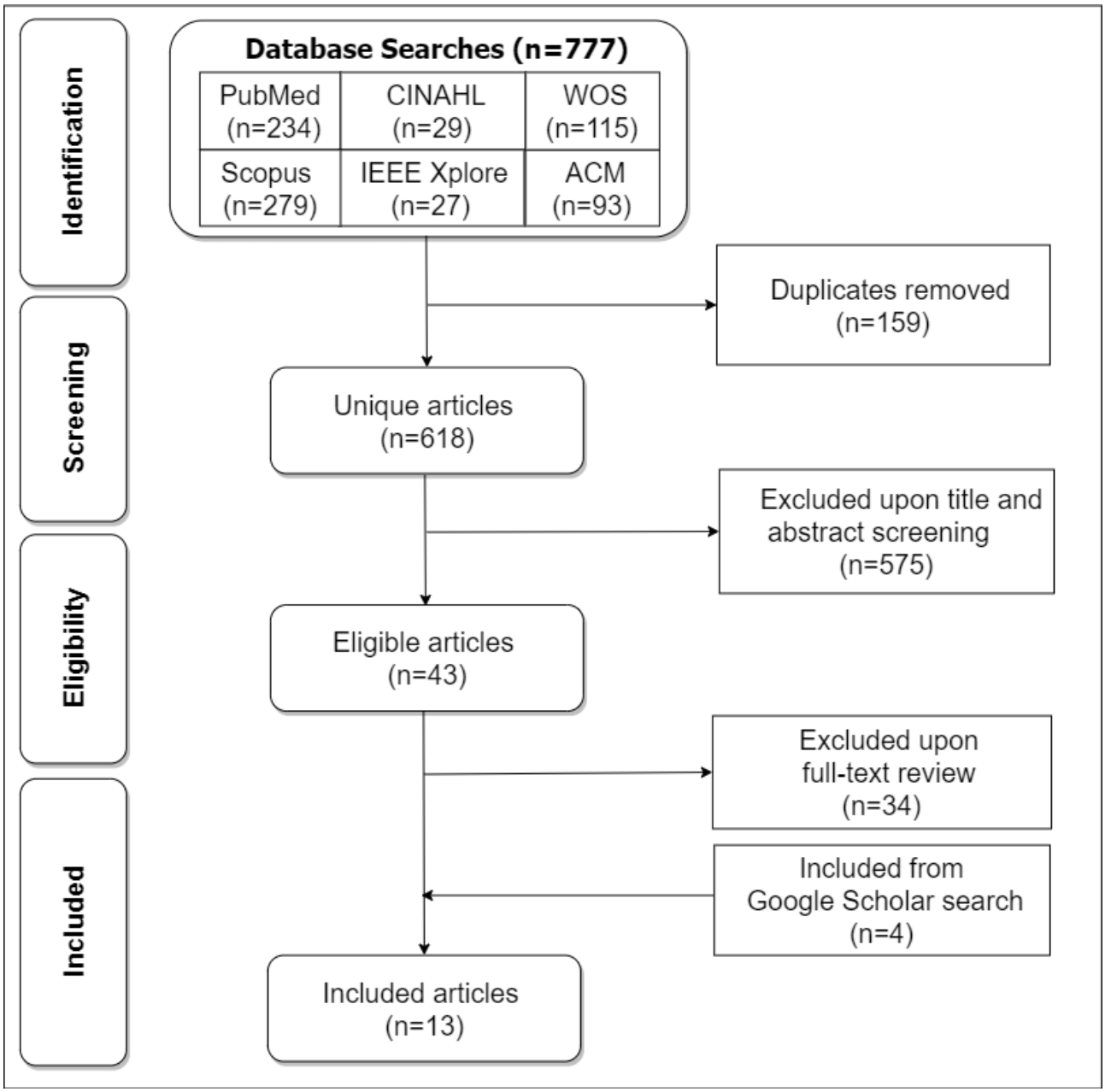
Seven databases, namely Scopus, CINAHL, PubMed (MEDLINE), IEEE Xplore Digital Library, Association for Computing Machinery (ACM) Digital Library, Web of Science, and Google Scholar, were searched. The first six databases were searched between October 30, 2020, and November 20, 2020, by using the following keywords: ("contact tracing" OR "contact-tracing" OR "exposure notification" OR "exposure-notification" OR "contact notification" OR "contact-notification" OR GAEN) AND (app OR apps OR application* OR technology* OR system OR systems) AND (percept* OR adopt* OR accept* OR uptake OR use OR usage) AND (covid* OR coronavirus OR SARS-CoV-2). The criterion used for the search was "ALL" (title, abstract, keyword, and full text). Furthermore, we searched Google Scholar for articles published between November 21, 2020, and January 31, 2021, to include any additional articles that we might have missed during our systematic search conducted before November 21, 2020.

Search Strategy

Figure 1 shows our search strategy for identifying, screening, and including relevant articles in our systematic review. The search strategy is based on the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) flowchart [13].

Two approaches were used in searching for articles to be included in the systematic review. The first approach was formal (systematic) and the second was informal (nonsystematic). In the formal approach, we searched six databases (PubMed, CINAHL, Web of Science, Scopus, IEEE Xplore, and ACM Digital Library) systematically, and retrieved 777 articles in total between October 30, 2020, and November 20, 2020.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) flowchart for the screening and inclusion of articles in the systematic review. ACM: Association for Computing Machinery; WOS: Web of Science.



In the screening phase, we removed 159 duplicates to arrive at 618 articles. In the eligibility phase, we screened out 575 articles to arrive at 43 articles. In the inclusion phase, we excluded 34 articles upon full-text review to arrive at 9 articles.

Second, in the informal approach, between November 21, 2020, and January 31, 2021, we searched Google Scholar from time to time to uncover more articles that might not have come up in the first phase of systematic search of the six databases between October 30, 2020, and November 20, 2020. By the end of January 31, 2021, altogether, we found 4 articles from the Google Scholar search, which we added to the initial 9 articles from the systematic search to arrive at 13 articles in total for the final systematic review.

Data Management

All articles retrieved from the non–Google Scholar databases were imported into Mendeley reference management system using Mendeley Web Importer, which was added to the Google Chrome browser. Upon merging all of the articles from the non–Google Scholar databases on Mendeley, we exported them to a Microsoft Excel spreadsheet to remove duplicates, screen the unique articles, and select the final eligible articles. Finally, we added the articles retrieved from the Google Scholar search

to the final eligible articles we arrived at, according to the PRISMA screening and selection flowchart (Figure 1). In the next stage of the review process, the relevant data characteristics (eg, author names, year of publication, type of study, facilitators, and barriers) will be extracted from the 13 included articles by the three authors after a full-text reading and review, and the results will be tabulated in a Microsoft Excel spreadsheet for final systematic analysis and synthesis.

Selection Process

Three authors initiated the screening, selection, and review of the articles retrieved from the non–Google Scholar databases and then proceeded to removing duplicates. Each author reviewed and screened an approximately equal number of articles based on titles and/or abstracts, excluding those that did not meet the eligibility criteria (see Figure 1). Articles that remained to be considered were labeled "maybe." Next, all three authors collaborated to determine eligibility of each of the articles labeled "maybe" for possible inclusion in the full-text review. Thereafter, each of the three authors carried out a full-text review on one-third of the eligible articles to arrive at 9 articles after excluding articles that did not meet the inclusion criteria. Finally, with the 4 articles retrieved from the Google Scholar search by the first author added, the three authors reviewed the final set of included articles collectively based on the inclusion criteria to confirm and validate their inclusion in the final systematic analysis and synthesis.

Data Collection Process

The PRISMA flowchart [13] was used to arrive at the 13 articles to be included in the systematic review. Going forward, each of the three authors will go through approximately one-third of the 13 articles to extract the key themes of interest and their corresponding values after reading the full text. When writing the systematic review article, the first author will confirm all of the extracted values by referring to the original articles, if need be.

Data Items

The themes of interest and the respective values that will be extracted from each article are shown in Table 1. These include author identification, study date, type of application, target audience, among other themes. For example, the author identification entails values such as the name of the authors and their citations. Moreover, the target audience comprises values such as the country of the target (studied) population, the sample size, and the average age of the population.

Table 1. Systematic analysis coding scheme.

Number	Criterion	Description
1	Identification	Name of authors
2	Study date	Month and year
3	Type of application	Description based, prototype
4	Target audience	Country, sample size, age
5	Type of study	Quantitative, qualitative, mixed
6	Outcome variable	Intention to download app, intention to install app, intention to use app, etc
7	Facilitators	Perceived usefulness, perceived trust, self-monitoring, etc
8	Barriers	Privacy concern, perceived technology risk, etc
9	Moderating variables	Age, gender, culture, etc
10	Findings or takeaways	Summary of the main findings and takeaways
11	Recommendations	Proposed guidelines for effective design of contact tracing apps
12	Opportunities for future studies	Suggested areas for future research based on the limitations of the study

Outcomes and Prioritization

As shown in Table 1, in the systematic review, we will search for behavioral outcomes such as the intention to download, install, or use the app. That is, in answering the third research question, "What are the adoption rates of contact tracing apps among their target audience?" for each of the empirical studies, we will be looking at, as an example, the overall rate regarding the intention to download, install, or use the contact tracing app. For instance, the percentage of study participants (especially nonadopters of contact tracing apps) who are willing to download the app under evaluation may be an indication of how the app may fair in real-life contexts, especially if the facilitators of contact tracing app adoption are prioritized. In addition, we will be looking at the levels of perception of key facilitators (eg, perceived usefulness [14]) and barriers (eg, privacy concern [15]) associated with contact tracing app adoption. For example, in a given study, "Did the participants perceive the contact tracing app described or prototyped as useful, trustworthy, etc?" We are interested in the overall scores of these constructs because, in the context of technology acceptance model, they have been found to be significant predictors or determinants of information system adoption [16-18]. Moreover, with regard to the first research question, "What are the key facilitators and barriers that are associated with the adoption of contact tracing apps?" we will be looking at studies that analyzed path models [19], structural equation models [20], or regression models. Particularly, we will be looking at the strongest predictors and the amount of variance in the outcome variables (eg, intention to use the app) explained by the predictors. The variance metric

(ie, coefficient of determination) will help us to understand the extent to which the factors that have been identified in the gray literature and empirically studied are able to explain the various outcome variables associated with contact tracing app adoption.

Data Syntheses

Using the three nonquantitative approaches, which include tabulation, graphical, and narrative approaches [21], we will synthesize the results of the empirical studies among those included in the systematic review. Moreover, we will carry out quantitative computation of metrics such as the percentage of studies that found that a given construct (eg, perceived usefulness) is a determinant of contact tracing app adoption. Finally, we will tabulate the adoption rate (ie, the percentage of participants in each study that are willing to adopt (eg, download, install, or use) a given contact tracing app under investigation.

Results

In this section, we present the tables and diagrams of the expected results from the systematic review. Table 2 addresses the first and second research questions. It shows the tabulation of the facilitators (which may comprise persuasive or motivational strategies) and barriers associated with the adoption of contact tracing apps in each included article. The facilitators and barriers will be organized into logical categories such as app utility, data security, facilitating conditions, app design, and ethical concerns. A positive sign (+) indicates a facilitator driving contact tracing app adoption and a negative sign (–) indicates a barrier hindering contact tracing app adoption (Table 2). A typical example of a facilitator and barrier in the app utility category is "perceived usefulness" and "doubt about effectiveness," respectively. Moreover, in the data security category, a typical example of a facilitator and barrier is "perceived trust" and "privacy concern," respectively. For example, Velicia-Martin et al [14] and Walrave et al [15] found that perceived usefulness (a facilitator) and privacy concern (a barrier), respectively, are associated with contact tracing app adoption. Finally, "%Total" indicates the percentage of the total reviewed articles that found a given factor (facilitator or barrier) to be (1) a significant determinant of contact tracing app adoption in quantitative studies involving correlational, regression, and path analyses and/or (2) a noteworthy theme in qualitative studies based on the thematic analysis of participants' comments.

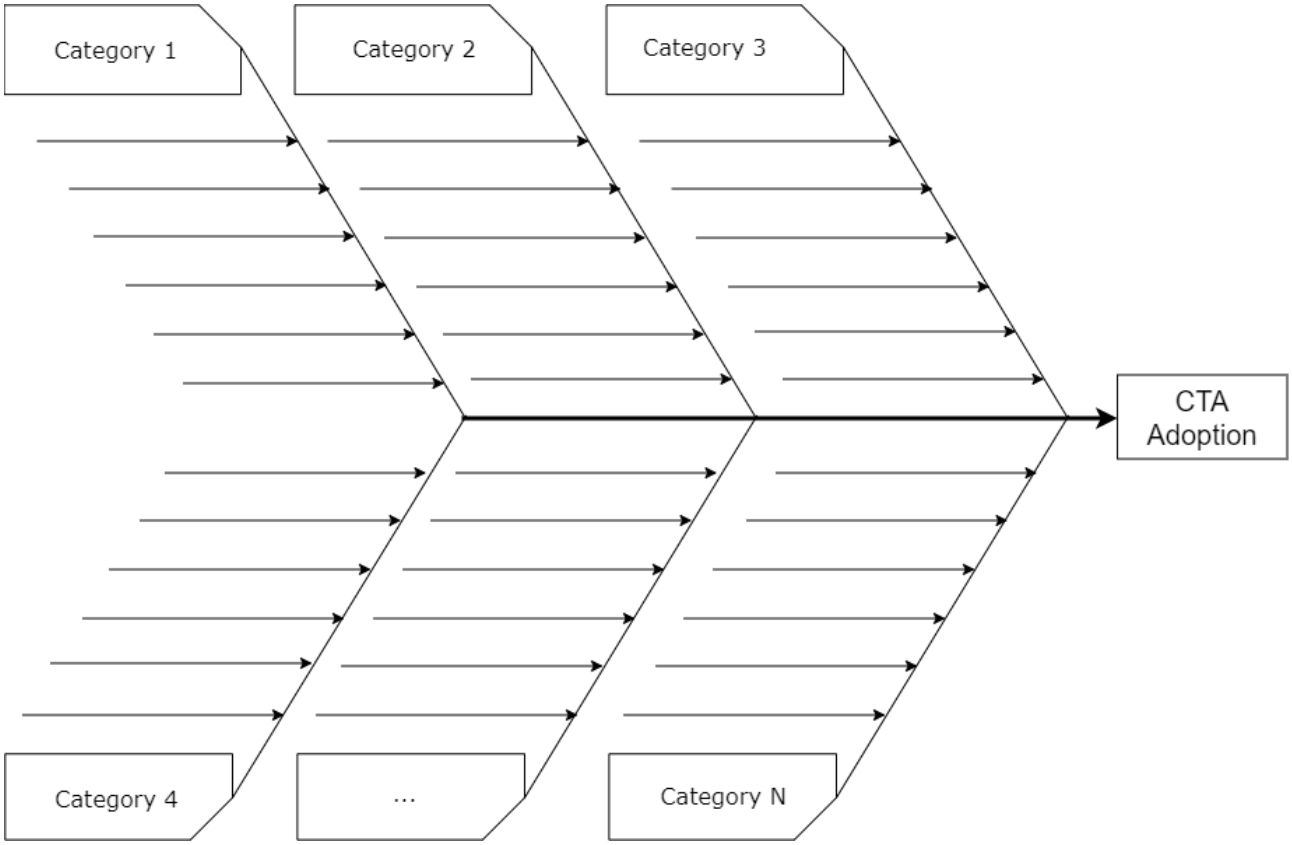
Table 2. Systematic tabulation of factors and barriers associated with contact tracing app adoption. A positive sign (+) indicates a facilitator and a negative sign (–) indicates a barrier.

Category and factor	Author 1	Author 2	…	Author N	% Total
Category 1					
Factor 1	+	N/A[a]	…	+	N1
Factor 2	–	–	…	–	N2
…	N/A	+	…	+	N3
Factor N	+	+	…	N/A	N4
Category 2					
Factor 1	+	N/A	…	+	N5
Factor 2	–	–	…	–	N6
…	N/A	+	…	+	N7
Factor N	+	+	…	N/A	N8
Category N					
Factor 1	+	N/A	…	+	N9
Factor 2	–	–	…	–	N10
…	N/A	+	…	+	N11
Factor N	+	+	…	N/A	N12

[a]N/A: not applicable.

Moreover, we aim to synthesize, visually and concisely, all of the findings (facilitators and barriers associated with contact tracing app adoption) as shown in the fishbone diagram in Figure 2. Similar to Table 2, the main factors that drive and hamper contact tracing app adoption are organized into logical categories such as app utility, data security, facilitating conditions, and ethical concerns. The fishbone diagram would help readers identify the factors of contact tracing app visually in one fell swoop without the interference of overwhelming details shown in Table 2. Finally, the fishbone diagram would serve as the main takeaway of the systematic review, which, given its portability, can easily be distributed among COVID-19 contact tracing app researchers and stakeholders.

Figure 2. Preliminary fishbone diagram showing the factors that influence the adoption of contact tracing apps. Arrows represent facilitators and barriers. CTA: contact tracing app.



Finally, Table 3 addresses the third research question aimed at uncovering the adoption rate of contact tracing apps in each of the articles included in the systematic review. The outcome variables may include target constructs such as intention to download, install, or use the app. The adoption rate metric (especially among contact tracing app nonadopters) will provide us with insights into the percentage of participants in a given national population that may be willing to adopt contact tracing apps to curb the spread of the virus compared with the percentage of participants in another national population.

Table 3. Percentage of participants in each study that were willing to adopt contact tracing apps.

Variable	Author 1	Author 2	…	Author N
Country	Country 1	Country 2	…	Country N
Outcome variable (OC)	OC1	OC2	….	OCN
Adoption rate (%)	N1	N1	…	NN

Discussion

Directions

We have presented the protocol for a systematic review of the main factors that influence the adoption of contact tracing apps. This review is necessary in the light of the low adoption rate reported for the contact tracing apps currently available on the market worldwide. Based on an informal (nonsystematic) combing of the literature, we hope to uncover facilitators and barriers to contact tracing app adoption, which revolve around app utility, ease of use, data security, and motivational or persuasive features. Our systematic review aims to make several contributions to the existing literature. For example, the fishbone-diagram framework (Figure 2), created to visually display the results, will allow the target audience to quickly and holistically identify the primary factors that influence contact tracing app adoption. It will serve as an overarching framework for presenting the key facilitators and barriers associated with the adoption of contact tracing apps to stakeholders, including public health authorities, researchers, designers, governments, and policymakers. Overall, the findings of the systematic review will help (1) researchers to uncover the gaps in contact tracing app adoption and address them in future research efforts, and (2) decision-makers and designers to focus on the principal adoption factors necessary to create better and more effective contact tracing apps that have the potential of increasing adoption among their target audiences. We hope to complete the tabulation of our results and writing the systematic review article, which will report the main findings, takeaways, and the lessons learned, by the end of August 2021.

Limitations

Our systematic review is subject to a number of limitations such as those arising from the risk of bias of the individual studies. Hence, in the review, individual studies will be analyzed for the risk of bias at the study level and overall. For example, for each of the studies, we hope to uncover limitations regarding small sample size and convenience sampling, which may affect the generalization of the study's findings to the larger target audience studied. The second risk of bias is the type of quantitative analysis conducted in the studies; for example, considering the relationships between the study variables, we will determine whether it is a regression analysis, path analysis, structural equation modeling, or correlational analysis. A correlational analysis is most likely to uncover a significant relationship between two variables given that the analysis is bivariate and not multivariate. According to Kaspar [22], many of the significant relationships between variables disappear in regression and path models that consider all independent variables simultaneously. Therefore, in the systematic analysis, we will identify studies with findings based on this type of analysis that can cause biased results. The third potential source of bias in the individual studies is the adoption rate metric, which may not be representative of the actual percentage among the population under study. For example, if a study found that 50% of the participants were willing to download a given contact tracing app if it were deployed in real life, this might not reflect the actual percentage of willing adopters in the wider population. The reason is that the participants of the study in question might be more technologically literate, educated, and well-informed about the utility of contact tracing apps than the wider population. Hence, they are more likely to adopt the contact tracing app under study compared with the average person in the general population who is less informed and, thus, more likely to be susceptible to misinformation about COVID-19.

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Conflicts of Interest

None declared.

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Abbreviations

ACM: Association for Computing Machinery
COVID: coronavirus disease
GAEN: Google/Apple Exposure Notification
PRISMA: Preferred Reporting Items for Systematic Review and Meta-analysis
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-analysis Protocols
RQ: research question
WOS: Web of Science

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Protocol

The Presence of Fungal and Parasitic Infections in Substances of Human Origin and Their Transmission via Transfusions and Transplantations: Protocol for Two Systematic Reviews

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Abstract

Background: The European Union Directives stipulate mandatory tests for the presence of any infections in donors and donations of substances of human origin (SoHO). In some circumstances, other pathogens, including fungi and parasites, may also pose a threat to the microbial safety of SoHO.

Objective: The aim of the two systematic reviews is to identify, collect, and evaluate scientific evidence for the presence of fungal and parasitic infections in donors and donations of SoHO, and their transmission via transfusion and transplantation.

Methods: An algorithmic search, one each for fungal and parasitic disease, was applied to 6 scientific databases (PubMed, EMBASE, Web of Science, Scopus, Cochrane Library [trials], and CINAHL). Additionally, manual and algorithmic searches were employed in 15 gray literature databases and 22 scientific organization websites. The criteria for eligibility included peer-reviewed publications and peer-reviewed abstract publications from conference proceedings examining the prevalence, incidence, odds ratios, risk ratios, and risk differences for the presence of fungi and parasites in donors and SoHO donations, and their transmission to recipients. Only studies that scrutinized the donors and donations of human blood, blood components, tissues, cells, and organs were considered eligible. Data extraction from eligible publications will be performed independently by two reviewers. Data synthesis will include a qualitative description of the studies lacking evidence suitable for a meta-analysis and a random or fixed-effect meta-analysis model for quantitative data synthesis.

Results: This is an ongoing study. The systematic reviews are funded by the European Centre for Disease Prevention and Control, and the results are expected to be presented by the end of 2021.

Conclusions: The systematic reviews will provide the basis for developing a risk assessment for fungal and parasitic disease transmission via SoHO.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42020160090; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020160090 ; PROSPERO International Prospective Register of Systematic Reviews CRD42020160110; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020160110

International Registered Report Identifier (IRRID): DERR1-10.2196/25674

(JMIR Res Protoc 2021;10(6):e25674) doi:10.2196/25674

KEYWORDS

fungal and parasitic infections; donor-derived substances; transplantation; transfusion

Introduction

The European Union Directives have set safety interventions to prevent transmission of infections through substances of human origin (SoHO) [1,2]. The safety interventions are essential given a steady increase in transplantations of human tissues and cells [3] and transfusion of blood and blood components [4]. The directives specified mandatory testing of all SoHO donors and donations [1,2,5] for certain viruses and bacteria only. However, additional microbial tests are necessary on certain SoHO donations depending on the epidemiological situation (eg, syphilis, malaria, cytomegalovirus, toxoplasma, Epstein-Barr virus, *Trypanosoma cruzi*) [5].

Surveillance data on the presence and transmission of pathogens via cells, tissue, and blood are currently collected at the national and European Union levels. However, no such data are yet available for organ transplantations [5]. Globally, fungal diseases kill >1.5 million and affect >1 billion people annually, although most of them are preventable [4]. Likewise, parasitic diseases kill >45,000 and affect >23 million people annually worldwide [6], impacting human health and quality of life considerably. Therefore, more studies are needed on the transmission of parasitic diseases via SoHO [3]. Inefficient prevention of the SoHO transmittable diseases poses a significant economic impact on the national health systems. It is, therefore, necessary to conduct a systematic, comprehensive evidence accumulation and data synthesis to assess the risks and identify prevention strategies for fungal and parasitic disease transmission via SoHO to guide the infection risk management. The systematic review process of this protocol aims to identify, collect, and evaluate the evidence of fungal and parasitic infection transmission via SoHO from infectious donors and contaminated donations. The systematic review research questions were identified considering the PICO (Population, Intervention, Comparison, and Outcome) approach [7], including all key elements associated with the two systematic reviews. The two main objectives of this study were to identify the evidence of fungal infections in SoHO donors and donations, and their transmission via transfusion and transplantation, and to identify the evidence of parasitic infections in SoHO donors and donations, and their transmission via transfusion and transplantation.

Methods

The systematic review protocols are registered with PROSPERO (International Prospective Register of Systematic Reviews); registration numbers: CRD42020160090, CRD42020160110 [8,9]. The PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-analyses–Protocols) 2015 checklist used to check the reporting of the current protocol [10] can be found in Multimedia Appendix 1. All authors contributed equally to the systematic reviews' tasks, drafting the current protocol, and reviewing and approving the final version of the current protocol.

We will employ the FINER (Feasible, Interesting, Novel, Ethical, and Relevant) approach [11] to test the applicability of the research questions.

FINER Outcome

Feasible

A pilot search demonstrated an adequate number of studies for inclusion in the systematic reviews. The algorithmic search in the PubMed database retrieved 2320 and 1895 publications on the relevant fungal and parasitic infections, respectively. Additionally, the technical expertise of the review team, the time allocation, and the available funding guarantee its successful completion.

Interesting

The research questions are interesting as the systematic reviews aim at providing vital information on mitigating the risk of fungal and parasitic diseases transmission via SoHO. This is significant because fungal diseases kill >1.5 million and affect >1 billion people annually globally [4], while parasitic diseases kill >45,000 and affect >23 million people annually worldwide [6]. The European Centre for Disease Prevention and Control (ECDC) identified the knowledge gap and invested in addressing the problem [5]. The funding organization (ECDC) approved the current protocol.

Novel

The systematic reviews will confirm or reject the earlier findings and produce new findings on the fungal and parasitic infections transmission risks via SoHO donations or contaminations, which would be used to develop future preventive interventions.

Ethical

There are no ethical concerns regarding the current systematic review processes, as it will be entirely based on evidence accumulation from earlier studies.

Relevant

The research questions are relevant to current scientific knowledge, clinical practices, and health policies.

Search Strategy

The selection of the information sources was based on the relation of scientific topics to the systematic review research questions and information retrieved from analysis regarding the optimal database combination for biomedical systematic reviews [12]. The review team split the review sources into three broad categories—scientific databases containing peer-reviewed publications, databases with gray literature, and scientific organization websites.

Scientific Databases

Scientific databases for peer-reviewed publications included PubMed, EMBASE, Web of Science, Scopus, Cochrane Library (trials), and CINAHL.

Gray Literature Databases

Databases for gray literature included JSTOR, OpenGrey, ROAR, ROARMAP, OpenDOAR, GreyNet, British Library, TextRelease, APO, bioRxiv, arXiv, Google Scholar, Infectious Disease Advisor, Healthfinder, and TRIP (Turning Research into Practice).

Scientific Organization Websites

Scientific organization websites for identifying peer-reviewed publications, technical reports, and guidelines containing original data included World Health Organization; European Commission; ECDC; Centers for Disease Control and Prevention (CDC); National Health System, United Kingdom; International Foundation for Care; National Health Information Center; Agency for Toxic Substances and Disease Registry; Food and Drug Administration; Indian Health Services; National Center for Chronic Disease Prevention and Health Promotion; National Center for Emerging and Zoonotic Infectious Diseases; National Center for Health Promotion and Disease Prevention, Veterans Health Administration; National Center for Human Immunodeficiency Virus, Sexually Transmitted Disease, and Tuberculosis Prevention, CDC; National Institutes of Health; National Institute of Environmental Health Sciences; Office of Public Health Genomics, CDC; American College of Preventive Medicine; Robert Koch Institute; Australian Department of Health and Aging; National Notifiable Diseases Surveillance System; and ClinicalTrials.gov.

Search Procedure

The search strategy was based on the guidelines of the Cochrane Library [7], while relevant PRISMA flowcharts [13] were used to maintain records during the systematic review process. Two independent investigators performed a pilot searching using the PubMed database in September 2019. Following several searching combinations, the review team shaped up two main pilot algorithms (for fungal and parasitic diseases) to be used independently for the scientific databases containing peer-reviewed publications. The algorithms were formed using the Boolean OR, AND, NOT, and several truncations (ie, *). The review team judged both fungal and parasitic diseases pilot algorithms as applicable and appropriate for the official searching procedure. Two members of the review team, PCD and CH, independently conducted the official searching for eligible publications in the selected scientific databases (since their inception to October 2019) for both fungal and parasitic diseases algorithms. These search algorithms were “translated” from one database to another so that the corresponding website search engine could recognize them. ADF and YK confirmed no disagreement between the team members (PCD and CH) in applying the algorithms in all 6 scientific databases. A detailed search history is provided in Multimedia Appendix 1.

The official searching procedure for the gray literature databases and the organizations' websites was accomplished by three members of the review team (PCD, CH, and KP). Following the selection process, a search for the reference lists of systematic reviews, meta-analyses, technical reports, and guidelines relevant to the research questions will be done. Finally, the reference lists of the eligible publications will be screened to identify any research questions–related publications missed out in the initial searching.

Inclusion Criteria

The inclusion criteria are set for the types of studies, types of participants, and extracted data items.

Study Types

The review team identified the following types of studies to be included as eligible in the systematic review: (1) peer-reviewed experimental, epidemiological studies of any methodological design and case reports that examined the prevalence, incidence, odds ratios, risk ratios, and risk differences of the presence of the fungal and parasitic infections in SoHO from an infectious donor or contaminated donation to recipients; (2) peer-reviewed in vitro studies that explored the presence of fungi and parasites in SoHO donors and donations, and transmission via SoHO to humans; (3) technical reports or guidelines by any relevant organizations, where eligible peer-reviewed publications and related original data can be detected; (4) articles from any organizations that investigated disease prevention (eg, guidelines) relevant to the research objectives; (5) outputs in any language; (6) no date limits will be applied in the selection of eligible publications; (7) only peer-reviewed conference proceedings will be eligible from the gray literature, as failure to recognize trials reported in conference proceedings may impose a risk of bias in the effect estimates [14].

Participants Type

The type of participants in the eligible studies will be humans. The term “substances of human origin” (ie, SoHO) refers to blood, blood components, tissues, cells, and organs. As a result, therapeutic (plasma derived–medicinal products) and diagnostic products derived from humans will not be included in the systematic review. Therefore, the interventions to be considered will be blood and blood components’ donations and transfusions in humans, and tissue, cell, and organ donations and transplantations in humans.

Other Extracted Data Items

The other data items that will be extracted from the databases include the following: (1) population demographics from eligible studies; (2) number of cases and percentages of fungal and parasitic infections in SoHO donors and donations, and their transmission via SoHO donations; (3) the prevalence of fungal and parasitic infections in SoHO donors and donations, and transmission via SoHO donations; (4) odds ratios, risk ratios, and risk differences of the fungal and parasitic infections among SoHO donors and donations, and their transmission risks via SoHO donations between intervention (eg, individual blood transfusion, transplantation, etc) and control groups (eg, healthy individuals, individuals not receiving a blood transfusion, transplantation, etc); (5) associations of donor derived SoHO–related fungal and parasitic disease transmission with demographic characteristics of the population and with any other factor susceptible to the infections; (6) diagnostic methods for the transmissions associated with the relevant SoHO donations (not those related to other exposures); (7) medications received by patients before and during diagnosis; (8) follow-up measures including hospitalizations and deaths; (9) risk factors

of the fungi and parasitic infections or contaminations in SoHO donors and donations, and transmissions via SoHO donations; (10) type of infection screening tests in SoHO donors; and (11) country and continent of the population of eligible studies.

Exclusion Criteria

The exclusion criteria will be: studies not identifying the transmission of the fungal and parasitic diseases via SoHO donations; animal studies; in vitro studies; reviews, systematic reviews, and meta-analyses; letters to editors and opinion papers; theses and dissertations; and gray literature besides the published peer-reviewed conference proceedings relevant to the systematic reviews' research questions.

Selection Process

Two members of the review team will select the eligible publications independently. A referee investigator will be asked to decide in case of a disagreement between the two reviewers. The Cohen kappa test will be used to measure the interrater agreement in selecting the eligible publications [15]. A study's eligibility will be decided by screening the titles and abstracts using the EndNote software files, where the retrieved publications will be saved. The selection review team will ensure the identification and exclusion of retracted publications. The team will also ensure locating the inaccessible eligible publications' full texts through emails to the lead authors and publication journals. The eligible publications without full texts will be listed in the systematic review with reasons. Finally, for transparency reasons, a complete list of the excluded publications will also be included in the systematic review.

Data Extraction

An individual data extraction form (Cochrane Library model) [7] will be incorporated for each eligible publication. Two reviewers will extract the data independently from the eligible publications. A referee investigator will make the ultimate decision in case of a disagreement between the reviewers. A priori pilot data extraction will be used to include any missing data that were not initially considered or extracted. The data will be collected as two tables in Excel format, one each for the fungal and the parasitic disease. The data extraction–review team members will contact the corresponding authors via email if the outcome data in the full-text articles are unclear.

Outcomes and Prioritization

The priority of the outcomes of this systematic review are as follows: (1) intervention type (ie, number of donations, blood or blood components transfusion, type of transplantation); (2) the association of the presence of fungal and parasitic infections in SoHO donors, donations, and their transmission through SoHO donations with any physiological and demographic characteristics of the populations, including aspects such as environmental conditions; (3) the prevalence of the presence of fungal and parasitic infections in SoHO donors, donations, and transmission via SoHO donations; (4) odds ratios, risk ratios, risk differences, and hazard ratios of fungal and parasitic infections or contaminations in SoHO donors, donations, and their transmission via SoHO donations; (5) cause of the infection in donors or the contamination of donation; (6) the type of screening test of infection and the donor types; (7) hospitalizations and deaths; (8) region (country and continent); and (9) diagnostic method.

Assessment of Methodological Quality

The review team will use the methodological design of each eligible publication to determine the risk of bias assessment. Three appropriate tools are going to be used: the Cochrane Library tool [16] for the risk of bias assessment in randomized controlled trials (RCT); the ROBINS-I tool (Risk of Bias in Nonrandomized Studies–of Interventions) [17] for the risk of bias assessment in non-RCT studies using an intervention, and the RTI item bank tool [18] for the risk of bias assessment in observational studies. Two reviewers will assess the risk of bias in the eligible publications independently, and a referee investigator will decide in case of a disagreement. The Cohen kappa test will be used to measure the interrater agreement in the evaluation results [15]. Finally, the risk of bias assessment results will be extracted in relevant tables and figures according to the Cochrane Library format [7].

Data Synthesis and Prospective Meta-analysis Methods

The eligible studies with data not suitable for meta-analysis will be summarized into a qualitative description. In the case of the eligible studies with pertinent data for meta-analysis, a random or fixed-effect meta-analysis model will be used to account for heterogeneity due to differences in study populations, types of infections, interventions, study durations, and other factors. All meta-analyses will be conducted using the RevMan 5.3 software (Nordic Cochrane Centre, The Cochrane Collaboration) [19].

The prevalence for meta-analysis will be calculated using the following formula [7]

Standard errors for the meta-analysis will be calculated using this formula [7]

Standard errors will then be used for weighted proportions, and the RevMan 5.3 software [19] will be used to generate the forest and funnel plots. The funnel plots will only be generated for those meta-analyses that include more than 10 studies [7]. The odds ratios, risk ratios, and risk differences for meta-analyses will be calculated using a dichotomous, inverse variance method, referring to infection incidences of the individuals with an intervention (ie, transfusion, transplantation) against infection incidences of individuals without any interventions. The weighted proportions of such meta-analyses will be calculated based on each study's sample size. The time-to-event outcomes (hazard ratio) for a meta-analysis will be calculated using the generic inverse variance, or an O and E variance fixed effect model [7].

The 95% CI and heterogeneity between studies will be evaluated using the I^2 statistic. The results for heterogeneity will be considered statistically significant at $P<.10$, while the I^2 index interpretations will be made based on earlier guidelines [7]. Small study effects, potentially caused by publication bias, will be assessed using the funnel plots [7]. The risk of bias

assessments will be incorporated in data synthesis and used for the forest plots [7]. Finally, the standardized mean difference (SMD) (ie, the difference in mean outcomes between groups/standard deviation of outcomes among participants) will be used for the meta-analysis studies that assess the same outcome using different measurement scales [7].

Meta-bias Assessment

The reporting of the eligible publications will be checked independently by two review team members, while a referee will make the final decision in case of a discrepancy between them. The interrater agreement in the evaluation results will be tested using the Cohen kappa test [15]. The 25-item checklist of the CONSORT (Consolidated Standards of Reporting Trials) [20] will be adopted for the eligible RCTs. The 22-item STROBE checklist (Strengthening the Reporting of Observational studies in Epidemiology) [21] will be employed for the eligible observational studies and published conference proceedings. A score will be calculated for each eligible study following a previous methodology [22]. The reporting scores of the eligible studies will not be used for assessing the methodological quality of the eligible studies; however, they will be used for measuring the reporting quality as a risk factor for the critical appraisal of eligible papers due to missing information [23].

Confidence in Cumulative Evidence

Two reviewers will independently appraise the implications and applicability of the findings of the systematic reviews using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) analysis [24]. The GRADE analysis rates the quality of the best available evidence, which can be used for developing healthcare recommendations and guidelines. The four-level GRADE ratings classify the quality of evidence as high, moderate, low, and very low. The low-quality evidence characteristics include an observational study, risk of bias, inconsistent results, indirectness, imprecision, and publication bias. The high-quality evidence characteristics include an RCT study, a large magnitude of effect, demonstration of a dose–response relationship, and if residual confounding factors that are plausibly expected to reduce or increase the demonstrated effect do not actually reduce or increase it. A critical appraisal of the current systematic review process will be performed using the AMSTAR (A Measurement Tool to Assess Systematic Reviews) checklist [25], a critical appraisal tool for assessing the quality of systematic reviews.

Results

This is an ongoing study. The systematic reviews are funded by the ECDC, and the results are expected to be announced by the end of 2021.

Discussion

Overview

The two systematic reviews aim to identify the scientific evidence on transmission risks of fungal and parasitic diseases via SoHO globally. The retrieved evidence would assist an evidence-based risk assessment of the fungal and parasitic transmission through SoHO donations and evaluating the available prevention strategies within the European Union. The study results will be used to create an evidence pool containing the geographical data for transmission risks, genetic, physiological, and demographic characteristics of the infected populations, the infection cause and the type of screening tests for donors, and diagnostic methods of the infections. It is also possible that a meta-analysis of these data will be incorporated, which will further strengthen the evidence-based risk assessment approach.

Strengths and Limitations

The systematic review process has many strengths. The protocol followed the PRISMA-P guidelines. The searching procedure used robust algorithms with standardized indexing terms to retrieve records that had different words to describe the same concept and information beyond the words in the title and abstract [7]. We will use well-established tools [16,18] to evaluate the included studies. Additionally, to reduce bias, two investigators will work independently on screening the data for eligibility, risk of bias assessment, data extraction, and the CONSORT and STROBE scores. The search procedure of the systematic reviews had no restrictions regarding the date of publication, study design, and language. The GRADE analysis will allow an excellent evaluation of the quality of the outcomes.

The systematic review process has limitations too. We excluded gray literature, incorporating a publication bias. Nevertheless, the inclusion of gray literature may itself introduce bias, and one reason to include the gray literature is the absence of peer-review sources [7]. Another limitation that we foresee is that we have accepted the peer-reviewed in vitro studies as eligible, even though it is scarce to identify such studies. We have included these studies to increase the transparency and validity of our systematic review process.

Conclusions

These systematic reviews will form the basis for developing a risk assessment of fungal and parasitic disease transmission via SoHO.

Acknowledgments

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Authors' Contributions

All authors contributed equally in drafting, writing, and reviewing the current protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P checklist and searches.
[DOCX File , 92 KB - resprot_v10i6e25674_app1.docx]

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Abbreviations

AMSTAR: A Measurement Tool to Assess Systematic Reviews
CONSORT: Consolidated Standards of Reporting Trials
ECDC: European Centre for Disease Prevention and Control
FINER: Feasible, Interesting, Novel, Ethical, and Relevant
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
PICO: Population, Intervention, Comparison, and Outcome
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-analyses–Protocols
PROSPERO: International Prospective Register of Systematic Reviews
RCT: randomized controlled trial
SMD: standardized mean difference
SoHO: substances of human origin
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
TRIP: Turning Research Into Practice

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Protocol

Risk Indicators for Early Childhood Caries in South Africa: Protocol for a Systematic Review

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Abstract

Background: Early childhood caries (ECC) is a common disorder characterized by the presence of one or more decayed (non-cavitated or cavitated lesions), missing (due to caries), or filled tooth surfaces of primary teeth in children 71 months old or younger. South Africa has a diverse population in terms of culture, education, income, and occupation. This diversity is due to the consequences of historical racial discrimination, poverty, unemployment, lack of accessibility to health services, and quality of education. These factors make South Africa unique, and the disease and risk profiles for this country differ from those of other countries at similar stages of development. For these reasons, it is important to identify the unique maternal and infant risk factors for ECC in the South African context.

Objective: The purpose of this study is to determine the risk factors associated with the incidence and prevalence of ECC in South Africa in children under the age of 6 years.

Methods: All cross-sectional and cohort studies documenting risk factors associated with the prevalence and incidence of dental disease and severity (decayed, missing, and filled scores) will be included. We will search 7 databases for eligible studies, and those included will be based on prespecified inclusion criteria. Only studies conducted with South African children who are aged 6 years and younger in which dental caries risk factors are documented will be included. There is no restriction on the time or language of publication. Included articles will be scrutinized for quality by using a risk of bias tool developed by the Joanna Briggs Institute. The results will be presented narratively, and if possible, a meta-analysis will be performed.

Results: The literature search was conducted in November 2020.

Conclusions: The results of this study will provide a framework to inform medical and dental personnel to highlight mothers and infants at risk of developing ECC.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42020216455; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=216455

International Registered Report Identifier (IRRID): DERR1-10.2196/26701

(JMIR Res Protoc 2021;10(6):e26701) doi:10.2196/26701

KEYWORDS

dmft; infant; risk factors; dental caries; South Africa; early childhood caries

Introduction

Noncommunicable diseases (NCDs), including early childhood caries (ECC), contribute to global public health challenges. Of the world's population, 26% are under the age of 16 years [1], and approximately 2.1 billion children are affected by NCDs [2]. Untreated dental caries in primary teeth is the tenth most prevalent health condition worldwide [3].

ECC is a common disorder characterized by the presence of one or more decayed (noncavitated or cavitated lesions), missing (due to caries), or filled tooth surfaces of primary teeth in children 71 months old or younger. Severe ECC is either any smooth tooth surface decay in children under 3 years old or one or more cavitated, missing (due to caries), or filled smooth tooth surfaces in the primary maxillary anterior teeth in children between the ages of 3 and 5 years [4].

Young children depend on either their parents or caregivers for their health needs and general well-being. For this reason, the responsibility of preventing NCDs such as ECC in this age group lies exclusively with their carers. There are several theoretical frameworks proposing the evolution of ECC [5-8] and an equal number of strategies aimed at preventing the disorder [9-12]. However, the battle against ECC continues.

In the past few decades, several researchers have investigated the etiology of ECC. Like dental caries, ECC occurs as an interplay of at least 4 factors: cariogenic bacteria, fermentable carbohydrates, a susceptible tooth surface, and time. Traditionally, *Streptococcus mutans* (*S. mutans*) has been implicated as the key microorganism of dental caries. Recent studies based on DNA and RNA extracted from carious lesions have revealed that *S. mutans* forms a small part of a diverse biome that interacts synergistically to initiate and enlarge a carious lesion [13]. Oral bacteria can metabolize fermentable carbohydrates such as monosaccharides resulting in an increased production of acids capable of demineralizing dental hard tissue, especially enamel, over a period of time [13]. Apart from the known causative factors, several risk factors are associated with ECC.

Both maternal and infant risk factors have been implicated in the initiation and evolution of ECC. These include socioeconomic status, level of parental education, maternal age, caregiver depression, Vitamin D deficiency, and immigration status. Dental epidemiologists have explored the relationship between ECC and various risk factors for many decades. Despite their efforts, there has been little agreement on the findings, and ECC remains a global challenge affecting countless children.

South Africa has a diverse population in terms of culture, education, income, and occupation. This diversity is due to the consequences of historical racial discrimination, poverty, unemployment, lack of accessibility to health services, and quality of education. Furthermore, there is a distinct divide in the socioeconomic standing of the South African population that results in inequalities in essential health and oral health care [14]. These factors make South Africa unique, and the disease and risk profiles may differ from those of other countries at similar stages of development. In South Africa, children with ECC treated in public state facilities often present for multiple extractions under dental general anesthesia [15]. Apart from the financial costs and long waiting lists, repeated use of general anesthesia in young children poses inherent risks [15].

The aim of this study is to identify the unique maternal and infant risk factors for ECC in a South African context. The authors are confident that the outcome of the present investigation will raise awareness among caregivers, oral health professionals, general practitioners, and other stakeholders [16].

Methods

This systematic review will collect and synthesize data to determine the maternal and infant risk factors for ECC in South Africa. This protocol will be conducted according to the PRISMA-P (Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols) guidelines [17]. The search strategy will only be used to identify published studies conducted within South Africa. An initial search was used to identify suitable articles. A search strategy will be developed for each database. The words in the title and abstracts will be screened to determine the initial suitability of the articles. All references of included articles will be perused for more suitable titles. The search strategy will include the following terms: (((“South Africa”) AND (children OR “peri-natal” OR paediatric OR pediatric OR neonatal OR infant)) AND (“risk factor*” OR risk or factor*)) AND (“early childhood caries” OR caries OR decay OR dmft OR dental OR oral OR PUFA).

Eligibility Criteria

Cross-sectional and cohort studies that report on the maternal and infant risk factors for ECC in South Africa will be included in the review. There will be no limitations pertaining to the date of publication. Studies published in all South African official languages will be included. Non-English articles will be translated by the Department of Foreign Languages at the University of the Western Cape or a reputable translation company. To validate the translations, this paper will cross-reference the original article with the English abstract (which is usually available online), and reverse translations will be conducted to ensure its validity.

Information Sources

Search Strategy

Two independent reviewers will search the identified search engines to locate both published and unpublished studies.

Study Selection and Data Management

Two reviewers will select studies for inclusion based on the inclusion and exclusion criteria. An initial search of PUBMED was undertaken to identify articles pertaining to the maternal and infant risk factors for ECC in South Africa. The text words contained in the titles and abstracts of relevant articles and the index terms will be used to develop a full search strategy for PubMed/Medline, Cochrane, Scopus, Academic Search Complete, Dentistry and Oral Science sources, CINAHL, and Science Direct. The search strategy, including all identified keywords and index terms, will be adapted for each database or information source.

Commentaries or letters and other grey literature will be excluded from this review.

Secondary searching (PEARLing) will be conducted (PEARLing is a search strategy where the reference lists of all the studies, whether included or excluded, are identified for possible inclusion). Manual searching will not be conducted due to the difficulty in replicating this method.

The literature search will be recorded in a data capture sheet (Multimedia Appendix 1) that will include the source, the date of search, the number of hits, and a reference link to the publications. This will be carried out after duplications have been resolved. Study selection will be blinded, and any disagreements will be resolved by discussion. A data extraction tool (Multimedia Appendix 2) will be used to guide reviewers on the data that would need to be extracted from selected articles. The extracted data will be recorded in an Excel spreadsheet and will include publication details, the setting of the research study, age of the population, gender, periodontal disease clinical determinants, number of cases, and total sample size. Rayyan [18] will be used to resolve duplications and record all reviewer decisions.

All studies will be included, regardless of methodological quality. The quality assessment of studies will be performed using the Joanna Briggs Institute Critical Appraisal Checklist for Studies [19]. There will be 2 reviewers involved in the quality assessment, and disagreements will be resolved through discussion.

A meta-analyses of studies with similar comparisons reporting the same outcomes will be conducted. This paper will use a random-effects model if there are 4 or more studies. This paper will report the results from studies not suitable for inclusion in a meta-analysis. There will be no I^2 cut-off point to assess heterogeneity. Meta-analysis will be performed using STATA 15.

Results

This review will be conducted from January 2021 to June 2021. The Prospero registration number is CRD42020216455**.** Two reviewers will be blinded at each stage of the process. Regular team meetings will be held to settle any disputes or differences between the reviewers' inclusions. This will serve to enhance the reliability and validity of the review process. All discussions will be recorded as evidence. There will be no conflict of interest within the team.

Study Selection

Papers will be uploaded into Rayyan [18] and screened in 2 stages. Two review authors will independently assess all the titles and abstracts of the identified studies against the inclusion criteria. For each study appearing to meet the inclusion criteria or where there is insufficient information to make a clear decision, the full text will be obtained, and 2 review authors will independently assess it to establish whether the study meets the inclusion criteria. Where agreement is not achieved, a third review author will be contacted. The searching process will include all eligible studies published before November 15, 2020. All eligible studies will be included, and authors will be contacted if any further clarification is needed.

After reading full-text articles, those that do not meet the inclusion criteria will be discarded. Details of the excluded studies and reasons for their exclusion will be documented in a "Characteristics of excluded studies" table. The reference list of all included studies will be investigated for further eligible studies.

Data Extraction and Management

Data Extraction and Recording Process

Two review authors will independently extract the data from the studies using a predefined data extraction form (initially piloted on a small sample of studies). Any discrepancies will be resolved through consultation with a third review author. If any information from the studies is unclear or missing, the authors of the original papers (where feasible) will be contacted for further information.

Study information data include author, title, year of publication, study design, and year that study was conducted.

Participant level data including maternal risks and infant risks, such as socio-demographic factors; dietary factors; oral hygiene factors; factors related to bottle or breast-feeding; oral bacterial flora; and other factors will be recorded.

Availability of Data and Materials

If study articles are not obtainable, a librarian will be consulted, and if the study is still not obtainable, the study will not be included in the qualitative or quantitative analysis.

Study Quality and Risk of Bias Assessment

The quality assessment of studies will be performed using the Joanna Briggs Institute Critical Appraisal Checklist for Studies reporting Prevalence Data [20].

Analysis of Study Findings

A meta-analysis of findings may be performed.

Results to Date

This protocol was registered with PROSPERO in November 2020, and the completed electronic searches were performed by November 15, 2020. The original search yielded 1366 articles. This study aims to highlight the risk factors associated with the incidence or prevalence of ECC in South Africa in children under the age of 6 years. The findings of this study will be used to provide stakeholders with the necessary tools to educate policymakers on the best framework to prevent or limit this disease and future NCDs in childhood and adolescence.

Discussion

Overview

The study aims to determine the maternal and infant risk factors that can contribute to the incidence or prevalence of dental caries in children under the age of 6 years in South Africa. Current evidence suggests that *S. mutans*, enamel defects, and presence of dental caries are responsible for the incidence of dental caries in this population [21]. However, with South Africa being the

most unequal county in the world with a Gini index of 63 [22], it is not surprising that there may be other risk factors such as sociodemographic factors that could be playing a role in the development of this disease.

Conclusions

There is a paucity of information on maternal and infant risk factors associated with the incidence or prevalence of ECC in South Africa. There is a need to synthesize the existing data to highlight risk factors that could limit the scourge of this preventable disease.

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Authors' Contributions

All the authors contributed equally to the development and writing of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[PDF File (Adobe PDF File), 46 KB - resprot_v10i6e26701_app1.pdf]

Multimedia Appendix 2
Data capture sheet.
[PDF File (Adobe PDF File), 47 KB - resprot_v10i6e26701_app2.pdf]

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Abbreviations

ECC: early childhood caries
NCD: noncommunicable disease
PRISMA-P: Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols

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Protocol

The Effectiveness and Usability of Online, Group-Based Interventions for People With Severe Obesity: Protocol for a Systematic Review

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Abstract

Background: Globally, obesity is a growing crisis. Despite obesity being preventable, over a quarter of the UK adult population is currently considered clinically obese (typically body mass index ≥35 kg/m^2). Access to treatment for people with severe obesity is limited by long wait times and local availability. Online and group-based interventions provide means of increasing the accessibility of obesity prevention and treatment services. However, there has been no prior review of the effectiveness of group-based interventions delivered online for people with severe obesity.

Objective: The purpose of this systematic review protocol is to provide an evaluation of the effectiveness and usability of different types of online, group-based interventions for people with severe obesity.

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) and the Population, Intervention, Comparator, Outcome, and Study (PICOS) frameworks were used to structure this review. The review will systematically search 7 databases: MEDLINE, Embase, the Cumulative Index of Nursing and Allied Health Literature, APA PsycNet, Web of Science, CENTRAL, and the ProQuest Dissertations and Theses databases. Two authors (MM-I and LB) will independently screen the titles and abstracts of identified articles, select studies for inclusion based on the eligibility criteria, and extract data into a standardized form. Any disagreements will be discussed and resolved by a third reviewer (EM) if necessary. Risk of bias will be assessed using the Cochrane Collaboration Risk of Bias 2 tool and a descriptive analysis will be used to evaluate effectiveness and usability.

Results: The systematic review has not yet been started. It is expected to be completed and submitted for publication by December 2021.

Conclusions: This systematic review will summarize the effectiveness and usability of online, group-based interventions for people with obesity. It will identify the types of online delivery that have the strongest support to help inform the development of more useful and engaging interventions for people with severe obesity.

Trial Registration: National Institute for Health Research, PROSPERO CRD42021227101; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021227101

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KEYWORDS

internet-based interventions; telemedicine; group-based interventions; obesity; severe obesity; obesity management; weight loss; weight reduction programs; diet therapy; exercise; systematic review; weight management

Introduction

Background

Obesity is a serious and growing crisis; over a quarter of UK adults are considered obese (26% of men and 29% of women) [1]. Adults with a BMI greater than or equal to 35 kg/m^2 are considered to have a very high health risk [2]. This is a significant concern, as obesity has been linked to several physical and mental health conditions, such as type 2 diabetes, heart disease, cancer, stroke, and depression [3,4]. The COVID-19 pandemic has only made obesity a more urgent health issue to tackle. Evidence to this point has identified a notably increased risk of severe COVID-19 symptoms, need for hospitalization and intensive care, and increased mortality for patients who are overweight and obese [5]. This has highlighted the need for sustained and effective interventions to improve physical activity and dietary behaviors to prevent a worsening impact on health outcomes [5].

The UK has a 4-tiered pathway for obesity services: tier 1 refers to universal obesity prevention services, tier 2 covers community-based lifestyle weight management services, tier 3 is specialist obesity services (provided by a multidisciplinary team), and tier 4 is surgery [6,7]. The higher tiers (3 and 4) are specifically targeted toward adults with high BMIs (≥40 kg/m^2, or 35 kg/m^2 with a comorbidity) [4].

In practice, access to these services is not universal. An All-Party Parliamentary Group found that more than one-third of people with obesity had not accessed any of these services, and almost 40% of those who did found the process moderately or incredibly difficult [8]. Additionally, of the 91% of Clinical CoMM-Issioning Groups (that tier 3 services fall under) that responded to a freedom of information request, less than 60% coMM-Issioned tier 3 services [8]. Likewise, in a survey conducted by Public Health England, people reported long waiting lists and a lack of local availability for tier 3 services [9]. A longitudinal cohort study found that almost three-quarters of people with severe obesity (BMI ≥35 kg/m^2) did not access any treatment over the course of 7 years; this figure was lower, but still high (almost 60%), for people with morbid obesity (BMI ≥40 kg/m^2) [10]. These statistics highlight a significant problem with access to and availability of obesity prevention services in the UK.

Rationale

There are several strategies that can help address the need for greater accessibility of interventions for people with severe obesity. Group-based interventions may improve accessibility by potentially reducing the resources needed to provide interventions by supporting more patients with fewer staff hours required. This also has the potential to reduce waiting times to access interventions [4]. Group-based interventions are a common tool to promote health behavior change [11] and previous systematic reviews have found that group-based interventions are generally effective at promoting physical activity and weight loss [12,13].

Another strategy that is increasingly used to improve accessibility to a variety of health interventions is the use of digital and online platforms of delivery. Online delivery strategies have become increasingly common as COVID-19 restrictions have forced services to adapt the way they provide support [14]. A wide variety of platforms have been used to deliver services, with mixed feedback from participants [14]. A previous systematic review found evidence suggesting that web-based interventions are more effective at promoting and maintaining weight loss than minimal or no interventions, but that evidence of their effectiveness compared with in-person interventions is mixed [15]. Another systematic review found that online interventions were more effective at promoting weight loss in the short term, but not the long term, compared with offline interventions [16]. A systematic review of mobile-based interventions for people who are overweight or obese also found evidence of their effectiveness in primary and secondary health care settings [17], but evidence for their effectiveness in general is mixed [18].

This suggests that online platforms have potential to support effective weight loss interventions, but that further research is needed to determine best practice.

Combining these 2 strategies (ie, group based and web based) could further improve the accessibility of interventions, particularly given the COVID-19 restrictions on in-person interactions. However, no previous systematic reviews were identified that examined online, group-based interventions for people with obesity. One systematic review did review online social network weight management interventions, but only included 5 studies and was focused specifically on social networks without including other types of online interventions [19]. Several searches of keywords (“online OR digital,” “group-based interventions OR group interventions OR group behaviour change,” and “weight loss OR obesity”) on PROSPERO failed to identify any systematic reviews that are currently exploring the effectiveness of different types of online, group-based interventions for people with obesity.

Therefore, there is a need for a systematic review of studies that evaluate online, group-based interventions for people with severe obesity to determine their effectiveness, usability, and the conditions which make them most effective and engaging for participants. An overview of the different types of online, group-based weight loss interventions will make it easier to identify best practices and contribute to the development of new online, group-based interventions that can best promote and maintain weight loss.

To focus the evaluation, this systematic review will examine 2 main research questions. First, what means of delivering online, group-based behavior change interventions for adults with severe obesity is the most effective at establishing and maintaining positive health behavior changes and weight loss? Second, what are the perceptions of the acceptability, usability, and overall user experience for different online, group-based behavior change interventions for adults with severe obesity?

Methods

Overview

The Population, Intervention, Comparator, Outcome, and Study (PICOS) template and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) [20] will be used to structure the review and to identify appropriate Medical Subject Headings (MeSH) for the literature search (Multimedia Appendix 1). This systematic review will be composed of a literature search, article selection, data extraction, quality appraisal, data analysis, and data synthesis. This review was prospectively registered on PROSPERO (reference number: CRD42021227101).

Eligibility Criteria

The PICOS-type framework (Table 1) is based on the research question stated above.

Table 1. PICOS framework.

Framework component	Description
Population	Adults (≥18 years) with severe obesity (defined for this review as BMI ≥35 kg/m^2)
Intervention	Online, group-based interventions aiming to change health behavior relating to obesity (physical activity and dietary behavior)
Comparator	Other types of group-based interventions, including comparisons with face-to-face, phone, and other online platforms than the main intervention
Outcomes	The primary objective is to identify the types of online platforms used for group-based interventions for people with obesity and their effectiveness. Therefore, the primary outcomes will be the effectiveness of the interventions at supporting behavior changes (physical activity and dietary behavior) and weight loss. Secondary outcomes will include levels of engagement with the intervention, and patient-reported experience (including measures of acceptability, usability, or satisfaction). Other secondary outcomes—including details about the intervention design, aim, and format—will also be examined.
Study types	Studies that evaluate at least one online, group-based intervention for people with severe obesity will be eligible (including randomized controlled trials, quantitative, qualitative, cohort, and case studies). Reviews, protocols, and papers that describe interventions without evaluating them will be excluded.

Search Strategy

Seven databases will be searched to find articles for this review: MEDLINE, Embase, CINAHL, APA PsycNet, Web of Science, the CENTRAL, and the ProQuest Dissertations and Theses databases. Key terms relating to online, group-based interventions for people with severe obesity were extracted from an initial review of the literature and used to develop the search terms and search strategy. Search terms will include MeSH terms and title / abstract keywords relating to online interventions, group-based interventions, and severe obesity. The search terms that will be used in this review are grouped into those 3 themes (Table 2) and the search string will be created using the following structure: online (MeSH OR Keywords) AND group-based (MeSH OR Keywords) AND severe obesity (MeSH OR Keywords). No date limit will be set. See Multimedia Appendix 2 for a sample search string.

Table 2. Search terms.

Component	MeSH	Keywords (in title or abstract)
Online	Internet-based intervention/ OR internet/ OR telemedicine/ OR videoconferencing/	Internet OR web OR online OR remote OR digital OR video* OR virtual OR technolog*
Group-based	Psychotherapy, Group/ OR Peer Group/ OR Group Processes/	(group* adj3 (based OR treatment* OR therap* OR virtual OR session* OR peer* OR support*)) OR “group intervention”
Severe obesity	exp obesity/ OR obesity management/	obesity OR obese OR specialist weight management OR Tier 3 weight management OR (BMI adj1 ("35" OR “40” OR “45”))

Inclusion Criteria

The review will include studies that evaluate online, group-based interventions for people with severe obesity (defined for this review as BMI ≥35 kg/m^2). Online, group-based interventions will be defined as an intervention delivered primarily online to a set of 3 or more people. Interventions that are primarily group based will be included, even if they have a small individual component. Interventions will need to target weight management for people with obesity but can focus on behavioral (eg, diet, physical activity) or physical (eg, weight loss or maintenance of weight loss) components. Interventions with comparisons to control groups with no intervention, waiting list or irrelevant interventions, minimal interventions, usual care, in-person interventions, or other online interventions will all be included.

Exclusion Criteria

Studies of children and adolescents (participants aged < 18) will be excluded. Studies that address diet or physical activity behavior changes with a primary purpose other than managing obesity or weight loss (eg, rehabilitation after surgery, chronic obstructive pulmonary disease, diabetes) will also be excluded. Interventions that are primarily one-on-one but have a small group-based component will be excluded.

Screening and Article Selection

The references identified from the database searches will be exported into a citation management software (EndNote X9; Clarivate Analytics) for storage and duplicate removal. There will be 2 stages of screening: (1) 2 independent reviewers (MM-I and LB) will screen the titles and abstracts and (2) 2 independent reviewers will screen the full text of the studies to determine final eligibility for inclusion. All disagreements between the reviewers will be discussed and a third reviewer (EM) will be consulted if consensus cannot be reached. A PRISMA flow diagram will be used to record the details of the screening and selection process to ensure study reproducibility.

Data Extraction

Two independent reviewers (MM-I and another reviewer) will examine the full text of all of the included articles to extract outcomes into a predetermined form (Textbox 1). Any disagreements between the reviewers will be discussed and resolved by a third reviewer (EM) if consensus cannot be reached.

Textbox 1. Article information and data extraction.

General study information

- Year of publication
- Country of study
- Sample demographics (including age, gender, target population)
- Initial sample size
- Analyzed sample size

Intervention

- Online platform
- Aim of intervention (eg, increase physical activity, improve dietary behavior)
- Group size
- Number and length of intervention sessions
- Intervention duration and follow-up periods
- Theory the intervention is based on (if any)
- Behavior change techniques [21] used in the intervention (if any)

Evaluation

- Outcomes measured
- Effect of intervention on behavior change outcomes
- Effect of intervention on health outcomes (eg, weight, BMI)
- Participant engagement (eg, drop-out rates, number of sessions attended)
- Acceptability
- Usability
- Participant satisfaction/feedback
- Other key performance indicators reported

Quality Appraisal and Risk of Bias Assessment

Two reviewers (MM-I and another reviewer) will independently assess the risk of bias of all of the included studies. Any disagreements will be discussed or resolved by a third reviewer (EM). The risk of bias of the randomized controlled trials will be assessed using the Cochrane Collaboration Risk of Bias 2 tool to assign high or low risk of bias, or some concerns [22,23]. Nonrandomized studies will be assessed using the ROBINS-I tool [24]. Figures will be created to summarize the risk of bias in each study and the extent of each bias across all studies.

Data Analysis and Synthesis

Because of the expected variety of study aims, measures, and reported outcomes, it is not likely that a meta-analysis will be feasible. However, the feasibility of a meta-analysis will be considered when studies have been assessed. A descriptive analysis will be conducted to summarize the extracted data.

General study information will be summarized in a table. Outcomes relating to the intervention will be synthesized quantitatively (eg, by providing the percentage of studies that used a particular platform, theory, or behavior change technique and had a particular aim and by providing the mean, median, and range for outcomes such as group size, number of sessions, and session duration).

The primary outcomes—the effect of the intervention on behavior change and health outcomes—will be quantified by providing the percentage of studies that found significant evidence of effectiveness. Substantial evidence of effectiveness will be defined as a significantly better performance of the intervention than the comparator. Behavior change and physical health outcomes will be considered separately.

Analysis of other outcomes, such as acceptability, usability, and patient feedback will be determined upon review of the studies, as they could be analyzed qualitatively or quantitatively depending on what is reported. Any qualitative data reported by the study will be assessed using a thematic analysis to identify similarities and differences in participant responses to the interventions. The risk of bias in the studies will be considered in the synthesis.

Results

The full systematic review is expected to be completed and submitted for publication by December 2021.

Discussion

A systematic review of the literature on online, group-based behavior change interventions for adults with severe obesity will contribute to the establishment of guidelines for best practice. With the strained capacity to provide specialist weight management services (also known as tier 3 services), and the additional constraints of the COVID-19 pandemic on group-based and face-to-face services, a better understanding of how group-based interventions can be effectively delivered remotely will help inform and improve the development of online interventions for adults with severe obesity in the UK. Based on the data, this section will explore what conclusions can be drawn, the limitations of the systematic review, and key topics for future research.

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Authors' Contributions

The review topic was conceived by all the authors collectively. MM-I wrote the protocol with revisions from DS, LB, JP, MT, RC, AC, and EM.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P checklist.
[DOC File , 82 KB - resprot_v10i6e26619_app1.doc]

Multimedia Appendix 2
Sample search.
[DOCX File , 15 KB - resprot_v10i6e26619_app2.docx]

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Abbreviations

MeSH: Medical Subject Headings
PICOS: Population, Intervention, Comparator, Outcome, and Study
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

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Protocol

Impact of Digital Educational Interventions to Support Parents Caring for Acutely Ill Children at Home and Factors That Affect Their Use: Protocol for a Systematic Review

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Abstract

Background: Urgent and emergency care health services are overburdened, and the use of these services by acutely ill infants and children is increasing. A large proportion of these visits could be sufficiently addressed by other health care professionals. Uncertainty about the severity of a child's symptoms is one of many factors that play a role in parents' decisions to take their children to emergency services, demonstrating the need for improved support for health literacy. Digital interventions are a potential tool to improve parents' knowledge, confidence, and self-efficacy at managing acute childhood illness. However, existing systematic reviews related to this topic need to be updated and expanded to provide a contemporary review of the impact, usability, and limitations of these solutions.

Objective: The purpose of this systematic review protocol is to present the method for an evaluation of the impact, usability, and limitations of different types of digital educational interventions to support parents caring for acutely ill children at home.

Methods: The review will be structured using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) and Population, Intervention, Comparator, and Outcome (PICO) frameworks. Five databases will be systematically searched for studies published in English during and after 2014: Medline, EMBASE, CINAHL, APA PsycNet, and Web of Science. Two reviewers will independently screen references' titles and abstracts, select studies for inclusion based on the eligibility criteria, and extract the data into a standardized form. Any disagreements will be discussed and resolved by a third reviewer if necessary. Risk of bias of all studies will be assessed using the Mixed-Methods Appraisal Tool (MMAT), and a descriptive analysis will be used to evaluate the outcomes reported.

Results: The systematic review will commence during 2021.

Conclusions: This systematic review will summarize the impact, usability, and limitations of digital interventions for parents with acutely ill children. It will provide an overview of the field; identify reported impacts on health and behavioral outcomes as well as parental knowledge, satisfaction, and decision making; and identify the factors that affect use to help inform the development of more effective and sustainable interventions.

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KEYWORDS

acute disease; telemedicine; child; pediatrics; childhood disease; childhood illness; health education; health literacy; help-seeking behavior; child health; digital intervention; mHealth; primary care; sick child

Introduction

Background

Uncertainty about the severity of a child's symptoms has been identified as a key factor prompting parents to seek unscheduled health care and present to emergency departments with acutely ill children or to delay accessing appropriate services [1,2]. Acute illness is typically defined as rapid onset, short-term illness [3,4]. In children, acute illnesses are mainly common, minor conditions like colds, viral rashes, ear infections, or vomiting [5]; however, they can also be severe [3]. Low health literacy has been found to be a factor in parental overestimates of child illness severity, increased urgency for seeking care, and increased use of emergency services [6,7]. There has been an increase in the use of urgent hospital services by children and infants across England in the past decade, including for nonurgent presentations [8-10]. Emergency services are more frequently used by children and young people than adults [8,11]. Estimates of the proportion of nonurgent Accident and Emergency (A&E) attendances range from 15% to 40%, many of which were by young children with minor illness [12]. A study published in 2014 found that approximately 10% of infants (<1 year old) attending A&E had no discernible medical abnormality [13], and a 2017 report of emergency attendance across Yorkshire and Humber determined that there was a 31% rate of nonurgent visits for children (with nonurgent defined for the study as an issue that could have been addressed by a general practitioner) [14]. This behavior is not unique to the United Kingdom; studies around the world have observed high rates of emergency services attendance for nonurgent conditions [15-18], with parental health literary identified as a potential factor in nonurgent attendances [16,17]. The 4-hour A&E target (95% of patients addressed within 4 hours) has not been achieved since 2013 [19], highlighting the current strain on urgent-care hospital resources. A review of factors affecting these behaviors found a range of different reasons, including (among others): parents' uncertainty and lack of confidence around recognizing problematic symptoms or evaluating their child's condition; mistrust of, or previous negative experiences with, clinicians; concerns about wasting clinicians' time; and being perceived negatively by clinicians [20].

This demonstrates the need for better access to primary care services or community-based support for acute pediatric illness and efforts to improve parental health literacy and confidence in determining whether, or which, treatment services are appropriate when a child is ill and how best to manage acute childhood illnesses [1,10,13]. This is particularly relevant in the current context of the COVID-19 pandemic, which has increased the burden on health care services. However, it is important to note that a link has been identified between greater accessibility of primary care services for children and reduced likelihood of visiting emergency services [21]. This suggests that parental educational interventions about recognizing signs and symptoms of acute illness are only one component of the problem and other factors affecting help-seeking behavior for parents with ill children will also need to be addressed in future studies.

Rationale

Many digital interventions have been developed to provide parents with guidance on how to care for acutely ill children and when it is necessary to seek medical treatment [22-24]. Digital interventions are interventions delivered using medical devices and other digital technologies (as some mobile apps and patient education interventions are not classified as medical devices) [25]. This definition includes a variety of sources such as mobile phones (as apps or text messages), websites, and smart (digitally connected) devices [26]. However, previous systematic reviews have found limited evidence to support the effectiveness of these digital interventions at increasing confidence, reducing anxiety, or improving treatment-seeking decisions [27,28].

The first systematic review to examine this topic was published in 2015 and included educational resources provided in any format: written, verbal, and electronic. It examined a variety of study types and outcome measurements, providing a good overview of the literature [28]. Given the rapid evolution of digital technology [29], the current state of digital interventions to support parents with acutely ill children has likely changed since that systematic review was published. A more recent review (published in 2020) only searched 2 databases and included 3 studies in the final review; it evaluated use and acceptability, accuracy of triage, and use of urgent services [27]. This suggests that it might not provide a sufficiently comprehensive overview of the variety of digital interventions available. Therefore, there is a need for an updated review and evaluation of the state of the literature on digital interventions for parents with acutely ill children to identify what is and is not effective and to inform further innovations.

Conscientious searches of keywords relating to digital intervention, parents, child health, acute disease, and treatment-seeking on PROSPERO [30] failed to find any in-progress systematic reviews on this topic. A new systematic review is needed to identify and evaluate all the published evidence of effectiveness for recently developed digital educational interventions that aim to improve support for parents' knowledge of acute childhood illness and their confidence and perceived self-efficacy at making the most appropriate care management decisions. An overview of the different types of digital interventions for which there is currently available evidence will help identify promising innovations and areas for improvement in the development and evaluation of these interventions.

The planned systematic review will focus on 4 key research questions to provide this overview. The first 2 questions are based on the research questions of a previous systematic review [28]:

1. How have these digital interventions been developed (eg, what technologies were used, and what steps were taken in their design to ensure accessibility, usability, and acceptability)?
2. What measures are used to evaluate the impact of these digital interventions at achieving their aim?
3. How do current digital interventions impact parents' knowledge of and experience with managing acute illness at home and use of various health care services for acute childhood illness?
4. What factors influence the usability and user perceptions of these interventions?

Methods

Overview

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) [31] and the Population, Intervention, Comparator, and Outcome (PICO) framework [32] will be used to structure the review. Appropriate Medical Subject Headings (MeSH) will be identified from a preliminary review of the literature. This systematic review will provide an update to a previous systematic review [28]. The first 2 research questions are the same as that previous review, and the third research question was added to include an assessment of usability and sustainability of the interventions, as this is an important component of their success. The systematic review will be composed of a literature search, article selection, data extraction, quality appraisal, data analysis, and data synthesis.

Parents and representatives of groups of parents (eg, Mothers Instinct, Meningitis Now, and Meningitis Research Foundation) were involved in the development and refinement of the review protocol. This involvement is valuable in ensuring that the review represents parents' perspectives, focuses on issues and questions that are both relevant and true to their experiences, and includes keywords and terms that the researchers might not otherwise have identified.

Eligibility Criteria

The population, intervention, comparator, outcome, and study (PICOS) type framework (Table 1) was developed in accordance with the review's research questions.

Table 1. Population, intervention, comparator, outcome, and study type (PICOS) framework.

Framework component	Description
Population	Parents and carers of children (aged 0-19 years) will be included. This includes any adult responsible for caring for the child, even if they are not the official guardian (eg, child minders, nursery nurses, teachers, extended family). It will exclude any interventions targeting children or adolescents as the primary user.
Intervention	Any digital intervention (mobile apps, web-based interventions, or smart devices) designed to support parents with acutely ill children by improving knowledge of signs and symptoms of acute childhood illness and decision making about health management and/or treatment-seeking behavior will be included.
Context	Interventions delivered in a variety of settings will be included. This includes both nonclinical settings (eg, homes, schools, and other community settings) and clinical settings (eg, out of hours, primary care, family medicine, general practitioner, ambulatory care, health helplines, and other health care services). Context can refer to both where the recruitment takes place and where the intervention is accessed by the parent. Interventions that recruit or are accessed online will also be included.
Outcomes	The primary objective is to identify the types of digital interventions used to support parents' health literacy and care of acutely ill children and their effectiveness. Therefore, primary outcomes are expected to include, but are not limited to, health literacy (knowledge and decision making), the confidence in making treatment-seeking decisions and caring for their child, levels of anxiety about the child's health, actual treatment-seeking behavior, levels and length of engagement with the intervention, and patient-reported experience (including measures of acceptability, usability, or satisfaction). Other outcomes that are reported by studies and deemed relevant will also be included (eg, the ability of the tools to identify a seriously ill child).
Study types	Observational studies (including qualitative studies) and cohort or randomized control trials will be included. Case studies and editorials will not be included. Literature reviews will be included in the search so that their references can be examined to identify any relevant papers not captured by our search terms but will not be included in the final review themselves. Papers describing the development of interventions that are evaluated in one of the studies will also be included.

Search Strategy

Five databases will be searched to find articles for this review: MEDLINE, CINAHL, Embase, PsycNET, and Web of Knowledge. Key terms relating to digital interventions to support parents with acutely ill children were extracted from an initial review of the literature and used to develop the search terms and search strategy. Search terms will include MeSH terms and keywords relating to digital interventions, children, acute illness, and health information. For this study, acute illness will include any short-term illness, whether minor or severe. Digital interventions will include any digital technologies with the aim of supporting parents or caregivers with children experiencing one or more of these short-term illnesses. An official diagnosis is not required, as the focus of the paper is on how the digital interventions enable parents to respond to children with symptoms of illness. The search terms that will be used in this review are grouped into those 4 themes (see Table 2), and the search string will be created using the following structure: digital interventions (MeSH OR Keywords) AND children (MeSH OR Keywords) AND acute illness (MeSH OR Keywords) AND health education (MeSH OR Keywords). See Multimedia Appendix 1 for a sample search string.

Table 2. Search terms.

Category	MeSH	Keywords (in title or abstract)
Digital interventions	Telemedicine OR Mobile Applications OR Internet-based Interventions OR Internet of Things	"mHealth" OR "mobile health" OR "eHealth" OR ((mobile OR phone OR smartphone OR cell) adj3 app*) OR web OR internet OR "online intervention" OR "web-based intervention" OR "digital intervention" OR virtual OR webpage* OR website* OR "smart device*" OR "smart medical devices" OR "smart tech*" OR tool OR resource OR program OR programme
Family	Child OR Infant OR Newborn OR Preschool Child OR Pediatrics OR Family OR Adolescent OR Adolescent Health OR Parents OR Caregivers OR Pregnant Women	pediatric* OR paediatric* OR child OR children OR kid OR kids OR infant* OR newborn* OR neonate* OR bab* OR babies OR toddler* OR schoolchild OR teen* OR adolescent* OR parent* OR carer* OR caregiver* OR "foster parent" OR childminder* OR "child minder*") OR pregnan*
Acute illness	Acute Disease OR Childhood Disease OR Injury OR Fever OR Cough OR Whooping Cough OR Diarrhea OR Earache OR Vomiting OR Respiratory Tract Infections OR Otitis OR Croup OR Bronchiolitis OR Seizures OR Exanthema OR Mucocutaneous Lymph Node Syndrome OR Conjunctivitis OR Chickenpox OR Epiglottitis OR Tonsillitis OR Common cold OR Influenza, Human OR Pharyngitis OR Meningitis OR Status Epilepticus OR Epilepsy OR Sepsis OR Virus Diseases	(acute OR "short term" OR "short-term" adj2 (illness* OR disease* OR sickness*)) OR (minor adj2 (illness* OR disease* OR sickness*)) OR unwell OR fever* OR febril* OR cough* OR diarrh* OR rash* OR vomit* OR earache* OR bronchiolit* OR (respirator* adj2 infection*) OR otitis OR croup OR seizure* OR rash OR rashes OR exanthem* OR kawasaki* OR conjunctivit* OR "chicken pox" OR chickenpox OR epiglottit* OR tonsillit* OR influenza OR flu OR "sore throat*" OR pharyngit* OR meningit* OR epilepsy OR sepsis OR septicemia OR septicaemia OR epilept* OR headache OR "neck pain"
Health education	Health Education OR Health Literacy OR Help-Seeking Behavior OR Information Seeking Behavior OR Access to Information OR Decision Support Techniques OR Decision Making OR Empowerment OR Prenatal Education OR Health Knowledge, Attitudes, Practice	"Health education" OR "health information" OR "health literacy" OR "information literacy" OR "information resource*" OR "treatment seeking" OR "help seeking" OR educat* OR counsel* OR "consultation behavior*" OR "consultation behavior*" OR (decision adj2 (aid* OR support OR guidance OR help)) OR "parent information" OR "home management" OR empowerment OR confidence OR self-efficacy OR ability OR knowledge OR ?understanding

Inclusion Criteria

The review will include studies published in English (based in any country) that evaluate digital interventions that aim to improve parents' health literacy and care for acutely ill children. This will include, but will not be limited to, tools to improve parents' knowledge of signs and symptoms of acute illness and deterioration, their confidence in assessing illness severity, their perceived self-efficacy in caring for their child, and their treatment-seeking behavior. Digital interventions can include mobile or web-based apps and websites. Studies that examine multicomponent interventions will be included given that there is a digital component of the intervention being evaluated.

The interventions will need to target parents with children (including pregnant women and their families) who have at least one acute illness or to provide education, information, or decision support to prepare parents for the event that a child becomes ill. It is expected that the majority of interventions will target parents with younger children, but the age of 19 years was set as the upper boundary to ensure that no relevant studies are missed in the search. In addition to parents, any caregivers responsible for children (for short or long periods of time) will be included. Studies with any or no comparator will be included.

Exclusion Criteria

Studies that do not include parents or caregivers responsible for children under the age of 19 years or that target the children (instead of parents or caregivers) as the primary user will be excluded. Depending on the number of eligible references identified in the search, this may be limited to a younger age in the systematic review.

Studies that were published before 2014 will also be excluded for 2 reasons: (1) Digital technology evolves rapidly [29], and this review is concerned with the current state of the field, and (2) this review provides an update and expansion to a previous systematic review conducted in 2014 [28] using 2 of the same research questions and similar search terms. Therefore, studies published before 2014 would likely have been captured in that review.

Studies that merely describe an intervention without evaluating it will be excluded, unless they describe the development of an intervention whose evaluation study is included in the review. Studies that are not published in English will be excluded, as there is no capacity for translation.

Screening and Article Selection

The citation management software EndNote X9 will be used to store the references and automatically remove any duplicates. References will be uploaded to a meta-analysis software to facilitate initial screening (based on inclusion and exclusion criteria key words), data extraction, and analysis. Two independent reviewers will then screen the remaining titles and abstracts and then conduct a full-text review to determine final eligibility for inclusion. Any disagreements about eligibility will be discussed by the 2 reviewers, and if no consensus can be reached, eligibility will be decided by a third reviewer. The details of the screening and selection process will be recorded using a PRISMA flow diagram to ensure study reproducibility.

The references of any relevant reviews found in the initial search will also be screened to identify any studies that may have been missed by the search. Once the final set of included studies has been determined, their references will be searched for published papers describing the development of those interventions. These linked papers will also be included in the final review.

Data Extraction

Two reviewers will independently examine the full texts of the included articles to extract outcomes into a predetermined form (see Textbox 1). Where the index paper does not include sufficient information about intervention development, linked (cited) publications will be used to provide the required data. As there are expected to be a variety of outcomes reported and not all are likely to have been anticipated, relevant outcomes reported by the studies that are not included in this table will be included in the final review. As with the screening, disagreements will first be discussed and then settled by a third reviewer if necessary.

Textbox 1. Article information and data to be extracted.

General study information

- Year of publication
- Country of study
- Sample demographics (including, but not limited to, any of the following that are reported: age, gender, target population, parental experience, socioeconomic status, health literacy, locality, health conditions)
- Initial sample size
- Analyzed sample size
- Length of follow-up

Intervention

- Digital platform
- Cost
- Development methods addressing accessibility/implementation
- Aim of intervention
- Intended time and place of use (eg, before seeking help, after seeking help)
- Training or guidance needed to use (if any)
- Specified age of children (if any)
- Specified type of acute illness (if any)
- Theory or logic model the intervention is based on (if any)
- Patient and public involvement in development (if any)

Evaluation

- Outcomes measured
- Health literacy (knowledge of illness and decision making); as there are a variety of tools used to measure health literacy [33], both the tool used and the finding will be extracted
- Skills to manage child illness
- Parental treatment-seeking behavior
- Parental characteristics (eg, uncertainty, anxiety, knowledge, confidence, reassurance, perceived self-efficacy)
- Acceptability
- Usability of platform
- Accessibility
- User experience (participant perceptions or feedback)
- Sustainability of use
- Other key performance indicators reported (eg, ability of tools to identify a seriously ill child)
- Limitations identified

Quality Appraisal and Risk of Bias Assessment

The quality and risk of bias of the included studies will be independently assessed by 2 reviewers, with disagreements discussed and resolved by a third reviewer if necessary. They will be measured using the Mixed-Methods Appraisal Tool (MMAT) [34]. Although this is a newer tool that has not been as comprehensively validated as other quality assessments, it was chosen because it will enable all of the included studies to be consistently assessed using the same criteria. The quality of all included randomized controlled trials and their overall performance for each bias will be summarized in figures.

Data Analysis and Synthesis

A meta-analysis is not expected to be feasible, due to the anticipated variety of study designs, measures, and reported outcomes. A descriptive analysis will be used to summarize the extracted data. The studies will also be analyzed separately depending on the age of the children. Where possible, they will be divided into 4 groups (0-4, 5-9, 10-14, 15-19 years) to align with the division used by Public Health England and the World Health Organization [35,36] and to allow comparison with national statistics. As there is a lack of standardized age bands for childhood, it is possible that some of the studies will target parents with children of ages that do not fit into a particular age group. If this occurs, it will be noted in the review and analyzed with the group(s) with which it is best aligned. The age-divided analysis will be conducted in addition to a general analysis to explore the possibility of age-related differences in interventions and their outcomes.

Patient and Public Involvement (PPI)

Our approach reflects best practice in health research [37]. Parents are central to the review, not only as expert team members but also in the search for information concerning how parents have been involved in the development, delivery, and evaluation of the interventions identified in our review.

Parents and representatives of groups of parents will continue to be involved in the review process. We do not expect patient and public involvement (PPI) experts to review individual papers as this is not their area of expertise. However, 2 representatives from meningitis awareness charities (JB, Meningitis Now, and RD, Meningitis Research Foundation) were involved in the revision of this protocol. We will ask parents and PPI representatives to review our findings from the review of included papers to ensure that any factors that may have affected parents' participation in projects are identified and the interpretation of the findings are grounded in the reality of life as a parent. In this way, we intend to ensure that the review is not biased towards an academic or clinical lens.

Results

The systematic review is expected to start in May 2021 and be completed by December 2021. However, given the current public health emergency, a firm timeline cannot be guaranteed.

Discussion

A systematic review of the literature about digital interventions to support parental decision-making for, and care of, acutely ill children will contribute to a better understanding of how these interventions can best support parents. Based on the data about impact, usability, and limitations that will be extracted from the studies, this section will explore what conclusions can be drawn, the limitations of the systematic review, and key areas for future research.

A better understanding of the current strengths and areas for improvement of these digital interventions has the potential to promote timely use of primary care services according to the severity of illness of the child. Given the lack of substantial evidence supporting the effectiveness of such interventions identified by previous reviews, the conclusions drawn from this review will help inform the development of improved digital interventions for parents. This will be particularly important for designing interventions to improve access for hard-to-reach populations and others who are vulnerable to digital exclusion.

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Authors' Contributions

The protocol was drafted by MMI with iterative input and revisions from SN, NB, MB, JB, LB, EC, BC, RD, PD, ML, DR, AT, and EM.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Sample search.
[DOCX File , 13 KB - resprot_v10i6e27504_app1.docx]

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Abbreviations

A&E: Accident and Emergency
MeSH: Medical Subject Headings
MMAT: Mixed-Methods Appraisal Tool
PICO: Population, Intervention, Comparator, and Outcome

PPI: patient and public involvement
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

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Proposal

Distributed Ledger Infrastructure to Verify Adverse Event Reporting (DeLIVER): Proposal for a Proof-of-Concept Study

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Abstract

Background: Adverse drug event reporting is critical for ensuring patient safety; however, numbers of reports have been declining. There is a need for a more user-friendly reporting system and for a means of verifying reports that have been filed.

Objective: This project has 2 main objectives: (1) to identify the perceived benefits and barriers in the current reporting of adverse events by patients and health care providers and (2) to develop a distributed ledger infrastructure and user interface to collect and collate adverse event reports to create a comprehensive and interoperable database.

Methods: A review of the literature will be conducted to identify the strengths and limitations of the current UK adverse event reporting system (the Yellow Card System). If insufficient information is found in this review, a survey will be created to collect data from system users. The results of these investigations will be incorporated into the development of a mobile and web app for adverse event reporting. A digital infrastructure will be built using distributed ledger technology to provide a means of linking reports with existing pharmaceutical tracking systems.

Results: The key outputs of this project will be the development of a digital infrastructure, including a backend distributed ledger system and an app-based user interface.

Conclusions: This infrastructure is expected to improve the accuracy and efficiency of adverse event reporting systems by enabling the monitoring of specific medicines or medical devices over their life course while protecting patients' personal health data.

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KEYWORDS

adverse drug reaction reporting systems; drug-related side effects and adverse reactions; blockchain; mobile applications; distributed ledger technology

Introduction

Background

It is essential that adverse drug reactions and medical device events are reported to provide accurate and comprehensive warning labels and restrict or remove products that present too high of a risk to patient safety [1]. However, the number of adverse events reported in the United Kingdom has been declining [2]. Mitigating the barriers associated with spontaneous reporting systems and ensuring that those reports are useful are essential components of ensuring patient safety

and reducing costs of post-market surveillance [3]. Therefore, this project aims to develop a distributed ledger infrastructure that will redesign the adverse event reporting and collecting process to improve patient care and safety.

Currently, the United Kingdom uses the Medicines and Healthcare products Regulatory Agency's (MHRA) Yellow Card Scheme (YCS) for adverse event reporting. Reports submitted to the MHRA are stored in a database, in compliance with General Data Protection Regulation (GDPR) requirements [4,5]. Access to deidentified data can be requested under the Freedom of Information Act, but is otherwise only accessible to MHRA staff and, in some circumstances, health researchers. Confidential information is only made available if necessary to achieve specific health purposes, with conditions in place to protect patient information as best as possible [5].

The YCS has contributed to the identification of serious safety issues [6]; however, several usability issues with the public interface have been identified [7]. The YCS was redesigned in 2012 based on recommendations [7] and launched an app in 2015 to help make reporting easier [8]. An international Med Safety app has been developed (in collaboration from the MHRA) as part of the Innovative Medicines Initiative WEB-Recognising Adverse Drug Reactions (WEB-RADR) project [9] to provide a platform for members of the public to report adverse events. These reports are then transmitted to the relevant national databases [9,10]. In the United Kingdom, the WEB-RADR2 project is ongoing and aims to facilitate information sharing between health care and regulatory systems (by mapping terminologies and connecting with electronic health records) and to provide its features through application programming interfaces (APIs), tools that will eventually replace the Yellow Card website [11-13].

However, while the WEB-RADR2 project work packages include improving connectivity, their backend system (Vigilance Hub) only appears to allow the tailoring of the app to suit the needs of specific regulators (ie, to manage aesthetics, translations, reporting forms, news, lists of authorized products, and app users) [14]. Therefore, there is still a need for an innovative infrastructure to support the improvements made in the reporting interfaces by providing a means of verification. Without this infrastructure, the benefits of improved interfaces will not be fully realized.

Given the regulatory changes with Brexit, a decentralized system with simplified information sharing and consent procedures could have significant economic value. The potential benefit of blockchain for the medical supply chain, including pharmacovigilance specifically, has been recognized [15]. It could reduce the time and effort needed to trace medicines associated with adverse events (eg, to link adverse events reported in the United Kingdom with medicines produced in the European Union). A distributed ledger infrastructure would enable parties throughout Europe (and throughout the supply chain) to add information to the database that can then be made accessible to all other relevant parties, avoiding potential regulatory and data security issues that may occur.

There is a large and growing global pharmacovigilance market [16]. In 2019, spontaneous reporting — such as reports made to the YCS — had the biggest pharmacovigilance market share. It is a cost-effective means of detecting adverse events and is commonly used by both regulatory agencies and pharmaceutical companies [17]. Therefore, there is significant potential value in improving systems of spontaneous reporting and in improving the traceability, verification, and quality management of those data.

Rationale

There is a need to improve confidence in shared data by considering provenance, traceability, verification, and quality management. The need is not to develop a new technology but to integrate existing technologies to develop a novel system to improve the specific challenge identified: the limitations and inefficiencies of the United Kingdom's current YCS.

One of the key issues is a lack of reporting, which could be due in part to usability problems with the current system. The only previous usability study identified issues such as difficulties navigating and using the online form and overly complex language, which increased the effort required to submit a report [7]. The YCS was redesigned on the basis of this study, but no further usability evaluations were identified. For members of the public and health care professionals to report more adverse events, they need to understand how and what to report, be capable of using the reporting system, and be motivated to report. Taking full advantage of adverse event reports (AERs) that are submitted requires a more interoperable system that can verify the provenance of AER data by linking with the pharmaceutical and medical device supply chains.

This project has significant potential value to many stakeholders. Economically, there is value for manufacturing and pharmaceutical companies. The distributed ledger infrastructure would make it easier to track and manage individual drugs and devices, reducing costs of more labor-intensive tracking processes. It could also potentially help companies avoid costs associated with adverse events by identifying and addressing any harmful side effects of the drug or device earlier. In the longer term, the infrastructure could be used to identify and track causes of adverse events and pinpoint whether the problem was due to the drug itself or an issue during production, such as contamination, mixed labels, or an inaccurate amount of the active ingredient [18]. It could also support common manufacturing problems related to documentation [19]. This would help companies document issues and engage in continuous process improvement, which would also help avoid costs associated with adverse events.

An improved reporting system would also benefit patients, clinicians, and pharmacists by reducing the time and effort needed to submit AERs, which is expected to help increase the number of reports submitted. This offers significant public health value for patients; identifying and addressing harmful side effects earlier could reduce the number of people who will suffer from them. It also has the potential to improve patient empowerment by increasing the clarity and ease of reporting. If patients feel confident in reporting side effects that they consider unacceptable and demanding alternatives, this empowerment could help drive innovation in the pharmaceutical market. Additionally, it would help reduce the significant

economic costs associated with adverse event–related hospitalizations for the UK National Health Service (NHS).

A more effective and efficient system for managing post-market surveillance data would have significant value for regulatory authorities and companies conducting their own post-market surveillance. It would help reduce costs associated with conducting post-market surveillance by reducing the effort needed to collect and compile all the relevant data. It could also provide new insights to inform guidance on the correct use of medicines and drugs.

There are also potential environmental benefits from making surveillance more efficient. Identifying and verifying problems with a medicine or medical device earlier could reduce the waste associated with producing and dispensing drugs that are ineffective or harmful.

Aims and Objectives

This project will optimize the integration of the medicines and medical devices supply chain to provide a means of verifying the provenance, and improving the quality, of AERs made by UK patients and health care professionals. It aims to address 2 key problems with the current system: lack of reporting and lack of verification. The first problem will be solved by developing an easy-to-use app interface for adverse event reporting. This could replace the current data collection system but replicate the types of data collected. The second problem will be solved by developing an infrastructure that will integrate adverse event reporting with the entire pharmaceutical supply chain, enabling report provenance to be verified and associated with specific medical products. Together, these solutions will optimize the quality of data and analyses that can be derived from AERs to better prevent fraud and identify any potential health risks early.

This project will improve on the current adverse event reporting system by developing an infrastructure that supports interoperability, can integrate information from different sources to trace specific medicines and medical devices over their lifespan, and thus corroborate reports of adverse events and enable more rapid action to be taken when adverse events are identified. Our project will be more user-friendly and accessible than the YCS and will disrupt the existing systems (including YCS and WEB-RADR2) by decentralizing them to provide better information flow, increase security, and, crucially, allow for the provenance of AERs to be validated. The key objectives of this project are to identify the perceived benefits and barriers in the current reporting of adverse events by patients and health care providers and develop a distributed ledger infrastructure and user interface that can collect and collate AERs to create a comprehensive and interoperable database.

Methods

Study Design

The study will follow the Population, Intervention, Comparator, Outcomes (PICO) model (Table 1).

Table 1. Population, Intervention, Comparator, Outcomes (PICO) model.

Component	Description
Population	The primary target customers and end users chosen for this project are UK health care professionals (HCPs) and members of the public. They were chosen because barriers to the usability and effectiveness of the United Kingdom's spontaneous reporting Yellow Card Scheme have been identified for both patients and health care professionals, including complex language, lack of feedback, lack of knowledge about the criteria for reporting, and lack of time to report [20-23].
Intervention	A new mobile and web app user interface will be developed, which is intended to increase user reporting of adverse events. A distributed ledger infrastructure will be developed to provide a means for regulatory agencies (like the MHRA[a]) to verify the provenance of the events reported to the app system by linking them to the medicines and medical devices supply chain.
Comparator	There is no comparator.
Outcomes	The outcomes are a prototype of the app and the distributed ledger infrastructure.

[a]MHRA: Medicines and Healthcare products Regulatory Agency.

Data Collection

To address the first objective, a review of the literature will be conducted to identify specific benefits and barriers in the current reporting of adverse events by patients and health care providers in the United Kingdom. If insufficient information is found, a survey will be developed and conducted to collect user feedback about the current system of reporting.

To inform the development of the digital infrastructure, literature and reports relating to the current operation of the YCS will also be investigated. This will help to ensure that problems not identified by patients and health care providers are also detected and can be addressed in the design of the new system.

Digital Infrastructure Development

A foundational level, based on distributed ledger technology, will form the infrastructure of the system, upon which applications can be built and provided. Farmatrust's blockchain solutions have been used to provide multisite, multistakeholder, end-to-end supply chain tracing of pharmaceutical products for governmental, regulatory, hospital, and industry organizations. This experience and previous developmental work will provide a strong base on which to develop a similar end-to-end supply chain tracing system that links AERs with existing pharmaceutical tracking systems.

The current backend of the adverse event reporting system will be examined to identify inefficiencies. The core infrastructure will be developed using distributed ledger technology. The

specific solution architecture to be used will be determined at this point, after further examination of the needs, inputs, and current limitations of the adverse event reporting system. A formal evaluation framework will be used to guide the development and ensure that the design choices fit the specific needs of the situation [24]. Interoperability with current and future databases and drug and medical device supply chain systems will be ensured by using the Fast Healthcare Interoperability Resources (FHIR) standard. This aspect of the project will also explore the options for governance processes to admit and remove actors from the system.

User Interface Development

Alongside the development of the system infrastructure, a mobile and web app will be developed to provide an easy-to-use and generally accessible interface for patients and health care providers to report adverse events to the system. This development will account for benefits and barriers identified in the literature and from user research.

Patient and Public Involvement

In line with the principles of user-centered design [25,26], members of the public and health care professionals will be recruited to collaborate on the development of the adverse event reporting app, to ensure that it is user-friendly and addresses their needs.

Ethics and Dissemination

The infrastructure will be built to comply with all GDPR and the British Data Protection Act (DPA 2018) requirements [27,28]. Potential ethical issues relating to the development of a digital infrastructure to record and verify personal and sensitive medical information will be identified from the literature and in discussions with the public representatives.

If user research is conducted, a participant information sheet will be produced and provided to participants upon recruitment before getting their informed consent. This will explain the study and detail their rights with respect to withdrawing and having their data removed. Data protection procedures will also be established and made clear.

A paper detailing the methods and results of this project will be submitted to academic peer-reviewed journals, conferences, and clinical meetings. The public representatives will also be consulted about the dissemination of the results of the study to the public in generally accessible formats.

Results

The key output of this project will be the development of a digital infrastructure for a new system of adverse event reporting, including a backend distributed ledger system and a mobile and web app user interface. The novel user interface will help to address the challenge of increasing adverse event reporting by patients and health care professionals. The distributed ledger system will provide a means of verifying this information using zero knowledge proof by tracking the medicine or medical device in question to confirm that the correct item was delivered to and used by the intended recipient for the correct purpose.

Discussion

The infrastructure developed will be able to use zero knowledge proofs to verify the provenance of AERs and reduce risks to patient confidentiality and data privacy. While data security and privacy concerns can never be completely avoided, these methods should provide a more secure system for confidential patient data. The decentralized nature of the system means that specific medicines or medical devices can be traced over their life course and reported adverse events can be linked to the specific product without compromising the patient's personal health data. This means that individual AERs can be verified by checking that the medicine or device in question has been dispensed and to the intended recipient. The traceability of specific products enables the system to highlight any discrepancies in the AER. A more user-friendly interface and a means of verifying reports are expected to increase ease of use, efficiency, and the quality and quantity of adverse event data reported.

Anticipated Impact

Estimates of the cost of preventable drug-related adverse events in the United Kingdom are in the range of £100-400 million a year [29-31]. A digital system that operates more efficiently, operates with lower costs, and increases the number of adverse events reported could save money by identifying problems earlier. A more efficient system that identifies and verifies adverse events earlier could also reduce waste. By reducing inefficiencies (ie, reducing the labor-intensive management of the existing adverse event reporting system), production of the suspect drugs or devices could be paused earlier to await investigation. This would avoid the production and shipping of many drugs or devices that would otherwise have been deployed and potentially recalled, reducing waste. The economic savings for pharmaceutical and manufacturing companies could free up money for increased investment in industrial digitalization research, as less money would be needed to deal with adverse events.

In addition to economic savings and reduced waste of resources, the proposed distributed ledger infrastructure will be open, interoperable, and able to provide zero knowledge proof, thus reducing concerns about data privacy and security. As patients are encouraged to report all side effects, even known ones [32], to enable more accurate understanding of the prevalence of side effects of drugs, this system will have the potential to capture a very large amount of real-world data. The openness, access, and accountability of the infrastructure will be a mechanism to enable collaborations and interaction between academia, health care systems, the established manufacturing sector, and smaller, start-up digital technology companies.

Risks

Given the level of innovation, the details of technical implementation will depend on factors such as interoperability gateway configurations, computational capacities required, and adoption by the end users. This risk will be mitigated by a development approach that will use the FHIR standard and user research to identify needs and barriers.

There are also potential risks from a health care perspective. Health care providers may be unwilling to report if concerned about disciplinary action; however, an anonymous and easy-to-use system should enable reporting to be more easily incorporated into routines in health care environments without personal risk. Flaws in the system could potentially expose patients to higher risk medicines and medical products, mitigated by careful design and testing before promoting for implementation and the use of zero knowledge proof encryption.

Future Directions

In this project, the infrastructure developed will be designed to replace the current YCS operated by the MHRA. The main barrier to implementing our distributed ledger infrastructure is whether the MHRA will accept the change in system. To verify the provenance of AERs, it will be necessary to link the reports with the pharmaceutical supply chain. Because barcode serialization technology is already used to label and track individual packets of medicine or medical devices [33], the Farmatrust system will provide the technology to link AERs with the serialized medicine or device. However, to do this, access will have to be granted via a wholesaler who can access the National Medicines Verification System (NMVS, or SecurMed in the United Kingdom) database that tracks the pharmaceutical supply chain [34].

Future studies will be needed to test the feasibility, usability, and efficacy of the system. As the front-end and back-end components could theoretically be implemented separately, separate evaluations could provide useful information on their independent impacts on adverse event reporting and pharmacovigilance. In the longer term, this project could easily be expanded and adapted for global use. It could provide a means of linking data across countries. Applications could be added to address the needs of specific stakeholders (eg, pharmaceutical and manufacturing companies) to identify relevant issues from the AERs and enable continuous improvements in products and processes.

There are many applications — beyond verifying AERs — that our infrastructure could support. For instance, because the system links AERs with the pharmaceutical supply chain, it could be used to trace individual packets of medicine or medical devices. This could be very valuable in the case of recalls — specific packets or devices could be tracked, and information about their distribution and dispensation almost instantly provided. Alerts could then be sent to wholesalers and recipients of the medicines or devices. The number of potential applications provide an opportunity for long-term growth and productivity, and these applications (eg, the particular method used to check the report with the supply chain database and create a report) can be protected with patents. After the feasibility study, we will aim to market this solution globally.

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Authors' Contributions

All authors collaborated on the development of the study topic and design of the study. MMI drafted the protocol, and final revision was conducted by EM.

Conflicts of Interest

NR and RS are both employees of FarmaTrust, a Blockchain AI company. These authors were involved in the conception and design of the study, but not in the decision to submit for publication. The final version of the manuscript was reviewed and approved by EM, who is independent from FarmaTrust.

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Abbreviations

AER: adverse event report
API: application programming interface
DPA: Data Protection Act
FHIR: Fast Healthcare Interoperability Resources
GDPR: General Data Protection Regulation
MHRA: Medicines and Healthcare products Regulatory Agency
NHS: National Health Service
NMVS: National Medicines Verification System
WEB-RADR: WEB-Recognising Adverse Drug Reactions
YCS: Yellow Card Scheme

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Protocol

Adaptation of a Live Video Mind–Body Program to a Web-Based Platform for English-Speaking Adults With Neurofibromatosis: Protocol for the NF-Web Study

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Abstract

Background: Neurofibromatosis (NF) is a rare genetic condition associated with lower but modifiable quality of life (QoL). Although a virtual live video program (Relaxation Response Resiliency Program for Neurofibromatosis [3RP-NF]; efficacy randomized controlled trial underway) that we created has been made available, ongoing barriers impede some patients from engaging in this intervention. A necessary next step is to develop a stand-alone web-based intervention that reduces barriers to accessing NF-specific psychosocial care.

Objective: First, we aim to develop a web-based platform (Neurofibromatosis-Web [NF-Web]) of our mind–body resiliency program (3RP-NF) through qualitative interviews with participants from an adult efficacy randomized controlled trial. Second, we aim to iteratively optimize the feasibility, acceptability, credibility, and satisfaction of the NF-Web platform through open pilot trials with participant exit interviews and explore quantitative outcomes within this sample. Here, we describe the protocol and study design, intervention, and analysis plan.

Methods: For aim 1, we will invite completers from our efficacy trial to participate in qualitative interviews. We will use data from these interviews to adapt the content of the live video program for asynchronous delivery and understand how to create a user-friendly format for an engaging web platform. For aim 2, we will enroll eligible participants recruited for the efficacy trial who could not enroll because of treatment barriers. Eligible participants will complete QoL, depression, anxiety, pain, treatment satisfaction, and program credibility measures at baseline and posttest. Inclusion criteria are identical to those for the efficacy trial, including stress and coping difficulties (self-report), no change in antidepressant medication in the past 3 months, no psychotherapy in the past 3 months, no major upcoming surgeries in the next 12 months, English speaking, ability to complete questionnaires on the web and participate in live video interventions, and consent before participation. The primary outcomes are feasibility, treatment satisfaction, and credibility. The secondary outcomes include physical, psychological, social, and environmental QoL; depression; anxiety; pain intensity; and pain interference. We will enroll at least two group cohorts and iteratively refine the program based on participant feedback after each cohort completes the open pilot trial.

Results: This trial is ongoing. We have completed the interviews (n=23) and analyzed the data to construct the website. Afterward, we will recruit our cohorts for the trial (approximately n=15/cohort; total=30). Recruitment will end by May 2021, with plans to analyze the data by October 2021.

Conclusions: We will develop the first web platform for people with NF with difficulties managing stress and NF symptoms and report on feasibility and preliminary effects in improving QoL and psychosocial functioning. NF-Web has potential to extend the reach of our 3RP-NF intervention by removing barriers to care, including lack of trained providers, scheduling difficulties, and appearance concerns.

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KEYWORDS

neurofibromatosis; quality of life; stress management; mind–body; asynchronous delivery; resiliency; mobile phone

Introduction

Background

Patients with neurofibromatosis (NF; NF1, NF2, or schwannomatosis) have lower but modifiable quality of life (QoL) [1], higher depression [2], anxiety [2], pain [1], stress, and social isolation [3] compared with the general population [4]. Given that NF is incurable, and current medical treatments have limited ability to eliminate symptoms, addressing modifiable psychosocial factors through tailored psychosocial interventions is essential to improve QoL in this population. Despite this need, patients with NF do not have access to tailored, in-person evidence-based psychological care because of barriers such as distance, cost, time or scheduling, and lack of trained providers. Our team at Massachusetts General Hospital used mixed methods approaches to adapt an evidence-based mind–body program for the specific needs of adults with NF (Relaxation Response Resiliency Program for Neurofibromatosis [3RP-NF]; NF1, NF2, or schwannomatosis) [3], adolescents with NF (Resilient Youth with NF) [5], and adults with NF2 who are deaf (Relaxation Response Resiliency Program for NF2) [6] for virtual delivery to bypass these barriers to care. In three single-blinded pilot randomized controlled trials (RCTs) [3,5,6], we have shown that these programs are feasible, acceptable, and superior to an attention placebo health education counterpart in improving QoL, pain, and psychosocial functioning. With funding from the United States Department of Defense (DoD), we are currently conducting fully powered efficacy trials of the 3RP-NF intervention in adults (aged 18 years or older) and adolescents (aged 12-17 years).

Although virtual delivery increased the reach of our intervention and allowed the recruitment of geographically diverse individuals, ongoing barriers impede all people with NF from enrolling. Our ongoing DoD-funded RCT receives interest from patients across the globe; yet, time-zone differences (eg, a difference of 10.5 hours between EST and Indian Standard Time); occupational or family obligations; limited and convenient scheduling (eg, 10 PM local time, weekend scheduling); 8-week, 90-minute weekly scheduling; and severe actual or perceived appearance concerns (eg, cutaneous and plexiform neurofibromas with facial tumors, palsy, café au lait spots, freckling) cause people to decline participation (approximately 30% who are contacted) [7]. As there is a lack of trained providers to administer evidence-based psychosocial care, a web-based platform (ie, a program hosted on a website server and created using HTML) in addition to the live videoconferencing program allows for asynchronous delivery of the intervention and could bypass these barriers to participation.

Objective

The purpose of this study is to develop the first web-based platform of a mind–body program for adults with NF with stress and difficulties in managing NF symptoms. Our first aim (aim 1) is to adapt the adult mind–body program, 3RP-NF, for web-based delivery using qualitative data from semistructured interviews with participants who completed the efficacy trial. To achieve this aim, we will collect information about the participants' experiences, perceptions of a web-based platform, and willingness to participate. We will use this information to develop a web-based platform—Neurofibromatosis Web (NF-Web)—that will be designed to be compatible with desktops, laptops, and mobile devices (eg, smartphones and tablets). We expect that participants from the efficacy trial will be willing to participate in semistructured interviews and provide meaningful feedback to inform the adaptation of the 3RP-NF intervention for web-based delivery. Our second aim (aim 2) is to optimize NF-Web through at least two subsequent open pilot studies with exit interviews. For each open pilot, we aim to optimize the feasibility and acceptability of NF-Web and explore the quantitative outcomes. We hypothesize that the final iteration of NF-Web will meet the a priori set feasibility and acceptability benchmarks [8-10]. We also hypothesize that participation in NF-Web will be associated with improvement in quantitative outcomes from baseline to posttest.

Related to the aims and scope of this pilot study, we will not be testing the use of different technologies for NF-Web delivery (eg, mobile and tablet vs desktop or laptop modalities); nor are we directly interested in the acceptability of such technologies (eg, the advantages of the website over the live video program). Rather, we are interested in studying the psychosocial program itself as a web-based tool to deliver the mind–body program to participants who typically have a higher burden when accessing psychosocial care. The creation of NF-Web essentially involves taking an efficacious program, which is delivered either in person or through live video by a trained clinical psychologist, and making it more accessible by delivering it through a web-based platform. Here, we describe our methodology for both the study aims.

Methods

Study Design

For aim 1, we will conduct individual qualitative semistructured interviews to adapt the 3RP-NF intervention for web-based delivery. For aim 2, we will conduct at least two subsequent open pilot studies of NF-Web to optimize feasibility and acceptability and explore changes in the quantitative outcomes (Figures 1 and 2). We will modify NF-Web after each open pilot to maximize feasibility and acceptability, as needed.

Figure 1. Qualitative study design.

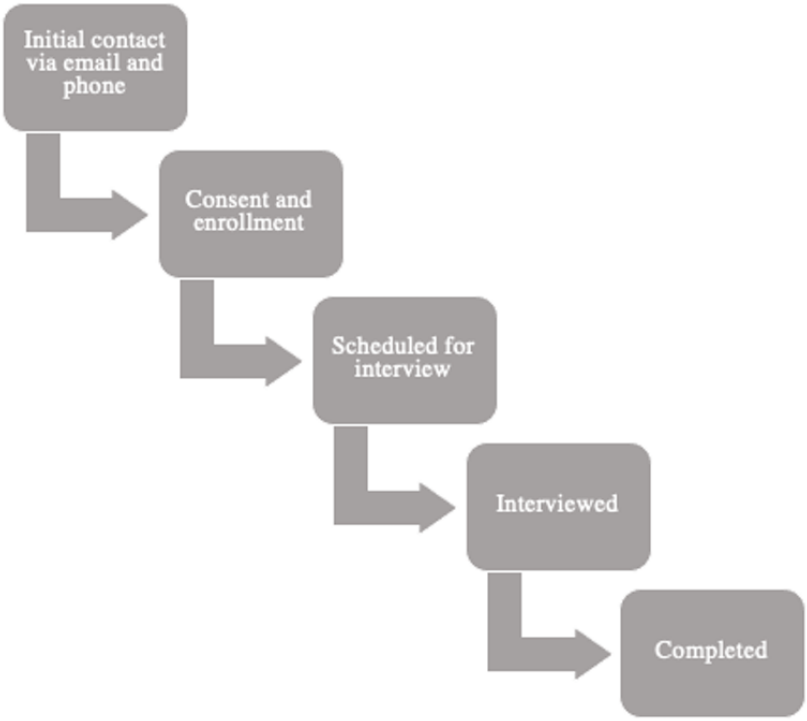
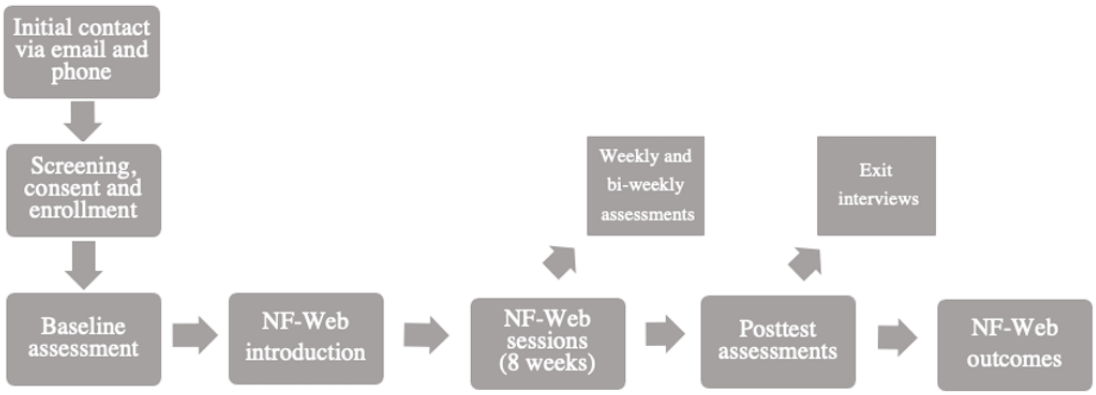


Figure 2. Open pilot study design. NF-Web: Neurofibromatosis-Web.



Setting

Studies related to both aims 1 and 2 will be conducted at a large northeastern academic medical center in the United States. Our use of virtual recruitment and web-based intervention delivery allows participants from the United States as well as the rest of the world to engage in the study at their convenience (eg, location, time of day, pace). We will recruit participants through our research tracking log that contains both efficacy trial completers (assessments complete at 1 year time point; aim 1) and participants who expressed interest in the 3RP-NF live video program but could not participate because of treatment barriers (aim 2).

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for this study are identical to those listed in the 3RP-NF trial [11] and are outlined in Textbox 1. The participants completed the study screening over live videoconferencing with the study staff. We assessed stress using the 4-item Perceived Stress Scale [12] (score≥6) [13].

Textbox 1. Study inclusion and exclusion criteria.

Inclusion Criteria

- Diagnosis of neurofibromatosis (NF; NF1, NF2, or schwannomatosis)
- Adults aged 18 years or older
- Full understanding of the informed consent process, study procedures, and assessments in English
- ≥Sixth grade reading level (self-report)
- Difficulties coping with NF symptoms (self-report)
- Score≥6 on the 4-item Perceived Stress Scale

Exclusion Criteria

- Major medical comorbidity, not NF-related, expected to worsen in the next 12 months
- Change in antidepressant medication (within past 3 months)
- Recent participation in cognitive behavioral therapy or relaxation therapy (within past 3 months)
- Has diagnosis of significant mental health conditions requiring immediate treatment (eg, untreated bipolar disorder, psychotic disorder, active substance dependence) by self-report and observation during prescreening
- Unable or unwilling to complete assessments electronically through REDCap (Research Electronic Data Capture; Vanderbilt University)
- Unable or unwilling to participate in web-based, self-guided sessions

Recruitment

For aim 1, we will first email participants who were randomized to the 3RP-NF intervention and completed the last assessment point of our efficacy trial and invite them to participate in a live video qualitative interview with a trained clinical psychologist with expertise in NF (50 min). We will use purposive sampling to achieve population-consistent representation of the three NF types (NF1, n=10; NF2, n=6; and schwannomatosis, n=4). We will recruit more participants if we do not achieve theme saturation. If participants meet enrollment criteria and are interested in participating, they will receive the consent form to review and return through secure email. After obtaining consent, we will schedule the participants for an interview.

For aim 2, we will recruit participants (n=30; approximately 15 per cohort) for the open pilot phase of NF-Web. These will be participants who previously expressed interest in participating in the live video program but ended up not participating because of treatment barriers. The study staff will describe the trial, and all participants will be screened by the study staff over the phone. The screening procedures are the same as those outlined in the 3RP-NF efficacy trial protocol [11].

Vidyo Software for Interviews

We will conduct the semistructured interviews using the secure, Health Insurance Portability and Accountability Act–approved, live videoconferencing software, Vidyo (Vidyo, Inc). After obtaining consent, we will email the participants the instructions to download, install, and access Vidyo on their personal webcam-equipped, internet-connected devices (eg, laptop and desktop computers, tablets). We expect many participants to have had the software installed for their previous efficacy trial participation. We will make telephone appointments available for those needing assistance with installing the software.

Screening and Enrollment

The clinical research coordinator (CRC) will obtain informed consent and ask the participants to return the signed consent form electronically through secure email. Participants are considered enrolled in the study when signed consent is received. The CRC will schedule a time with each enrolled participant for their individual semistructured video interview. We will provide an additional overview of the study procedures at the beginning of each interview. The study interviewer will ensure that the participants understand the study procedures and that we will audio record the interview. The participants will be interviewed on (1) experiences of living with NF; (2) experience during the live video program (ie, efficacy trial); (3) attitudes and perceptions of NF-Web, including participation barriers and facilitators; (4) perceptions about modifying session content and skills; and (5) considerations for decreasing barriers to participation. We will save audio on a secure and password-protected computer.

For aim 2, we will recruit participants who could not participate in the efficacy trial using the tracking log for our efficacy RCT. We will email or call the potential participants. We will screen participants over the phone to ensure that the eligibility criteria are met. The research staff will cover important components of the study protocol, and we will ask eligible participants to return the informed consent document to the CRC electronically through secure email.

Treatment Conditions

3RP-NF Program

We anticipate that the core content of the 3RP-NF intervention [11] will remain the same, with modifications focused primarily on content delivery and participant engagement. Briefly, the 3RP-NF intervention combines mind–body skills, including relaxation response elicitation with cognitive behavioral approaches and perspectives from positive psychology, into a

virtual, multimodal intervention to increase coping strategies for those dealing with NF symptoms and associated stress. Core elements of the original 3RP-NF intervention include (1) relaxation response practice (eg, breath awareness, body scan, meditation, and mindfulness), (2) cognitive behavioral coping skills (eg, enhancing awareness of the connection among emotions, thoughts, and behavior), (3) positive psychology skills (eg, appreciation, empathy, and humor), and (4) healthy behaviors (eg, diet, exercise, and sleep). The session titles from the adult efficacy trial are presented in Textbox 2 [11].

Textbox 2. Session outline of Relaxation Resiliency Response Program for Neurofibromatosis and the web-based platform: session week and respective session title.

Week 1

- Symptom management, stress management, and resiliency training

Week 2

- The relaxation response

Week 3

- Stress and symptom awareness for patients with neurofibromatosis

Week 4

- Mending mind and body of patients with neurofibromatosis

Week 5

- Creating an adaptive perspective

Week 6

- Promoting positivity

Week 7

- Healing states of mind

Week 8

- Humor, empathy, and staying resilient

NF-Web Platform and Procedures

NF-Web is a website version of the 3RP-NF program [11]. We anticipate that NF-Web will have 8 sessions (Textbox 2) with content presented in multiple modalities (eg, written, audio, video, interactive components) and administered entirely on the web without a live clinician.

After participants provide consent and complete baseline assessments, we will send them an email with detailed information on how to begin the web-based intervention (ie, *NF-Web Account Setup* email). NF-Web will require a secure log-in to access content with a username assigned by the study staff (eg, MGHNFW01) and a unique password. The CRC will keep a log of all usernames and passwords on a password-protected computer. We will give participants website instructions through email and review the terms and conditions of use provided on the website, which will include limits to confidentiality (risks similar to usual internet use; disclosure at their discretion) and ways to protect their information. The study staff will be available to answer all participant questions and concerns during the initial account creation and setup for the program.

After enrollment, participants will log in to NF-Web and progress through the web-based program at their own pace for 8 weeks (streaming video content embedded from YouTube; no software download required). Each week, participants will view session content consisting of mind–body video modules, audio recordings, written text, quizzes, and homework assignments (submitted through email or the web platform) from the 3RP-NF program. The participants will have access to completed session content from previous weeks as they await the following week's session after completing the weekly assignments (viewing videos, completing in-session exercises and quizzes). In addition, participants will be informed of the optional discussion board where they can directly post content (deidentified for the trial owing to institutional review board requirements; data used to potentially assess user experience and engagement ethnographically). The participants will also have the option (ie, opt in or out) at the beginning of the program to receive daily or weekly sessions and skill practice reminders through email and text messages. Sessions will be unlocked by the study staff and administered weekly to the participants to pace their learning and practice (ie, new content available each week). We will have 2 cohorts of participants for each round (2 rounds of approximately 15 each, n=30) to attempt simulation of the NF-Web platform components (eg, discussion board use and monitoring, administrative tasks). The treatment fidelity for NF-Web mirrors that of the efficacy trial [11], with the addition that all materials for NF-Web will be prerecorded. At

any point during the study, the participants will be able to ask nonurgent questions by sending an email to the study staff through a secure website form on NF-Web. This approach to the website may be modified or adapted before being finalized based on participant feedback gathered in the aim 1 exercise.

Considerations for Participant Safety During a Virtually Delivered Program

Participant safety is evaluated at multiple study points. Participants complete the Patient Health Questionnaire (9-item version) [14] to measure depressive symptomatology at baseline and posttest, which includes a question related to suicidality. If a participant reports thoughts of self-harm or suicidality, the CRC and principal investigator (PI) are notified, and the PI will contact the participant within 24 hours to conduct a risk assessment. Safety is always prioritized over study participation. If it is determined that participants need a higher level of care, they will be provided with information about resources for care, as appropriate. Participants who do not require higher levels of care may continue in the study and are monitored throughout the posttest. The same risk-related assessments are conducted once more at the posttest, and the same response procedure is followed.

Assessments

For aim 1, we will conduct participant interviews through a secure video platform, Vidyo, and audio record and code qualitative content. Participant demographic data will be available from previous participation in the efficacy trial. The interview data will be used to develop and refine the NF-Web platform.

For aim 2, participants will complete web-based surveys through REDCap (Research Electronic Data Capture) [15], including reliable and valid measures. All measurements are presented in Table 1 and directly mirror the efficacy trial, with the exception of weekly or biweekly assessments throughout the NF-Web program.

Table 1. Neurofibromatosis-Web program measures and assessment time points.

Construct	Measure or description	Outcome	Time point
Demographic	Demographics include age, gender, race, education, yearly income, and marital status.	Descriptive	Baseline
Quality of life	The WHOQOL-BREF[a] [16] assesses subjective quality of life in 4 domains: physical, psychological, social, and environmental.	Primary	Baseline, posttest
Depression	The Patient Health Questionnaire for Depression-9 [14] assesses depressive symptoms and severity consistent with *DSM-5*[b] criteria of major depression.	Secondary	Baseline, posttest
Anxiety	The Generalized Anxiety Disorder Scale-7 [17] assesses anxiety symptoms and severity consistent with *DSM-5* criteria of generalized anxiety.	Secondary	Baseline, posttest
Pain intensity	The 11-point Numeric Rating Scale [18] assesses intensity of pain experience.	Secondary	Baseline, posttest
Pain interference	The Brief Pain Inventory [19] pain interference subscale assesses intrusion of pain experience on daily functioning.	Secondary	Baseline, posttest
Quality of life (abbreviated)	The WHOQOL-BREF [16] (abbreviated items) assesses subjective general quality of life and quality of life satisfaction with two items.	Exploratory	Weekly
Depression (brief)	The Patient Health Questionnaire-2 [20] assesses frequency of depressed mood and anhedonia.	Exploratory	Biweekly
Anxiety (brief)	The Generalized Anxiety Disorder-2 [21] assesses frequency and severity of generalized anxiety symptoms.	Exploratory	Weekly
State affect	The Positive and Negative Affect Scale–Short Form [22] assesses state positive and negative affect.	Exploratory	Weekly
Website user experience	User Experience Questionnaire [23] assesses patient overall experience using the website.	Exploratory	Weekly
Treatment satisfaction	The Client Satisfaction Questionnaire [24] assesses patient satisfaction with the web-based program.	Primary	Posttest
Treatment credibility	The Credibility Questionnaire [25] assesses how believable, convincing, and logical patients perceive the web-based program to be.	Primary	Posttest

[a]WHOQOL-BREF: World Health Organization Quality of Life Instrument, Short Form.

[b]*DSM-5*: *Diagnostic and Statistical Manual of Mental Disorders-5*.

We will send the participants a secure link through REDCap [15] to complete baseline assessments within a week of beginning the intervention. If a consented participant does not complete the questionnaires after a week of being sent the link, we will contact the participant and assist them in completing the questionnaires over the phone. The participants will also be sent weekly surveys throughout the program with less strict enforcement of assessment adherence owing to the aim of feasibility testing and because these time points do not affect primary or secondary outcomes. The participants will be emailed a reminder within 24 hours of the final session to complete the posttest assessments, and the CRC will call within three days

if they have not completed the assessments. If a participant does not complete the posttest measures, the PI will continue contact attempts through phone and/or email as needed within two weeks of completing the last session. Any participants who are unreachable by the second full week (ie, 14 days) after posttest administration will be deemed lost to follow-up. We will conduct exit interviews lasting approximately 15 minutes at the participants' convenience to gather feedback on their participation, including suggestions for program improvements, barriers and facilitators of program engagement, and the internet device they used to access the program (eg, mobile and tablet vs desktop).

Data Analysis

For aim 1, we will transcribe and analyze qualitative data from participants using NVivo 10 qualitative data analysis software (QSR International) [26]. Each interview will be transcribed and coded after the collection. We will use a thematic content analysis informed by framework [27] and inductive–deductive hybrid [28] methods. Themes will be extracted to inform the adaptations of NF-Web.

For aim 2, we will test feasibility according to the proportion of participants who agree to participate from those who express interest. Acceptability will be calculated as the number of participants who complete the web program and provide a posttest from those who start the program. We will assess the credibility of the web program using the Credibility Questionnaire (means, SDs, and IQRs) [25]. We will measure satisfaction with the web program using the Client Satisfaction Questionnaire (means, SDs, and IQRs) [24]. We will measure user experience with the User Experience Questionnaire (means, SDs, and IQRs) [23] and qualitative exit interview data. Upon completion, we will explore within-group improvements in NF-Web from baseline to posttest. Our hypotheses are that there will be positive within-group improvements in the secondary outcomes of NF-Web.

For our quantitative analyses, we plan to use linear contrasts to compare changes in secondary (QoL, emotional distress, pain) variables from baseline to posttest within the NF-Web intervention. For QoL outcomes that have established minimal clinically important differences [29], we will consider improvements from baseline to posttest to be clinically meaningful if the mean improvement is above 6.25.

We expect to use SPSS 25 software (IBM Corporation) for the statistical analyses, with an analytic strategy that mirrors the efficacy trial [11]. As our study is a small open pilot trial, we will not be adequately powered to detect within-group or between-groups differences for quantitative outcomes. We will also not be able to examine demographic variables beyond their descriptive aspects. Even so, baseline to posttest will be explored for each outcome in NF-Web, with descriptive statistics and signals of improvement being reported as relevant. If the NF-Web program confirms the primary outcomes (feasibility or acceptability) and trends positively for the secondary outcomes, we will consider this to be preliminary evidence that NF-Web is a useful psychosocial web-based program.

Data Management

We will store the collected data in a secure location on computers with password protection to maximize confidentiality and security. We will assign each subject a unique, anonymous identifier that is associated with all collected data, including questionnaires and subject-completed logs. Any paper data files will be stored in a secure, locked location that is only accessible to the study team, and these files only include coded subject identification. In addition, all electronic questionnaire data are stored on REDCap [15], a web-based, Health Insurance Portability and Accountability Act–compliant data system available through our academic medical center.

Results

The NF-Web open pilot clinical trial is ongoing. As of April 2020, we completed the qualitative interviews (n=23) and analyzed the data to construct the first version of the website for our open pilot study. We successfully recruited both cohorts of patients to participate in the trial with the goal of recruiting 30 individuals in total being met (n=24 completed posttest after completing the program). We ended the open pilot trial in May 2021. We aim to complete data analyses by October 2021 and then prepare NF-Web for dissemination in accordance with the results of the fully powered efficacy trial for adults with NF.

Discussion

Comparison With Prior Work

Patients diagnosed with NF have a lower but modifiable QoL. Virtual mind–body interventions developed to improve stress management and QoL in people with NF are feasible, acceptable, and beneficial [3,5,6]. However, most patients with NF still struggle to access specialized, evidence-based psychological treatment, even with virtual adaptations. This paper describes the study design and specific strategies used to conduct qualitative interviews with adult patients diagnosed with NF from our ongoing efficacy trial to inform the development of a novel web-based platform to teach resiliency skills and stress management to improve QoL in people with NF. We provide details on the protocol and the potential benefits and challenges of delivering psychosocial care using a web-based platform. We also discuss the methods of monitoring and addressing participant progress and safety throughout the program.

This protocol presents a novel method for delivering care to patients with rare diseases across the globe and provides invaluable information for future trials using asynchronous platforms to deliver psychological care. The web-based program retains the evidence-based mind–body skills associated with improved QoL and psychosocial functioning [11], while providing a cost-effective and scalable delivery modality that could be implemented effortlessly with few human resources. In addition, all program materials could be seamlessly delivered through the website with cumbersome aspects of the live program (eg, homework submission, materials, and resources) found in 1 place. In the future, this program could also be easily translated and culturally adapted for delivery to

non–English-speaking patients with NF worldwide. Video content can also be designed to have download capability so that individuals with low broadband connections can store the videos locally on their devices and watch without interruption. Such web-based programs have been developed for other medical populations with a psychosocial profile similar to that of NF (eg, chronic pain, diabetes) [26,27] and have been shown to be feasible, accepted by patients, and in some cases as effective as virtual or in-person interventions [30]. NF-Web represents a potential first-line treatment for patients with NF-specific psychosocial difficulties.

Similar to the DoD trial, we aim to implement and disseminate NF-Web in conjunction with the live video program throughout NF centers across the world, as well as through the Children's Tumor Foundation (CTF) and local foundations. This program addresses the need for programs that require greater human resources to be addressed by streamlining psychosocial treatment for adults with NF. The web-based treatment model can be used to inform other populations within the NF community (adolescents, families), as well as other medical illness populations.

Strengths and Limitations

Even with adaptation, there are limitations to consider in the proposed study. First, diverse recruitment poses a barrier to the generalizability of the findings. Previous trials, including our adult efficacy trial, have enrolled mostly middle-class, higher-educated White female patients. We hope that with stronger relationships and involvement from foundations within the NF community, we can maximize opportunities to recruit diverse patients. Although a geographically diverse sample may have its own limitations (eg, differences between geographic regions and major language differences), it also serves as a strength of the program by promoting more flexibility (eg, participants are not bound to a schedule and can participate in their own time) not seen in the live video program. Our use of a geographically diverse sample is consistent with our other NF trials. Second, the live video program is only available in English. Recorded video offers opportunities to provide multilingual subtitles, which can aid program delivery; however, verbal and written materials are currently offered in English only, which limits the individuals who may participate. Finally, although the rationale is to develop a program that can be inclusive of people with barriers to live virtual psychosocial treatment (eg, scheduling, appearance concerns), there are other barriers for participants that NF-Web will not address yet, including participants without technology resources or those with limited financial means.

Conclusions

Our protocol describes the plans to develop the first-ever stand-alone web-based program to address the psychosocial needs of adults with NF1, NF2, and schwannomatosis. Improvement in outcomes and results related to feasibility, attrition, credibility, and satisfaction will inform implementation of the web-based platform in future clinical trials and other NF populations (eg, adolescents with NF1 and NF2, parents of children with NF1 and NF2, adults with NF2 who are deaf). The results also have the potential to inform adaptations of web-based programs for other medical and non–English-speaking populations.

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Authors' Contributions

EGL and AMV designed the study and share a role as co-PIs. EGL, SWH, and AMV coauthored the manuscript. PJP assisted with proofing the protocol and manuscript and managed the institutional review board approval and aim 1 study processes.

Conflicts of Interest

AMV reported receiving funding from the DoD and the National Institutes of Health and serving on the scientific advisory board for the Calm app outside of the submitted work. EGL, SWH, and PJP have no financial interests to disclose.

Multimedia Appendix 1
Peer-review report by the Neurofibromatosis Northeast Medical and Science Committee.
[PDF File (Adobe PDF File), 166 KB - resprot_v10i6e27526_app1.pdf]

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Abbreviations

3RP-NF: Relaxation Response Resiliency Program for Neurofibromatosis
CRC: clinical research coordinator
CTF: Children's Tumor Foundation
DoD: Department of Defense
NF: neurofibromatosis
NF-Web: Neurofibromatosis-Web
PI: principal investigator
QoL: quality of life
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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Protocol

Monitoring Diagnostic Safety Risks in Emergency Departments: Protocol for a Machine Learning Study

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Abstract

Background: Diagnostic decision making, especially in emergency departments, is a highly complex cognitive process that involves uncertainty and susceptibility to errors. A combination of factors, including patient factors (eg, history, behaviors, complexity, and comorbidity), provider-care team factors (eg, cognitive load and information gathering and synthesis), and system factors (eg, health information technology, crowding, shift-based work, and interruptions) may contribute to diagnostic errors. Using electronic triggers to identify records of patients with certain patterns of care, such as escalation of care, has been useful to screen for diagnostic errors. Once errors are identified, sophisticated data analytics and machine learning techniques can be applied to existing electronic health record (EHR) data sets to shed light on potential risk factors influencing diagnostic decision making.

Objective: This study aims to identify variables associated with diagnostic errors in emergency departments using large-scale EHR data and machine learning techniques.

Methods: This study plans to use trigger algorithms within EHR data repositories to generate a large data set of records that are labeled *trigger-positive* or *trigger-negative*, depending on whether they meet certain criteria. Samples from both data sets will be validated using medical record reviews, upon which we expect to find a higher number of diagnostic safety events in the trigger-positive subset. Machine learning will be used to evaluate relationships between certain patient factors, provider-care team factors, and system-level risk factors and diagnostic safety signals in the statistically matched groups of trigger-positive and trigger-negative charts.

Results: This federally funded study was approved by the institutional review board of 2 academic medical centers with affiliated community hospitals. Trigger queries are being developed at both organizations, and sample cohorts will be labeled using the triggers. Machine learning techniques such as association rule mining, chi-square automated interaction detection, and classification and regression trees will be used to discover important variables that could be incorporated within future clinical decision support systems to help identify and reduce risks that contribute to diagnostic errors.

Conclusions: The use of large EHR data sets and machine learning to investigate risk factors (related to the patient, provider-care team, and system-level) in the diagnostic process may help create future mechanisms for monitoring diagnostic safety.

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KEYWORDS

diagnostic error; emergency department; machine learning; electronic health records; electronic triggers

Introduction

Background

Diagnostic decision making is a complex cognitive process involving uncertainty and susceptibility to errors. According to the National Academies of Science, Engineering, and Medicine, diagnostic error is defined as the "failure to establish an accurate and timely explanation of the patient's health problem(s) or communicate that explanation to the patient" [1]. Approximately 30% of malpractice claims and more than 8% of adverse events in medicine are related to diagnostic errors [2], yet most are never reported [3]. Other researchers reported a 15% rate of diagnostic error in clinical medicine [2], with 5% of adults misdiagnosed annually in outpatient care [1,4] and about 15%-30% in the context of the emergency departments (EDs) [5].

The ED, in particular, is known as a *natural laboratory for the study of errors* [3], with a high prevalence of diagnostic errors [3]. Time-pressured decision making in a high-paced, high-volume, and chaotic ED environment increases the risk of erroneous diagnostic decisions [6]. Diagnostic errors are one of the most common types of errors in the ED [3]. Although precise error rates are lacking, they involve 65% of all closed malpractice claims [7]. A conservative estimate suggests that 1 out of every 10 diagnoses is subject to some level of error, and half of the errors cause harm or escalation of the health condition [1,8-10]. This results in approximately 7 million harmful errors out of the 139 million annual ED visits in the United States, making diagnostic safety a high priority for ED-related research [11].

Errors occurring in the ED often have multifactorial origins [12], and little is known about these factors [13]. In the absence of a unified taxonomy for contributing factors [14,15], the National Academies of Science, Engineering, and Medicine report [1] *Improving Diagnosis in Health Care* highlighted that the diagnostic process is not limited to the patient-provider interaction, and errors may result from the complex interplay of parameters related to patients (eg, health literacy, presenting symptoms, complexity, and behaviors), provider-care teams (eg, the cognitive load on providers and information gathering and synthesis), and systems (eg, health information technology, crowding, and interruptions).

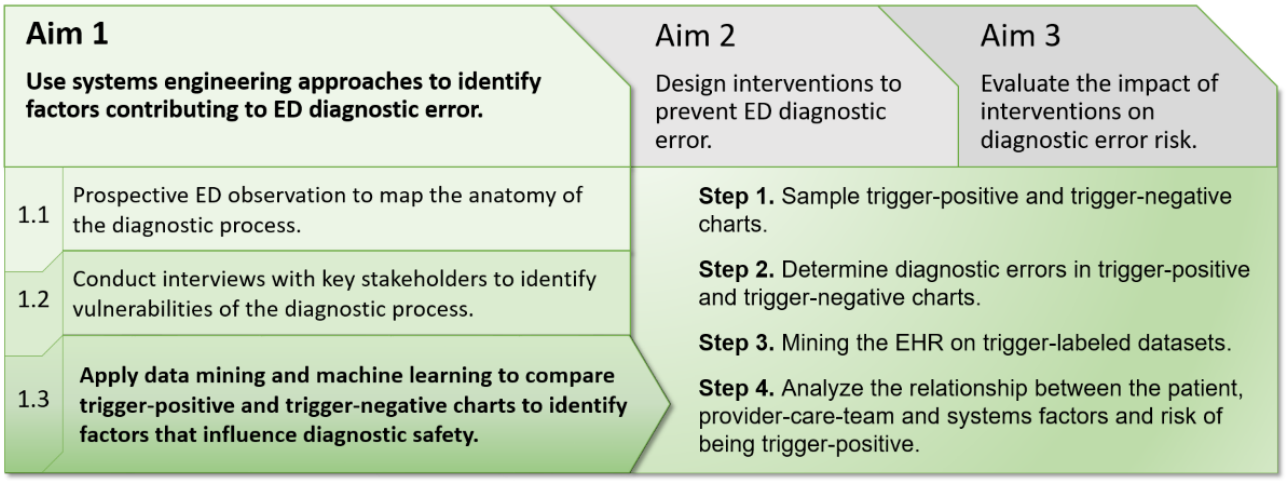
There is an urgent need to design, implement, and develop novel methods to identify and reduce the risks related to the diagnostic process in complex ED microsystems. These methods should account for the dynamics of human-system interaction during the diagnostic process and address the inherent risks involved in these interactions. Efficiently screening large and ever-growing data sets, such as electronic health records (EHRs), can help identify cases with diagnostic errors and associated risk factors for mitigation strategies [16]. Data mining can be used to identify these factors and study their influence on diagnostic errors.

Data mining is a knowledge discovery method [17] that encompasses various algorithms to identify patterns and trends in large-scale data sets [18,19], such as EHRs. Previous research has shown the application of data mining techniques in the extraction of useful knowledge from large data sets in the fields of medicine and biology [20]. These algorithms use data to help scientists find input variables that have a significant relationship with the output variable. Most advancements in this type of analysis are achieved by incorporating techniques such as association rule mining (ARM), classification and regression trees (CART), and chi-square automated interaction detection (CHAID). ARM aims to extract frequent patterns, meaningful correlations, or causal structures within a data set [21] that satisfy the predefined minimum support and confidence from a given database [18]. This technique has been used in detecting disease co-occurrence, discovering adverse drug reactions, identifying risk factors for heart disease, and surveilling public health [22]. In contrast, decision trees are known to be effective in a variety of domains, with CART and CHAID being the two most popular decision tree techniques [17]. They are used to model the relationship between predictor variables and the outcome variable by recursive partitioning of large heterogeneous data sets into two or more homogeneous nodes [23].

Objective

This protocol describes the application of data mining and machine learning techniques to understand diagnosis-associated risks in the ED and improve diagnostic safety. It focuses only on aim 1.3 of the recent *Improving Diagnosis in Emergency and Acute Care–Learning Laboratory* (IDEA-LL) grant awarded by the Agency for Healthcare Research and Quality (Figure 1). IDEA-LL is an actionable and patient-centered program for diagnostic safety surveillance and intervention based on the available data in EHRs. Diagnostic safety events will be identified through a review of EHR *triggers* related to events that are known to be associated with errors in the diagnosis process. After validation using EHR data, data mining and machine learning techniques will be utilized to compare an at-risk, trigger-positive sample with trigger-negative charts. This specific part of the grant will provide evidence-based guidance to identify factors with the highest prevalence among the trigger-positive cases and information that will be used in future projects (aim 2) to identify causal relationships and inform the design of decision support systems.

Figure 1. The 3 aims of the Agency for Healthcare Research and Quality-funded Improving Diagnosis in Emergency and Acute Care–Learning Laboratory project and the detailed steps of this study specifically focusing on aim 1.3 to identify patient-, provider-care team–, and system-level–factors affecting the risk for diagnostic error. ED: emergency department; EHR: electronic health record.



Methods

Setting

Population and Site Participation

Patient encounters from 4 EDs will be used in this study, including 2 from the Mayo Clinic system and 2 from the University of Michigan Health System. The institutional review boards from participating institutions approved the study protocol (19-009115, HUM00173662, 1696020-1). In this study, we will extract clinical data as part of data mining using triggers and compare them with nontriggered charts through the EHR systems at 4 EDs. Diversity of racial and ethnic backgrounds is represented in the 4 EDs by including all ages, races, ethnicities, and genders.

Sample Size Justifications and Power Calculation

We will estimate the sample size based on a power analysis with a two-tailed α=.05 and power of 85% for a predefined number of 10 independent variables that predict the diagnostic error yes or no outcome.

Sampling for Control

The control includes visits that do not meet the criteria for any trigger. We will include all ED visits in the two health systems for the entire study period (July 1, 2017-December 31, 2019). For each trigger-positive case, we will match a single trigger-negative encounter based on the availability of cases through a hierarchical procedure, which matches the encounters based on age group, gender, provider, the reason for visit, and the arrival date and time. This one-to-one matching of trigger-positive and trigger-negative cases will also help to eliminate the imbalance classes. To accommodate the potential heterogeneity across sites, the measurements will be reported as site-specific quartiles [24]. For patients with multiple ED or hospital visits during the study period, each record will be considered separately.

Variables

Quantitative Variables

A variety of factors with potential influence on the diagnostic process will be extracted from both the EHR and other standalone databases at the 2 sites. Existing literature has provided information on factors related to patients, providers, and system-level parameters and the interactions of these parameters in the ED (eg, patient-per-provider ratio and patient length of stay), which can be explored further [8,13,24-29]. Several additional variables that can be extracted from the EHR will be under consideration. The number of unexpected ED visits could be associated with a higher risk of diagnostic error [8,25]. ED crowding is a complex issue related to both system-level and patient-level factors (complexity and acuity) [28] and is associated with an increased risk for patient safety, including treatment delays, reduced quality of care, and increased morbidity and mortality [24]. Prolonged ED length of stay correlates with increased patient mortality [27]. High workloads, lack of control, and communication failures may lead to patient safety risks [29]. Iordache et al [30] showed that direct and indirect care time together are significant discriminators between EDs because of the differences between their patient care profiles and unit characteristics. Prescribing error rates are shown to significantly increase if physicians are interrupted or are multitasking [31]. Textbox 1 provides a general overview of these 3 categories.

Textbox 1. The three main categories of risk factors to be explored in this study.

Patient Factors

- Demographics
- Emergency department (ED) visit history
- Complexity and comorbidity

Provider-Care Team Factors

- Shift schedule and workload
- Patient-per-provider ratio
- Interruptions and trauma

System Factors

- ED boarding
- Emergency severity index triage distribution
- Total direct and indirect care time

Qualitative Variables

Qualitative analysis of the ED environments, such as the cognitive load on individual providers, is outside the focus of this study but is under exploration in another aim of this grant. However, we will study factors such as patient acuity, patient volume, waiting times, number of ED providers per shift, and number of boarded ED patients (admitted to inpatient unit but still in ED because of lack of inpatient space) in the system as proxies for some of the qualitative factors such as the cognitive load.

Data Quality and Safety Monitoring

We will evaluate compliance with the study methodology, quality of available data, patient protection, and adherence to Good Clinical Practice guidelines. We anticipate differences in terms of practice among the sites that may impact data quality. To ensure that the practice differences are accounted for, we recruited clinicians at each site to determine important differences and help customize the trigger algorithms. In addition, data consistency and completeness will be audited using data queries designed in accordance with standard techniques. Meanwhile, potential inconsistencies and missing values will be identified during the clinician chart reviews to design and apply adequate data imputations.

The EHR systems at both sites are the same, and we use standard measurements through health systems, with some minor customizations. These standard measurements will work as proxies to better identify conditions that may result in an error, so we do not anticipate that differences in practices across sites will affect data quality. Inconsistent data will be used to examine and enhance the validity of the defined measures (triggers) and assess their performance characteristics as predictive values. Data will be screened for missing values, and most of the missing data elements will be replaced by the closest available proxy in the EHR. As both sites use Epic as their official EHR system, care providers and Epic specialists at both sites will be engaged in this discussion to accommodate potential deployment variations. In the rare event of technical problems, remaining missingness will be adequately handled by missing data techniques such as data imputation or maximum likelihood estimations [5]. Incorrect data entries in the Epic system are very difficult to identify because of the lack of other reference ground truths. However, we will perform a data cleaning procedure to ensure the meaningfulness of temporal information, and incorrect timings (such as negative values for the length of stay) will be replaced by approximations based on the follow-up events. We will also report the missing data rate and dropout rates.

Conduct of the Study

Overview

This study aims to identify the factors that may interfere with the diagnostic process in the ED that potentially lead to missed, delayed, or incorrect diagnoses. On the basis of our previous work, we will use a series of electronic triggers (triggers) to identify ED encounters with potential diagnostic errors from the EHR database. Each trigger has a predefined set of inclusion and exclusion criteria implemented in Structured Query Language (SQL) and configured for specifications of each site in the study. Each site currently uses an Epic EHR system with minimal variations owing to its specific needs. These differences will be identified and accounted for after the focus interviews with the providers. The Epic specialists at both sites are in constant communication with the research team to apply the most accurate mapping of the factors and parameters between the 2 sites. The protocol is thought to be generalizable to other EHR systems, as we emphasize the analysis of common ED concepts rather than database variables specific to Epic. All SQL queries can be modified to match other systems (eg, Cerner) by matching concepts and keywords. Table 1 provides an initial list of 6 EHR-based triggers proposed in IDEA-LL after reviewing the literature on current triggers, surveying medical directors, and using a Delphi consensus process [32]. We will start our study with the first 3 triggers, including the unscheduled visit within 10 days resulting in admission, care escalation to intensive care unit within 24 hours, or death in the ED or within 24 hours of ED departure time. If for any reason,

one or more of the triggers do not perform well, the triggers from the backup set will be used.

Table 1. Proposed electronic trigger algorithms for identifying diagnostic errors.

Trigger algorithm	Description
Initial set of triggers	
Trigger 1: unscheduled return	Unscheduled return visit with admission within 7 to 10 days from the index ED[a] visit.
Trigger 2: care escalation	Care escalation from the inpatient unit to the ICU[b] within 6, 12, or 24 hours with ED attribution.
Trigger 3: death	All deaths in the ED or within 24 hours of admission—exclusive of palliative care.
Backup set of triggers	
Trigger 4: change of service	A proxy for the discrepancy in diagnosis may be the change of service in 48 hours (admitted medical, changed to surgical).
Trigger 5: nonadmitted returns	Return visits not resulting in admission with new interventions (eg, diagnostic test that was abnormal, new medication).
Trigger 6: high-risk conditions	New diagnosis or symptom-disease dyads (eg dizziness-stroke [33] and abdominal pain-appendicitis [34]).

[a]ED: emergency department.

[b]ICU: intensive care unit.

We will perform a retrospective review of a selected sample of both trigger-positive and trigger-negative medical records to identify the presence or absence of diagnostic errors using the Revised Safer Dx, a validated instrument for categorizing the presence of diagnostic errors [35]. We will then compare these 2 large cohorts to evaluate associations of potential contributing factors with trigger-positive cohorts using sophisticated data mining techniques. To conduct this study, we will accomplish the following 4 steps.

Step 1: Sampling of Trigger-Positive and Trigger-Negative Charts

This step will apply the EHR-based trigger algorithms (Table 1) to the EHR data repositories that include ED encounters at the 2 sites, creating large data sets of statistically matched groups (for demographics and medical comorbidity or severity) for trigger-positive and trigger-negative (control) charts [36]. The inclusion and exclusion criteria for individual triggers will be refined after an iterative review of random samples of charts. We anticipate using 3 triggers that have the best predictive value for diagnostic errors.

Step 2: Determination of Diagnostic Errors in Trigger-Positive and Trigger-Negative Charts

This step aims to determine whether diagnostic errors are statistically more likely to appear in trigger-positive charts. We will investigate the presence of diagnostic error through manual review of a sample of trigger-positive and trigger-negative charts using the Revised Safer Dx instrument [35]. For each trigger, we will calculate the odds ratio of a diagnostic error for both trigger-positive and trigger-negative groups and perform appropriate hypothesis tests to decide if trigger-positive charts are more likely to result in a diagnostic error.

Step 3: Mining the EHR on the Extracted Trigger-Labeled Data Sets

The triggers for which we fail to reject the null hypothesis will be selected for further analysis. We will use EHR-based queries to automatically label ED patient charts as trigger-positive or negative. This data set also includes several potential predictive factors extracted from the EHR, in addition to the trigger labels. We will also consider factors previously underinvestigated but recognized anecdotally, as listed in Textbox 1, for the 3 categories of patient-related, provider-related, and system-related factors. Some factors can be directly extracted from the EHR database, such as arrival time, ED arrival rate, emergency severity index triage algorithm distribution, that is, severity of ED workload. We will ensure equal distribution of trigger-positive and trigger-negative data sets by the site. We can overlay these 3 sets of factors to mirror each patient's journey during the ED stay.

For example, consider a hypothetical 70-year-old patient presenting to the ED with left flank pain. The partial information flow associated with this patient's ED visit is illustrated in Figure 2, where patient-related diagnostic events are demonstrated by time. Figure 3 demonstrates important contextual information such as ED volume, waiting room census, and patient arrival rate, all of which can impact or delay the diagnostic process. The 2 figures provide a side-by-side example of variations in patient- and system-level factors that could influence the prevalence of diagnostic error. Such associations among these factors can only be identified by considering all possible influencers in the ED environment.

Figure 2. Example of emergency department visit information flow. CT: computerized tomography; ECG: electrocardiogram; EMR: Electronic medical record; IV: intravenous; PT/INR: Prothrombin time and international normalized ratio.

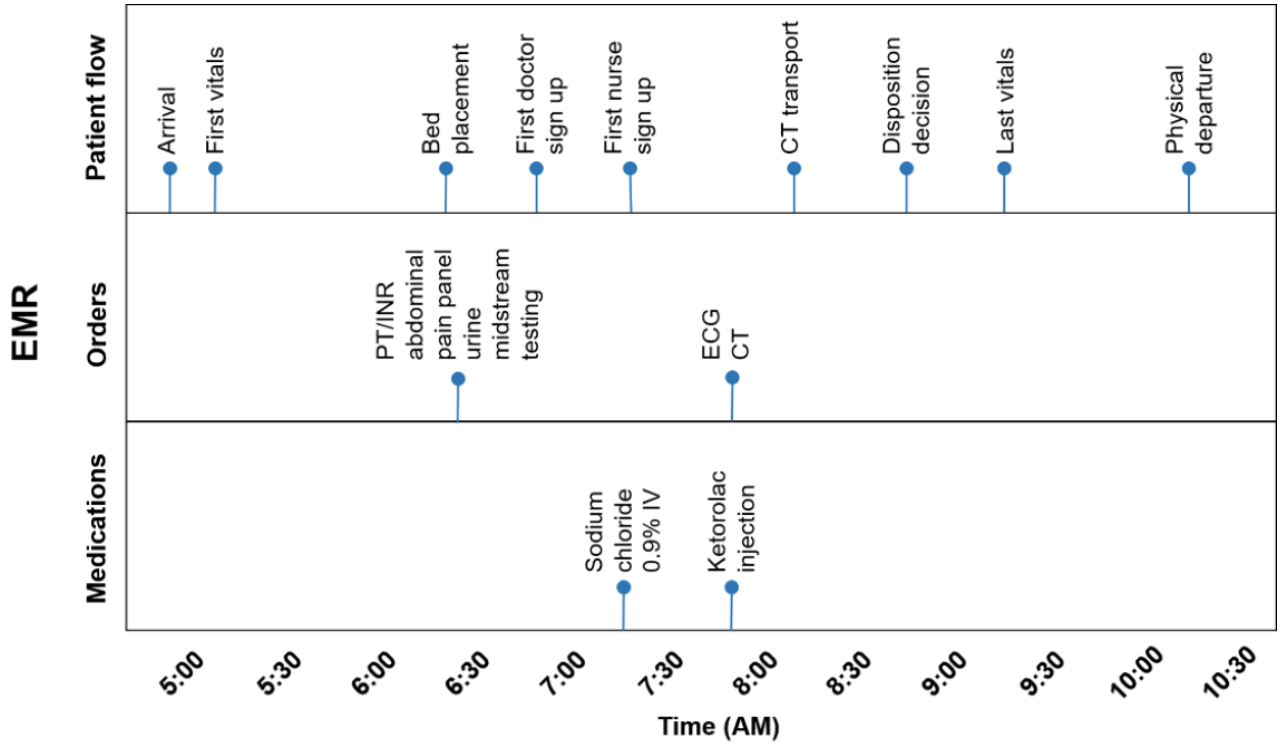
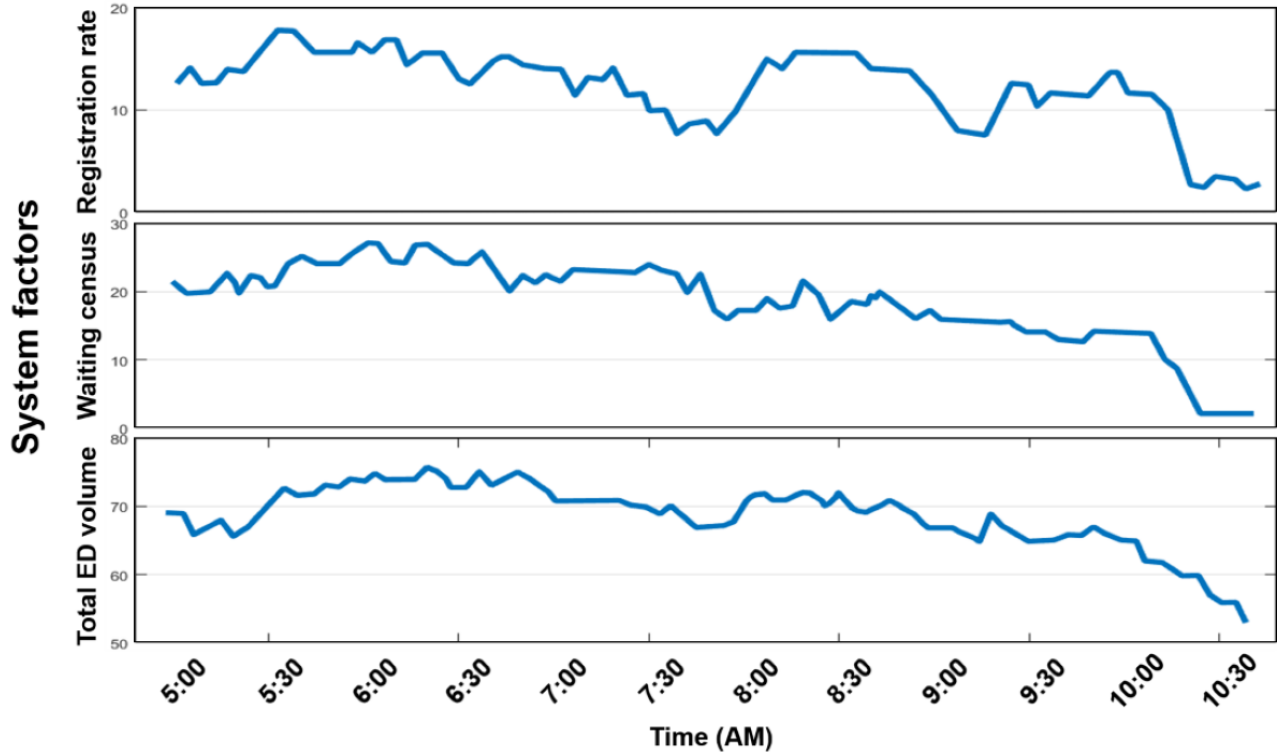


Figure 3. Emergency department context impacting the diagnostic process. ED: emergency department.



Step 4: Analysis of the Relationship Among Patient, Provider-Care Team, and System Factors and the Risk of Being Trigger-Positive

Overview

This step aims to analyze the trigger-labeled data sets obtained from the 2 institutions using different machine learning and data mining techniques. Data mining is a prevalent and effective technique for extracting nontrivial, implicit, previously unknown, and potentially useful knowledge from large data sources [37]. Discovering significant information related to disease diagnosis from medical databases is possible by applying techniques such as ARM [22], CHAID, and CART.

Association Rule Mining

ARM has been successfully applied in various medical contexts, from the discovery of adverse drug reactions to the identification of risk factors for heart disease [22]. ARM is one of the most significant unsupervised methods for pattern recognition [37], which explores frequently occurring patterns to find hidden associations between different factors. ARM will estimate the likelihood of trigger-positive risk through different factor combinations. Its predictive a priori model combines confidence and support into a single measure of predictive accuracy and discovers the best associations among the factors in large data sets [38]. Rules extracted by this method are usually represented in IF-THEN form, which makes it easier for medical experts to interpret and comprehend medical analysis [22].

Chi-square Automated Interaction Detection

CHAID is a decision tree algorithm that determines splitting based on statistical tests and has been used to model the relationship between the predictor variables and the outcome variable in many medical applications, such as identifying factors influencing inpatient mortality [17]. In our study, CHAID will help answer the question "Which combination of factors leads to higher trigger-positive risk and therefore a higher relative risk of diagnostic error?" CHAID splits the target into two or more categories using an exploratory analysis of the relationship between a dependent factor and several predictor factors [39]. To see if splitting the sample based on these predictors leads to statistically significant discrimination in the dependent measure (trigger labels), various independent factors will be evaluated using the chi-square test [40]. Despite regression, CHAID is capable of illustrating variable clusters through an iterative process. Adjusted *P* value measures are used to determine the best value of the partition or the best split, and splitting on a larger chi-square statistic indicates a more significant partition.

Classification and Regression Trees

CART analysis is another tree-based nonparametric data mining technique frequently used in medical diagnosis studies [23]. It has been widely used in the literature for both classification and interpretation tasks, such as identifying important predictive factors for persistent shoulder pain [41], ranking the risk factors for *Schistosoma mansoni* reinfection [42], and analyzing the risk factors of hypertension [43]. CART divides a large heterogeneous data set into smaller, more homogeneous nodes by employing recursive partitioning based on a target variable [23]. The significance of these decision rules is the definition of subgroups of patients and the most relevant interactions between them [44].

Results

The entire study cohort is well specified and labeled by trigger scripts, and the data are undergoing cleaning and preparation for subsequent steps. Following the completion of this study, we expect to characterize common factors associated with both trigger-positive and trigger-negative charts by applying multiple machine learning-based factor analysis techniques. These algorithms explore different combinations of factors within all trigger-positive and trigger-negative cases to identify meaningful interactions of risk factors concerning each trigger. We have already provided a list of potentially important EHR-based factors for the triggers based on our literature review and previous experiences in practice. As listed in Textbox 2, some of these factors are common among all 3 triggers, and some are specific to a trigger based on the definition. We will also expand and explore a list of previously underinvestigated but recognized anecdotally as potential patient-, provider-care team–, and system-related factors that could be approximated by these variables (eg, estimating the effect of the cognitive burden by system and provider variables such as ED crowding).

Textbox 2. List of potential electronic health record–based predictor variables extracted from previous studies.

Factors Across All Triggers

- Demographics (eg, age and sex)
- Emergency department (ED) encounter (date and time [D/T])
- Chief complaints
- Clinical impression (tenth revision of the International Statistical Classification of Diseases and Related Health Problems [ICD10])
- Final ED diagnosis (ICD10)
- Hospital admission diagnosis
- ED length of stay
- Number of lab tests

Trigger 1: Specific Factors

- Previous ED departure (D/T)
- Previous ED disposition
- Return ED arrival (D/T)
- Return ED disposition
- Return ED type
- Return ED chief complaints
- Return ED clinical impression
- Return ED diagnosis (ICD10)
- Return hospital diagnosis

Trigger 2: Specific Factors

- ED discharge (D/T)
- Hospital disposition
- Next unit
- Intensive care unit (ICU) unit
- Time-to-ICU (hours)

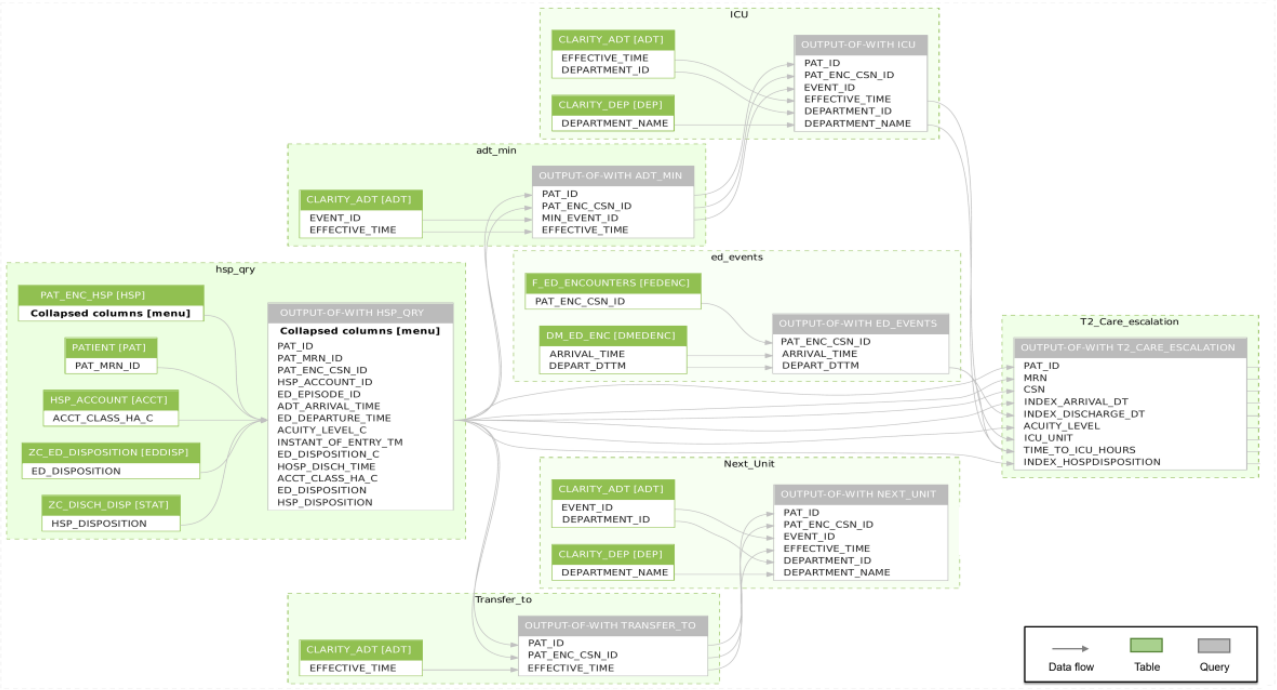
Trigger 3: Specific Factors

- ED discharge (D/T)
- ED disposition
- ED departure (D/T)
- ED unit
- Discharge-to-death (hours)
- Hospital disposition

We have also updated the SQL queries of all 3 triggers to be compatible with the EHR databases at both sites. ED patients' evaluations against each trigger are performed upon the execution of these queries on each EHR database. We reinforced multiple inclusion and exclusion criteria to the queries to ensure that test data or irrelevant information do not affect our selections. All queries share common information related to the initial encounter, followed by specific factors collected for each trigger separately. Figure 4 shows an example relational database schema on how different factors are being invoked and matched from multiple database tables to identify encounters with an escalation in the care condition, denoted by trigger 2.

The outcomes of this project include an improved understanding of the risk factors contributing to diagnostic error in the ED. The data could be used to inform EHR-based decision support systems for better prediction of the risk of diagnostic error in the ED. The first exploratory results of the project are expected to be submitted for publication by mid-2021.

Figure 4. Emergency department patients' evaluation against each trigger is done upon executing these queries on each electronic health record database. This figure is an example relational database schema on how relevant electronic health record–based predictive factors are being invoked from multiple database tables to build up a record of escalations in the care condition, denoted by trigger-2. Abbreviations in the figure represent arbitrary variable names as examples.



Discussion

Relevance

A strategy to address diagnostic error is the better use of health information technology and EHR data [45]. This project expands upon previous work on diagnostic errors by investigating risk factors through data mining techniques applied to EHR data. In particular, we aim to generate information relevant to the future design of a dynamic ED-based decision support system to enhance the quality of emergency care through large-scale analysis of EHR records. As a result of using unbiased machine learning techniques, we will find previously unexplored associations. These novel associations will help future investigations into causal risk factors for diagnostic errors.

Building on this in the future (Figure 1, aim 3), we will use machine learning approaches with patient and frontline provider factors to develop a real-time, dynamic, trigger-based EHR diagnostic error risk prediction tool. This will inform clinicians of potential risks based on the patients' EHR records that could be preventable or addressed through appropriate intervention.

In contrast, interfacing with other systems such as health information exchanges may improve the completeness of clinical information on patients and may help improve the predictive value of triggers (such as when a return visit was in a nearby ED that participated in a health information exchange vs not). We will be open to exploring all kinds of such interactions, and if we see *signals* regarding medications or other systematic alerts, we will study them further by obtaining clinician's insights for face validity and accuracy. Although we are not specifically focused on drug or medication-related events, if they contribute to the diagnostic process and breakdowns, they will be included as covariates.

Limitations and Strengths

We anticipate some difficulties and potential limitations to our forthcoming project. First, although we have based our analysis on the patients' medical records, it is notable that this information is not always available at all sites. Our method potentially cannot be extended to EDs that do not have an integrated EHR system, as different EDs might use incompatible EHR systems to ours, which at least requires an adaptation phase. We intentionally chose the community and academic sites to learn more about the potential difference and have recruited clinicians at each site to determine important differences and help customize the trigger algorithms. We also believe that by incorporating commonly accepted and standard measurements in this study, any future translation to other health systems would be possible by a simple mapping to the database elements of the target EHR system.

Second, our approach to investigate the risk of diagnostic error for ED patients with care escalation or death within a certain period from ED discharge will not include many events, including those that occur within the same ED encounter, possible events in other hospitals, and flag records that meet trigger criteria but are not associated with diagnostic error. We will attempt to update our data exploration approach to reduce the rate of such false-positive triggers. Conversely, a strength of our study is that the simultaneous investigation of 2 separate health systems with both adult and pediatric EDs reduces the chance of biased conclusions. These limitations are balanced by several unique strengths of this study to help identify

potentially associated contributory factors of diagnostic error in the ED.

Conclusions

The use of sophisticated data mining techniques to compare trigger-positive and trigger-negative records will enrich the list of risk factors that lead to diagnostic errors. To the best of our knowledge, this is the first application of exploratory decision tree techniques such as CART and CHAID to determine the relative importance of associated predictors of diagnostic error. Such techniques will help identify risk factors of diagnostic error using EHR data and inform the development of future dynamic ED-based decision support systems for monitoring and improving diagnostic safety.

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Conflicts of Interest

None declared.

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Abbreviations

ARM: association rule mining
CART: classification and regression tree
CHAID: chi-square automated interaction detection
ED: emergency department
EHR: electronic health record
IDEA-LL: Improving Diagnosis in Emergency and Acute Care–Learning Laboratory
SQL: Structured Query Language

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Protocol

The GIMEMA-ALLIANCE Digital Health Platform for Patients With Hematologic Malignancies in the COVID-19 Pandemic and Postpandemic Era: Protocol for a Multicenter, Prospective, Observational Study

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Abstract

Background: The COVID-19 pandemic has raised unprecedented challenges in the management of patients with cancer and has increased the demands for digital health tools that, for example, could facilitate remote monitoring of patients. Based on this, the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) has recently developed a digital health tool dedicated to patients with hematologic malignancies: the GIMEMA-ALLIANCE platform.

Objective: The main objectives of this web-based platform are to generate relevant data to better understand quality of life, symptoms, and medication adherence during the COVID-19 pandemic and postpandemic era; to develop a prospective real-life registry on outcomes of patients with hematologic cancer, with or without a diagnosis of COVID-19; and to facilitate patient-centered care in routine practice.

Methods: The platform consists of physician- and patient-secure portals and enables electronic patient-reported outcome (ePRO) assessments with real-time graphical presentation to physicians of individual patient symptoms and quality-of-life outcomes. Automated alerts are sent to treating hematologists based on the following predetermined criteria: presence of clinically important problems and symptoms, problems with adherence to therapy, and risk of COVID-19 diagnosis. The platform also allows physicians to set up video consultations. Clinical information regarding disease and treatment as well as clinical and survival outcomes are also prospectively collected.

Results: Recruitment of participants started in December 2020. As of April 2021, a total of 116 patients have been enrolled in this study. Use of this platform may help to improve patient-physician communication and help hematologists in the early recognition of clinically important problems and symptoms of their patients. More than 20 community and university-based hospitals have currently agreed to participate. In addition to patient-reported outcome data, the prospective collection of disease- and treatment-related information, as well as data on possible COVID-19 diagnosis and COVID-19 vaccination, will allow the development of a large database to also identify subgroups of patients at risk of poor outcomes.

Conclusions: Data generated via this platform will help to answer clinically relevant questions for patients with hematologic malignancies during the COVID-19 pandemic and postpandemic era. The use of the GIMEMA-ALLIANCE platform in routine practice may also contribute to enhancing patient-centered care.

Trial Registration: ClinicalTrials.gov NCT04581187; https://clinicaltrials.gov/ct2/show/NCT04581187
International Registered Report Identifier (IRRID): PRR1-10.2196/25271

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KEYWORDS

digital health; hematology; leukemia; lymphoma; multiple myeloma; patient-reported outcomes; quality of life; symptoms; COVID-19

Introduction

Background

The COVID-19 pandemic has recently transformed health care delivery all over the world by also remarkably increasing the complexity of clinical decision making in oncology [1].

Approaches to obviate the need for physical meeting between patients and health care providers (ie, telephone calls, communication by mail, and mobile phone apps) are now more frequently preferred to limit the risk of virus spread among uninfected patients [2]. A rapid integration of digital health technologies in the health care system is being embraced in several countries to achieve a new balance between self-isolation and health care delivery [3,4]. Addressing the physical and mental health-related concerns of patients is now critical [5] and may have major implications. For example, empirical data indicate that patients' anxiety related to the COVID-19 pandemic may be associated with the risk of underestimating important symptoms of hematologic malignancies, thereby delaying diagnosis and appropriate treatment [6].

The COVID-19 emergency has prompted new questions about how to integrate the vulnerability of patients with cancer—because of either the disease itself, the effects of cancer treatments, or additional comorbidities—with the risk of COVID-19 [7].

Management of patients with hematologic malignancies during the COVID-19 pandemic can be particularly challenging for several reasons, including the need for expert supportive care services, which can be substantially limited during the current clinical scenario. For example, careful evaluation of how long patients with leukemia can be managed without in-person follow-up visits, blood tests, and therapies, as well as close monitoring of potential complications during therapy, are now critical components of patient management during this global pandemic [8]. Therefore, special recommendations to optimize treatments for patients with hematologic malignancies during the COVID-19 pandemic have been recently published [8]. A recent multicenter study, which included a large sample of more than 500 adult patients with hematologic malignancies who required hospitalization for COVID-19, also indicated high mortality rates [9]. This study showed that patients with hematologic malignancies with COVID-19 had worse outcomes than both the general population with COVID-19 and patients with hematologic malignancies without COVID-19 [9].

The Added Value of Patient-Reported Outcome Assessment in Routine Cancer Care

There is now convincing evidence of the clinical value of systematic collection and use of patient-reported outcomes (PROs) in routine cancer practice [10,11]. Also, empirical data indicating that PROs, including symptoms and functional aspects, provide independent prognostic data for survival [12,13] further reinforces the need to more systematically assess PROs, as they provide unique information that cannot be captured via traditional clinical measures or laboratory exams.

Regular assessment of PROs in daily practice has been shown to provide a number of positive effects with regard to, for example, improved symptom control, timely identification of physical and psychosocial needs, improved patient-physician communication, and improved health-related quality of life (HRQoL) and emotional well-being, without increasing patient management activities for health care professionals [10,11,14-21].

Digital health technology now allows implementation of electronic PRO (ePRO) measures that patients can complete, for example, remotely via web platforms. Results obtained by completing ePROs via these platforms are typically graphically displayed in real time and available for physicians and clinical staff.

Notably, one randomized controlled trial (RCT) conducted in patients with advanced solid cancer reported that web-based self-reporting of symptoms with automated alerts to clinicians for severe or worsening symptoms was not only associated with a reduced number of emergency room visits and hospitalizations but also with significant improvement in overall survival [14,22]. Similarly, another RCT in patients with advanced-stage lung cancer showed that a web-mediated follow-up algorithm based on self-reported symptoms also improved overall survival [23]. A more recent RCT conducted in patients with solid cancer, who were mainly treated with curative intent, showed that real-time monitoring with ePROs improved physical well-being and self-efficacy without increasing hospital workload, and authors concluded that online symptom monitoring is a feasible approach to be implemented in routine care [24].

The key advantages of using ePROs during the COVID-19 pandemic have been recently highlighted [25] and these may include the following: the prevention of the occurrence of severe adverse events and the prompt management of medical needs. While some challenges exist to the implementation of ePRO instruments into routine practice, such as technical and organizational factors, a number of actions can be put in place

to maximize efficiency and ensure successful collection of ePROs [26].

Study Rationale and Hypotheses

Italy was one of the most severely affected countries by the COVID-19 pandemic in early 2020 [27], putting enormous pressure on hematology departments across the country.

The current pandemic represents an opportunity to further boost use of digital health technologies in the hematology arena and maximize the use of remote ePRO data collection in patients with hematologic malignancies. As recently observed, the COVID-19 pandemic has precipitated a shift to remote technology-enabled care [24].

In this new clinical scenario, the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) led the development of a dedicated digital health tool for patients with hematologic malignancies. The tool was called *An online platform to improve patient-centered care during the COVID-19 pandemic: A GIMEMA surveillance program in hematologic malignancies* (ALLIANCE)—the GIMEMA-ALLIANCE platform.

GIMEMA is a nonprofit research organization with a long-standing history of clinical research in hematology; it consists of a well-established network of about 150 affiliated hematology centers throughout Italy, including both community and university-based hospitals, plus a data center located in Rome that coordinates research activities. The GIMEMA-ALLIANCE platform was devised in collaboration with Evaluation Software Development (ESD), a well-established spin-off digital health company, whose key product is the Computer-based Health Evaluation System (CHES) infrastructure. CHES is a tool for the electronic collection, calculation, analyses, and presentation of PROs. CHES is used worldwide in more than 75 hospitals and research institutions for the electronic capture of medical and PRO data [28,29].

We hypothesize that use of the GIMEMA-ALLIANCE platform in patients with hematologic malignancies would facilitate a more patient-centered care approach and would support hematologists in the earlier recognition of clinically important problems and symptoms of their patients. By using this platform, we also aimed to collect disease- and treatment-related information, as well as prospective PRO data, to answer important research questions.

Objectives

The main objectives of the GIMEMA-ALLIANCE platform are as follows:

1. To generate relevant data to better understand quality of life, symptoms, and medication adherence in adult patients with hematologic malignancies during the COVID-19 pandemic and postpandemic era, and to identify subgroups of patients at higher risk of poor outcomes.
2. To develop a large prospective real-life registry on cancer treatment outcomes of patients with hematologic cancer, with or without a diagnosis of COVID-19.
3. To facilitate patient-centered care in routine practice by using ePRO measures with automated alerts sent to treating hematologists.

Methods

Study Participants

Considering that we aimed to use the platform with patients seen in daily practice, very broad inclusion criteria were set up. Inclusion criteria were as follows: (1) diagnosis of any hematologic malignancy according to the 2016 World Health Organization classification [30], (2) adult patients (≥18 years of age), and (3) written informed consent. Exclusion criteria included (1) major cognitive deficits or psychiatric problems hampering a self-reported evaluation and (2) inability to read and understand the local language. Patients enrolled in clinical trials are still eligible for this protocol, and this information is recorded in the case report forms (CRFs) at the time of entry in this study to be used for sensitivity analyses.

Ethics Approval, Consent to Participate, and Trial Registration

This study is currently funded by GIMEMA and was approved by the Ethics Committee of the University of Sapienza, Rome (study reference No. 5822, Protocol 366/2020). Documented informed consent must be obtained for all patients. By means of the information sheet, all eligible patients will be informed about the aims of the project, the procedures to participate in the project, and the strict confidentiality of the patients' data. It will be emphasized that participation is voluntary and that it might contribute to defining a more personalized and timely therapeutic approach. It will be also highlighted that either refusing to join the study or withdrawing afterwards at any time will not prejudice the patient's subsequent care. This trial was registered at ClinicalTrials.gov (NCT04581187).

Patient Recruitment Procedures

After approval by the local Ethics Committee of each participating center, patients who meet the inclusion criteria will be invited to participate by authorized investigators. At present, 27 centers have agreed to participate. Eligible patients willing to participate will be given a written information sheet and asked to sign the informed consent form. Considering the challenges posed by the pandemic, with inevitably less frequent face-to-face access in the hospital, and in line with current Italian regulatory guidelines, consent may also be anticipated, for example, via telephone or email [31].

All eligible and consenting patients will be registered in the platform via the dedicated physician portal, which allows for the downloading of patient log-in details and basic instructions to access the patient portal, to be handed over to patients.

Study Design and Logistics

This is a multicenter prospective observational study led by GIMEMA. All data will be centrally collected and analyzed at the GIMEMA Data Center, which operates according to high-quality and transparent standards of clinical research, as certified by the European Clinical Research Infrastructure Network (ECRIN) [32]. ECRIN certification ensures that a data

center meets several procedural standards with respect to different aspects of clinical research. These include the design, development, and validation of CRFs; data entry and data management; coding of variables; validation of databases; and statistical analysis. ECRIN certification also concerns the management of information technology infrastructure; data security, storage, and access; and back-up procedures.

The platform will be open for 2 years to register new patients who will be followed up for 2 years from the date of registration; the platform consists of two password-protected secure portals, one for physicians [33] and one for patients [34]. Data security of the web-collection system in this study is fully compliant with the highest standards of security of data protection (see details in the next paragraph).

Once a participating center obtains local ethical approval and it is officially ready (ie, having sorted out all administrative steps to receive access to the platform by the GIMEMA Data Center), a training session is organized by the GIMEMA-ALLIANCE management team with the on-site clinical staff of the participating hospital. The session broadly aims at instructing the local staff in using the platform and in interpreting patient-reported data. A brief practical guide is also sent to the clinical staff at study start-up. A study newsletter is circulated on a regular basis to provide feedback on study progress and to invite users to report any questions or requests of assistance to the GIMEMA-ALLIANCE management team at their email address.

The Architecture of the GIMEMA-ALLIANCE Platform

All clinical and patient-reported data in this study will be collected through the dedicated web platform using the CHES infrastructure [28]. CHES is a sophisticated web-based software tool specifically designed for ePRO questionnaire administration, real-time graphical presentation of individual patient results, and clinical and PRO data collection, storage, and analysis. This platform runs in all common web browsers, devices, and operating systems; it has already been implemented in a number of national and international institutions engaging clinical studies with electronic capture of medical and PRO data as well as PRO data collection in routine oncology care [35-40]. Since CHES is a web-based application, the communication between the client (ie, browser) and the server needs to be protected from being read or modified by an attacker. This is done by only allowing Secure Sockets Layer–encrypted communication (ie, https). The https encrypts the data between the client and the server, so no other person can read or modify the data sent from the client to the server and from the server to the client. These secure web links are used for all participants within the CHES system: administrators, physicians, and patients. To further ensure data security, the system is divided into two different zones, the so-called trusted and untrusted zones. These zones are realized by two different servers that differ in their accessibility. The server in the trusted zone is only accessible within the GIMEMA network, whereas the server in the untrusted zone is accessible via the World Wide Web. A network connection exists only from the trusted zone to the untrusted zone but not vice versa. All sensitive patient data are stored in the trusted zone. Only data that cannot be linked to a patient are stored in the untrusted zone. To fetch data from the untrusted zone (eg, the completed survey), a software service runs in the trusted zone that merges the data from the untrusted zone into the database of the trusted zone. Only the trusted zone knows the mapping of the anonymous patient ID from the untrusted zone to the actual patient ID in the trusted zone (Figure 1).

For accessing the system, two different weblinks exist. One weblink is used to access the patient portal in the untrusted zone, whereas the other weblink is used to access the physician portal in the trusted zone. Any system access requires at least a username and a password. Furthermore, for accessing the physician portal, a two-factor authentication mechanism is in place that requires each physician to enter a 6-digit code that is sent to his or her mobile phone when trying to log in. This token is valid only once and expires after 3 minutes if not used. The credentials for the physician portal will be provided by the GIMEMA-ALLIANCE management team to all investigators, who have been previously authorized to access the physician portal, prior to the study start date at each participating center. The credentials to the patient portal will be provided by the local investigators to the patients enrolled at their participating center. The physician web interface is designed for an easy-to-use approach, allowing quick access to all of their patients' relevant data and real-time access to a visual summary of patient-reported information via the web browser of each patient enrolled within the same hospital. The physicians will hand out a flyer to their patients containing the individual credentials, along with the weblink to access the patient portal.

Once the patient is entered into the dedicated portal, three modules are displayed (Figure 2). The first module mainly aims at collecting patient-reported information on quality of life, symptoms, and medication adherence (ie, the ALLIANCE survey, which is described in detail in the next section). The second module can be used by patients to provide real-time information to their treating hematologists regarding a potential risk of SARS-CoV-2 infection or a confirmed COVID-19 diagnosis. Items included in this module are as follows: having received a confirmed diagnosis of COVID-19, having been in close contact with someone with a COVID-19 diagnosis, having reported a fever of more than 37.5 °C, and having experienced breathing difficulty, cough, or an altered sense of smell and/or taste over the last 2 weeks. The third module consists of the video consultation area, which allows patients to have online visits with their physicians and allows the actual scheduling of online visits via a user-friendly agenda.

Figure 1. Main workflow of the GIMEMA-ALLIANCE platform. ALLIANCE: An online platform to improve patient-centered care during the COVID-19 pandemic: A GIMEMA surveillance program in hematologic malignancies; CHES: Computer-based Health Evaluation System; GIMEMA: Gruppo Italiano Malattie Ematologiche dell'Adulto.

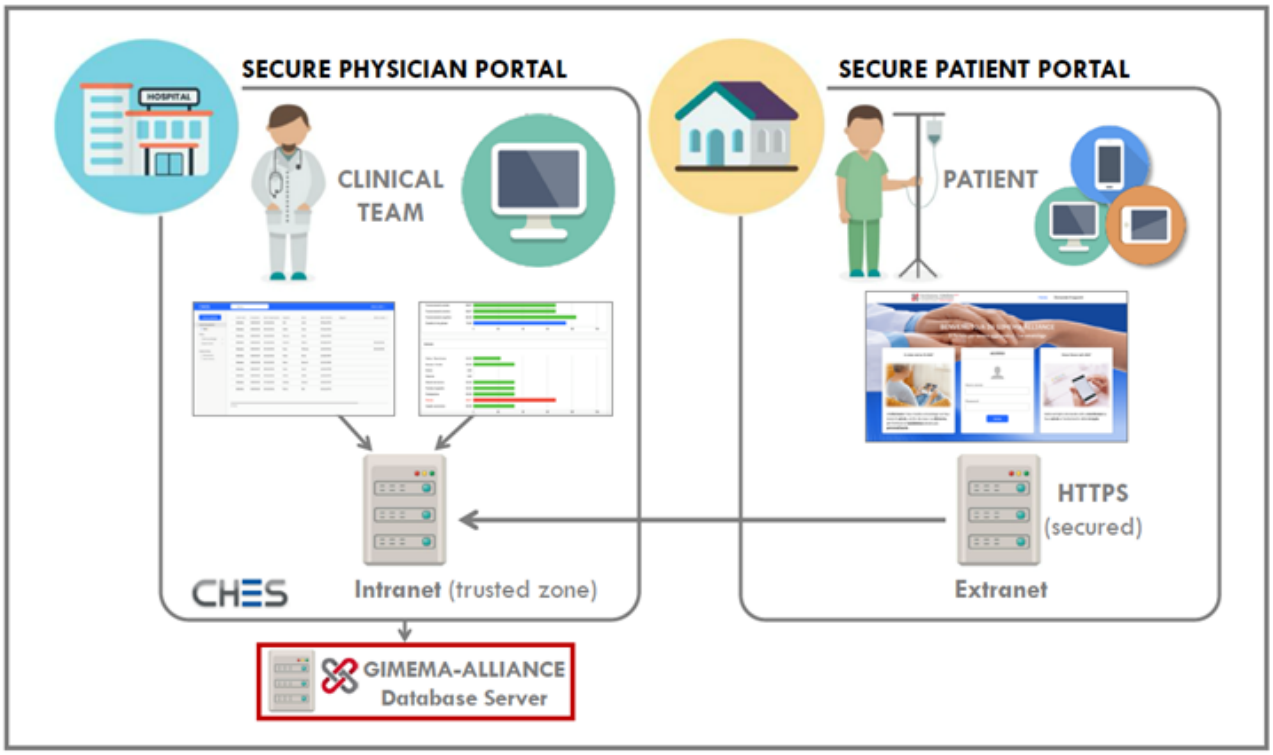


Figure 2. GIMEMA-ALLIANCE patient portal. ALLIANCE: An online platform to improve patient-centered care during the COVID-19 pandemic: A GIMEMA surveillance program in hematologic malignancies; GIMEMA: Gruppo Italiano Malattie Ematologiche dell'Adulto.

The ALLIANCE Survey

The first module of the patient portal includes the ALLIANCE survey, which aims to assess the patient's perspective on the following broad areas: global health status and quality of life, functional aspects, symptoms, and problems with adherence to therapy. In addition, a few information items (eg, questions about social support) are only included in the first survey. From the second assessment on, these few additional information items will no longer be requested of patients.

Just after registration in the study, patients will be asked by their treating hematologist to complete the survey at their earliest convenience. Considering the real-life nature of the study, and the wide range of clinical scenarios that could be represented in this platform, no prespecified time points for completion have been preplanned. In any case, the platform is designed to send regular reminders to patients to complete the survey, with the first one being sent after 1 week from date of registration, that is, if the first survey has not been completed within the first week of registration.

Global health status and quality of life, functional aspects, and symptoms are evaluated with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core (QLQ-C30) and ad hoc items from the EORTC Item Library. The EORTC QLQ-C30 is a brief, multidimensional HRQoL measure consisting of 30 items; the measure includes five functional scales (ie, physical, role, emotional, social, and cognitive), three symptoms (ie, fatigue, nausea and vomiting, and pain), a global health status and quality of life scale, and six single items (ie, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) [41]. To further increase the sensitivity of HRQoL measurement for patients with hematologic malignancies, four ad hoc items from the EORTC Item Library are also included [42].

The decision on items to be included in the survey from the EORTC Item Library was based on clinical grounds after discussion with physicians involved in the project, on which symptoms not already covered by the EORTC QLQ-C30 would be most relevant for the majority of patients with hematologic malignancies. Also, we limited the inclusion to only four additional symptoms to reduce response burden as much as possible. Specifically, two items stemmed from the EORTC Quality of Life Questionnaire–Chronic Lymphocytic Leukemia (QLQ-CLL17) module (ie, night sweats and bone pain), and two items stemmed from the EORTC Quality of Life Questionnaire–Chronic Myeloid Leukemia (QLQ-CML24) module (ie, headache and muscular cramps).

We used the EORTC QLQ-C30 questionnaire, as it covers not only functional aspects, global health status, and HRQoL of patients, but it also includes a core set of cancer symptoms that we considered important to monitor in our patients. This questionnaire has been used in a number of studies of patients with hematologic malignancies [43], and its measurement invariance in the setting of hematology has been supported [44]. In addition, the EORTC QLQ-C30 also allows the calculation of a single summary score, which has been validated across the whole spectrum of both solid and hematologic malignancies [45,46] and may be helpful in future analyses with data collected in our platform. Indeed, recent empirical data in the real-world setting, for example, have shown that this EORTC QLQ-C30 summary score has a strong prognostic value for overall survival across a wide range of cancer populations above and beyond that provided by traditional clinical and sociodemographic variables [12]. Furthermore, international general population normative data are available for this questionnaire [47], thereby facilitating future comparisons of the profiles of our patients with reference values. Finally, the availability of recently established evidence-based criteria for the definition of clinically important problems and symptoms that can be used to ease interpretation of data in daily clinical practice [35] is an additional key strength we valued highly for the inclusion of the EORTC QLQ-C30 in our platform. Indeed, as previously observed, one of the key challenges to the successful implementation of PRO data with health information technologies for use in routine care is clinician understanding of how to interpret and respond to PRO information [48].

Medication adherence is evaluated with the Adherence to Refills and Medications Scale (ARMS). We used the shortened 7-item version of the ARMS (ie, ARMS-7), which is a brief self-reported validated measure of medication adherence and correlates very highly with the full 12-item measure [49,50]. Each of the items allows patients to express, on a 4-point scale, how often they do not take or refill their medications under different circumstances. Scores on the ARMS-7 range from 7 to 28, with lower scores indicating better adherence; in addition, the scale is available in Italian.

Adherence to oral anticancer therapies is a known problem, and several factors have been found to be associated with poor medication-taking behaviors, including both treatment-related aspects and personal patient factors [51]. Considering the potential negative effects of suboptimal adherence on clinical efficacy, and the fact that many patients with hematologic malignancies are now treated with oral drugs, we aim to also include in the platform a brief and easy-to-use self-reported measure to assess medication adherence. Among the available self-report adherence measures that can be used in clinical practice [52], we selected the ARMS, which has been shown to be a valid and reliable scale, with optimal performance characteristics among patients with low literacy as well [49]. We considered this latter characteristic of critical importance for inclusion in our platform, considering that we aimed to capture this type of data in real life, hence, approaching patients with various levels of education.

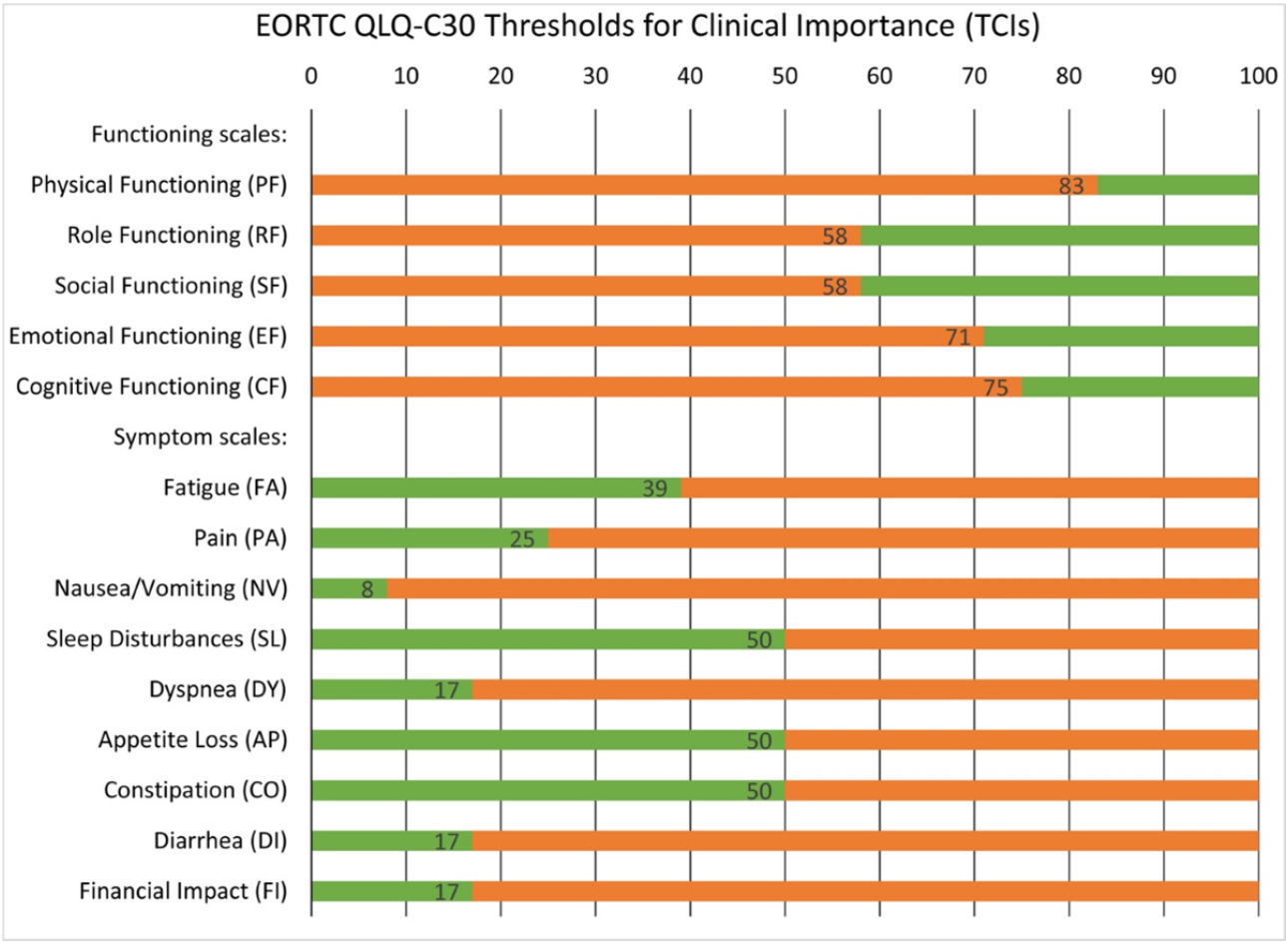
Active Monitoring of Patients Via the GIMEMA-ALLIANCE Platform

Currently, the platform triggers automated email alerts to the treating hematologist based on the following criteria:

1. Presence of clinically important problems and symptoms.
2. Problems with adherence to therapy.
3. Risk of COVID-19 diagnosis.

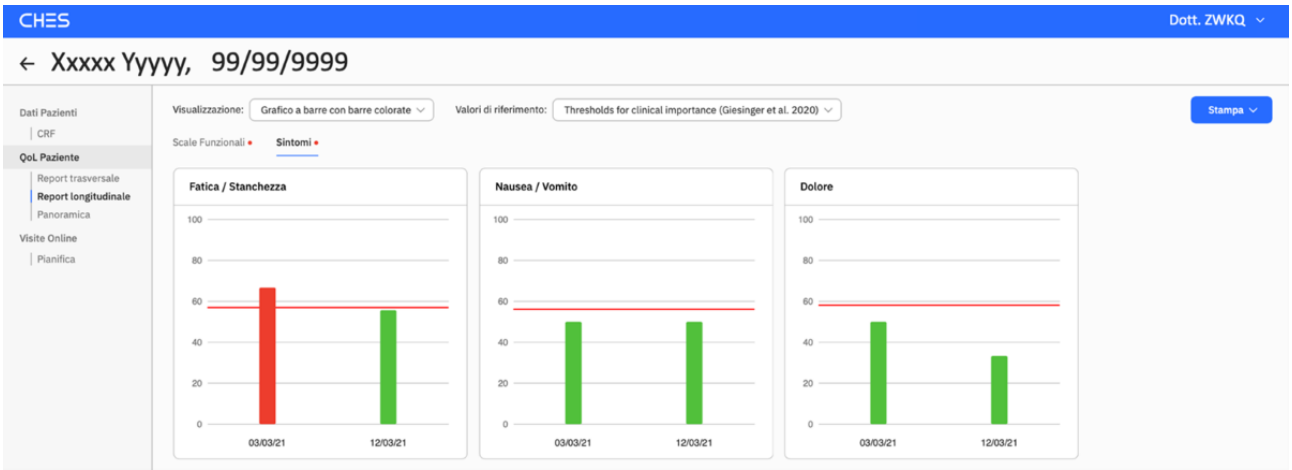
The definition of *clinically important* problems and symptoms is based on previously defined thresholds for functional aspects (eg, physical and emotional functioning) and key cancer symptoms from the EORTC QLQ-C30 [35]. These thresholds for clinical importance were established to detect health problems that limit a patient's daily life, cause worry to the patient and/or to his or her partner or family, or require help or care; all of these are criteria that have previously been identified as making a health problem relevant for the clinical encounter [35]. The scale-specific thresholds used are reported in Figure 3.

Figure 3. EORTC QLQ-C30 thresholds for clinical importance (TCIs). TCIs are shown inside the bars. Patient scores in the orange range of the bar (ie, below the TCI for functioning scales or above the TCI for symptom scales) indicate clinically important problems or symptoms. Reprinted from Giesinger et al (2020) [35]). EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire–Core.



Through their portal, physicians have real-time access to a visual summary of patient-reported information, with red bars flagging clinically important problems and symptoms. To further facilitate the timely recognition of potential problems of their patients, email alerts sent to physicians also contains a link directly connecting to the graphical summary generated by the patient ratings. Figure 4 depicts an example of a graphical display of patient-reported symptoms.

Figure 4. Example of graphical display of results of patient-reported symptoms available on the physician portal. The red vertical bar indicates a clinically important symptom.



Our working definition of potential problems with adherence to therapy is based on the scoring instructions for the ARMS-7 questionnaire, which is used in the platform to assess medication adherence. The overall score from this questionnaire ranges from 7 (best adherence) to 28 (worst adherence) [49,53], and it can be dichotomized as 7 or >7. A score equal to 7 indicates an optimal adherence, while any score larger than 7 indicates some degree of nonadherence. Therefore, we designed the platform

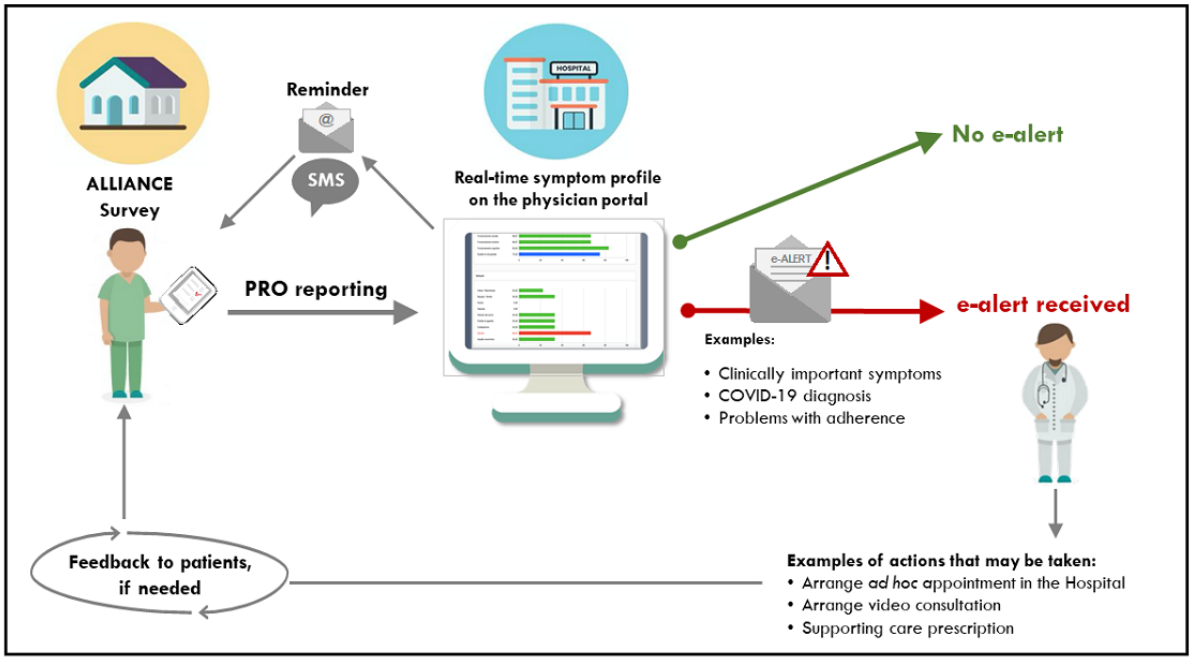
to send an alert for adherence if the total score from ARMS-7 is higher than 7.

Based on patients' answers to items included in the *risk of COVID-19 diagnosis* module, the platform automatically generates real-time alerts if at least one of them is checked to be true. This alerting procedure aims to enhance physician ability to more proactively engage patients who are at heightened risk of being diagnosed with COVID-19 or who may have been actually diagnosed with the disease.

However, considering the real-life nature of this study involving several centers, the alerting algorithm currently implemented for triggering alerts could be further refined or revised during the study period. Such information will be recorded in study files.

Physicians are free to decide on which action they feel to be most appropriate for their patients. For example, depending on the type and/or frequency of patient-generated alerts, they could (1) arrange an ad hoc face-to-face visit in the hospital, (2) arrange a video consultation, (3) refer the patient to other specialists, or (4) simply contact the patient by phone to further understand the patient's needs. The workflow of the alerting procedure is summarized in Figure 5.

Figure 5. Schematic workflow of the patient-generated alerts to the medical team. ALLIANCE: An online platform to improve patient-centered care during the COVID-19 pandemic: A GIMEMA surveillance program in hematologic malignancies; PRO: patient-reported outcome.



Automated alerts are only meant to help physicians in the early recognition of potential problems of their patients; therefore, predetermined actions in response to specific alerts are not suggested by the platform. Considering the large heterogeneity of patient characteristics and types of specific treatments patients may receive, we did not recommend specific actions to take in response to alerts.

In any case, information about actions taken by physicians will be collected with ad hoc surveys sent to them, to understand how the platform might have helped them in the clinical management of their patients. These surveys will include questions about actions taken after having received an alert, such as *no action taken*, *phone call with the patient* to further understand the patient's needs, *video consultation*, or having arranged a *visit in the hospital* or *referral to other specialists*. In addition, the survey will ask the physician about the frequency of his or her access to the platform and will also include 14 questions about acceptability and feasibility of the portal; responses could include, for example, "Use of the platform improved my understanding of the actual patient burden of symptoms" or "I think that the platform might be improved by additional features."

Physician-Reported Information

The physician portal also includes a set of CRFs that are to be completed by the treating hematologists at baseline (ie, at study entry) and at regular intervals. Also, ad hoc CRFs are to be completed regarding COVID-19 diagnosis and COVID-19 vaccination, if applicable. Table 1 provides a summary of CRFs currently uploaded in the physician portal.

The baseline form will require a number of sociodemographic as well as disease- and treatment-related variables. Some key information items collected in this form are provided Textbox 1.

Table 1. Summary and timeline of case report form (CRF) completion by the investigator.

CRFs to be completed	Frequency of completion	Timeline	Purpose
Registration checklist	Once	At the time of registration in the platform	To confirm eligibility criteria
Baseline form	Once	At the time of study entry	To comprehensively understand patients' characteristics and disease status at study entry
Follow-up form	On a regular basis	Every 3 months	To monitor treatment, disease progression, and status of patient (including survival status) at follow-up
COVID-19 form	As appropriate	Only in the case of confirmed diagnosis with COVID-19	To collect information on COVID-19 severity, symptoms, and outcomes
COVID-19 vaccine form	As appropriate	Only in the case that patients receive a COVID-19 vaccine	To better understand the implications of having received a vaccine

Textbox 1. The main clinical and sociodemographic variables included in the baseline case report form to be completed at study entry.

Selected key variables:

- Type of hematologic malignancy
- Date of initial diagnosis
- Patient date of birth
- Sex
- Education level
- Smoking status
- Type and number of comorbidities
- Eastern Cooperative Oncology Group performance status
- Status of patient at study entry: options include newly diagnosed and yet untreated, initial diagnosis and receiving first-line treatment, in remission and not receiving treatment, in remission and receiving consolidation or maintenance treatment, stable but not in remission, and relapsed or refractory
- Ongoing treatment (if applicable)

The follow-up form will be completed every 3 months and will require basic data about ongoing therapy, any major toxicity, response to therapy, as well as survival status. In addition, the COVID-19 form, which will be completed only if the patient receives a diagnosis of COVID-19, will require specific information related to COVID-19 occurrence and related treatment history, hospitalization, symptoms, and outcomes, including survival. Similarly, a COVID-19 vaccination form is available to be completed, as appropriate, to collect information on date and type of vaccine received.

However, given the evolving situation of the COVID-19 pandemic, additional information regarding the patient's medical history or clinical course of the disease (eg, details on disease characteristics, treatments, and possible complications) may be further requested of investigators, who may be asked to answer specific research questions of clinical relevance.

Statistical Analysis

Given the nature of this study, a formal calculation of sample size and power was not performed. However, at the time of study design, we determined that 400 patients in 2 years was a reasonable estimate of the overall enrollment of this study. Each patient enrolled in this study will be followed up for 2 years from the date of registration. All the analyses described below will be performed overall and by patient subgroups (eg, either by type of hematologic disease at study entry, type of treatment, or diagnosis of COVID-19). We will estimate the trajectories over time of the scores from the scales from all PRO questionnaires by either a generalized linear mixed model (GLMM) or a growth curve model [54], depending on the actual observed timing of PRO assessments, to prospectively monitor HRQoL, symptoms, and adherence to therapy. We will also assess the prevalence over time of clinically important problems and symptoms, as measured by the EORTC QLQ-C30, using the GLMM. For each scale, the clinical relevance of HRQoL problems will be determined according to previously published thresholds [35]. The GLMM approach will be used to investigate factors associated with physical and mental health concerns and adherence to therapy. Depending on the type of outcome to be investigated, we will use either the GLMM, the Cox proportional hazards model, or the Fine-Gray model for competing risks [55] to assess the impact on patient outcomes (eg, survival outcomes) of key factors, including the diagnosis of COVID-19.

The clinical strategies adopted by physicians in response to patient-generated alerts, as well as patient characteristics and information about disease course and outcomes, will be summarized using means, proportions, medians, and interquartile

ranges, according to the type of variable. Possible cross-sectional comparisons of outcomes between subgroups of patients, based on, for example, type of hematologic disease, type of treatment, or diagnosis of COVID-19, will be assessed using either Fisher exact, chi-square, Wilcoxon-Mann-Whitney, or Kruskal-Wallis tests, according to the type of variable.

Results

Recruitment of participants started in December 2020. As of April 2021, a total of 116 patients have been enrolled in this study. The main outcomes from this project will include longitudinal patterns of patients' self-reported health issues and needs related to their overall quality of life, symptoms, and medication adherence. In addition, the real-time flow of information between patients and their physicians will possibly improve communication and help physicians in adopting more timely interventions. Data accumulated via this platform may also lay the groundwork to better understand the implications of a COVID-19 diagnosis on the midterm to long-term mental and physical health of patients with hematologic malignancies.

All findings will be disseminated in international peer-reviewed journals and abstracts presented at major international conferences. The study coordinators and the GIMEMA Data Center must approve all publications, abstracts, and presentations based on patients included in this study. Given the paucity of information on the effects of COVID-19 in patients with cancer and the importance of promptly providing new information to the scientific community, as well as in the best interest of patients, interim analyses and publications are foreseen during the recruitment period.

Discussion

We expect this platform to eventually become a large database containing information on the clinical course of the disease, patient-reported quality of life, and symptom profiles of patients with hematologic malignancies. Data collected in this platform will also allow us to compare the outcomes of patients with hematologic malignancies who may have been diagnosed with COVID-19 with those without COVID-19. Indeed, there is evidence indicating that the COVID-19 pandemic poses major risks to patients with hematologic malignancies [9].

We also note that this new platform, whose development was prompted by the global pandemic, can be an opportunity to further boost a shift toward a more patient-centered healthcare paradigm in the hematology arena. An essential aspect of the platform is that of being based on PROs, hence, making the patient's input a critical aspect for its functioning.

This platform has been devised to be used across all hematologic malignancies and can also be customized with additional specific modules and functionalities, for example, to address the needs of specific hematologic populations or to address specific research questions. The GIMEMA-ALLIANCE infrastructure may also be used for the conduct of multiple studies. Finally, having been purposely devised as a multilingual web-based tool, it can be easily used in international contexts and implemented for use in other countries. Therefore, given the enormous pressure put on health care systems since the surge of the COVID-19 pandemic and the urgent need to implement digital health tools that can facilitate cancer care, we also welcome international collaborators to join our efforts in this area.

Conflicts of Interest

BH holds intellectual property rights on the CHES software tool.

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Abbreviations

ALLIANCE: An online platform to improve patient-centered care during the COVID-19 pandemic: A GIMEMA surveillance program in hematologic malignancies
ARMS: Adherence to Refills and Medications Scale
ARMS-7: 7-item version of the Adherence to Refills and Medications Scale
CHES: Computer-based Health Evaluation System
CRF: case report form
ECRIN: European Clinical Research Infrastructure Network
EORTC: European Organisation for Research and Treatment of Cancer
ePRO: electronic patient-reported outcome
ESD: Evaluation Software Development
GIMEMA: Gruppo Italiano Malattie Ematologiche dell'Adulto
GLMM: generalized linear mixed model
HRQoL: health-related quality of life
PRO: patient-reported outcome
QLQ-C30: Quality of Life Questionnaire–Core
QLQ-CLL17: Quality of Life Questionnaire–Chronic Lymphocytic Leukemia
QLQ-CML24: Quality of Life Questionnaire–Chronic Myeloid Leukemia
RCT: randomized controlled trial

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Protocol

STAR Duodecim eHealth Tool to Recognize Chronic Disease Risk Factors and Change Unhealthy Lifestyle Choices Among the Long-Term Unemployed: Protocol for a Mixed Methods Validation Study

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Abstract

Background: Lifestyle choices and socioeconomic status have a significant impact on the expected onset of diseases, age of death, and risk factors concerning long-term illnesses and morbidity. STAR is an online health examination tool, which gives users a report that includes an evaluation of their life expectancy and an estimated risk for developing common long-term illnesses based on questions about health, characteristics, lifestyle, and quality of life.

Objective: The goals of this study are to (1) review the capacity of STAR to recognize morbidity risks in comparison to a traditional nurse-led health examination and patient-reported health challenges; (2) evaluate the user experience and usability of STAR; and (3) assess the potential impact of STAR on the health confidence and motivation of patients to make healthier lifestyle choices.

Methods: This mixed methods validation study will consist of a quantitative part (questionnaires) and a qualitative part (phone interviews and open-ended questions from the questionnaires). The participants will include 100 long-term unemployed individuals attending a health check for the unemployed. The participants will be recruited from three Finnish public health centers in Espoo, Hämeenlinna, and Tampere. At the health centers, the participants will use STAR and attend a nurse's health check. Surveys with multiple-choice and open-ended questions will be collected from the participants, the nurse, and a study assistant. The questionnaires include questions about the participant's background and health challenges from the patient and nurse points of view, as well as questions about how well the health challenges matched the STAR report. The questionnaires also gather data about user experience, health confidence, and usability of STAR. A study assistant will fill out an observer's form containing questions about use time and possible problems encountered while using STAR. A sample of the unemployed participants will be interviewed by telephone subsequently. For the quantitative data, descriptive statistics and a reliability analysis will be performed, and mean sum scores will be computed for the study variables. Thematic analysis of the qualitative data will be performed.

Results: This study was approved by the Ethics Committee of the Expert Responsibility Area of Tampere University Hospital in June 2020 (ETL Code R20067). Data collection will begin in June 2021 and will take approximately 3-6 months.

Conclusions: Online health examinations can improve the effectiveness of primary prevention in health care by supporting efficient evidence-based morbidity risk estimation and motivating patients to change unhealthy behaviors. A multimethod approach is used to allow for assessment of the tool's usefulness from the points of view of both professionals and patients. This study will

further provide a rich understanding of how the tool can be used as part of routine health checks, and how and why the tool may or may not motivate users for making healthier lifestyle choices.

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KEYWORDS

eHealth; risk assessment; long-term unemployed; expected age of death; online intervention; risk factors; chronic illnesses; primary prevention; online health check; long-term; multimorbidity; health care services; examination; evaluation; lifestyle

Introduction

Background

Long-term illnesses and multimorbidity have become more common, thus reducing quality of life and increasing the demand for health care services [1,2]. Lifestyle choices have a significant impact on the expected onset of diseases, age of death, risk factors concerning long-term illnesses, and multimorbidity [1,3-5]. Preventable lifestyle-related risk factors affecting chronic morbidity and mortality have been recognized, most notably smoking, the harmful use of alcohol, physical inactivity, and an unhealthy diet [5,6].

eHealth uses digital information and communication technologies for health, demonstrating growing potential to make health services more accessible, efficient, and cost-effective [7,8]. eHealth interventions aimed at assessing lifestyle-related risk factors could be one possible way to improve primary prevention in public health care [9-11]. An online health-related risk behavior intervention can be used to acquire clinical health behavior information, help health care professionals with standardized risk estimation, and motivate the patient to change unhealthy behaviors [9]. Web-based interventions focusing on health behavior–related risks have been reported to have an overall positive effect on the user's health, resulting in positive behavior changes [11-13]. Assessing multiple lifestyle-related risks at the same time provides an opportunity to review one's health comprehensively and target multiple health-related risk behaviors simultaneously [9]. Such interventions have been received well by patients compared to interventions targeting only one health-related behavior [9,12-14].

The long-term unemployed comprise a particular subgroup that could greatly benefit from such interventions [15]. Long-term unemployment is linked to greater than average morbidity, earlier expected age of death, and increased risk of mortality [15,16]. Long-term unemployment is defined as having been unemployed for 12 months or more [17]. The duration of unemployment increases the burden of disease [18]. Unemployment also affects self-assessed health negatively, and the strongest association is found in people with a lower socioeconomic status, weak social networks, and health-related reasons for unemployment [19]. There have been studies on online health checks and internet-based risk assessments of subgroups such as the employed, but there have been few studies focusing on online health checks for the unemployed [20].

There has been growing interest in studying the use of eHealth tools in preventing and treating chronic illnesses [21]. Although there are also some mixed results, positive evidence has been found on the effect of online health interventions in several different fields [8-14,21-23]. A systematic review of mobile and online health lifestyle interventions found them to have an up to 12-month positive effect on health [23]. A meta-analysis of computer-tailored interventions for health behavior change [11] found a clinically and statistically significant effect on all four health behaviors of focus. However, the effect of the intervention decreased over time; thus, more studies about the sustained effect are needed [11,23].

There is a huge variety of health risk calculators available online. A systematic review of online cardiovascular disease risk calculators found wide variation in risk assessment models, risk presentation, and results [24]. The study also found the risk calculators to have overall poor actionability, and that the available risk calculators often lack clinical validity. The information provided by risk calculators can help health care professionals to identify correct risk categories more accurately and also improve the likelihood of prescribing medicine to high-risk patients, thereby helping with decision-making [25]. A systematic review of decision aids used in clinical encounters reported that clinical decision systems improve satisfaction with medical decision-making; furthermore, clinicians found the information provided to be helpful [26].

An individual's perception of the likelihood and severity of a disease is a critical determinant of health behavior [27,28]. In addition to risk perceptions, a systematic literature review reported that motivation, support, and feedback are the most influential factors in changing health-related behavior with eHealth tools [29]. The lack of these same factors is also cited most often as a barrier to use. Goal-setting and self-regulation, rewards, user-friendliness, accessibility, and access to remote help are also mentioned as facilitating factors, while lack of resources or priority, negative support, lack of information, issues with technology, and sociodemographic barriers are listed as barriers of use. A scoping review of the usability and utility of eHealth for physical activity counseling in primary health care centers also found technical problems and the complexity of programs to be notable usability barriers to eHealth [30].

A systematic review of sociodemographic factors influencing the use of eHealth in people with chronic diseases found that the people who could benefit the most from eHealth interventions are usually not using them. The authors suggested tailoring the interventions to be more personal, making them more accessible, and using them to complement health care [31]. Another systematic review suggested making the digital health interventions more visible to the public, incorporating

communication with health care professionals and people with similar health problems, and involving clinical organizations or clinicians to promote and validate digital health interventions [32]. Similar recommendations were also made in other studies [33,34].

Intervention

The STAR Duodecim Health Check and Coaching Program (hereafter, STAR) is a general online health examination developed by Duodecim Publishing Company Ltd and the Finnish Institute of Health and Welfare [35-37]. The abbreviation STAR comes from the Finnish words for an online health check. STAR assesses the user's health, lifestyle, and mental well-being, and provides users a report including an evaluation of life expectancy and the estimated risk of developing the following common long-term illnesses: coronary heart disease, stroke, diabetes, and dementia. The report is based on approximately 40 questions regarding the user's health, demographic characteristics, lifestyle, and quality of life. The report also has suggestions on how to change to a healthier lifestyle, reduce the multimorbidity and long-term illness risks, and lengthen life expectancy. STAR and its report are further described in Multimedia Appendix 1. The life expectancy evaluation and the risk evaluations are based on previous Finnish studies, namely the Finriski, Autoklinikka, and Minisuomi studies [35,38-40].

Previous studies of STAR have mainly focused on creating a persuasive system design [41-43]. One of these studies established that consumers found the health feedback of STAR and its online coaching program to be too general; they instead desired more personalized feedback [41]. In general, the consumers had a favorable impression of STAR and there were no concerns with its credibility. In addition, a 2-year follow-up study on STAR's online training programs was performed in Finland, showing moderate positive improvement on stress, gratitude, and confidence in the future, although the effect decreased over the 2-year follow-up period [43]. The study included over 40,000 participants, which is a sign of interest in eHealth and its possibilities, although only 15% of the participants continued to the 2-year follow-up point.

STAR can be used either as a self-led program or integrated to a health care system. Duodecim's STAR Pro allows medical professionals to view their patients' STAR reports, which can be used, for example, to help with decision-making and as a useful means to review the patient's health and lifestyle choices. The user, be it the patient or the health care professional, can use their email to log in to the website. The service is cloud-based. STAR is available to approximately 2 million Finns as part of public health care service choices in selected areas of Finland, including in Vantaa, Salo, Seinäjoki, and the Keski-Uudenmaa municipal consortium [37,44-47]. STAR also has online training programs for maintaining health. There are currently six different themes: exercise, healthy nutrition, sleep, weight control, strengthening mental resources, and everyday stress control. The STAR report recommends these programs to the user based on the answers given. After using STAR for the first time, users can log in again with their email address to perform a new health check, follow their progress, or start the online training programs.

Study Objectives

The aim of this study is to help validate STAR as a risk assessment–based online health examination. The primary objectives of this study are to review STAR's ability to recognize health challenges among the long-term unemployed and to assess the potential of STAR to make a positive impact on the lifestyle choices of the unemployed.

The specific goals of this study are to: (1) review the capacity of STAR to recognize morbidity risks in comparison with a traditional nurse-led health examination and patient-reported health challenges; (2) evaluate the user experience and usability of STAR; and (3) assess the potential impact of STAR on the health confidence and motivation of patients to make healthier lifestyle choices.

Methods

Recruitment

People who have been unemployed for at least 12 months, are over 18 years old, and are participating in a health check for long-term unemployed people will be recruited for this study. Finland has a public health care system organized and financed by municipalities, and every resident is entitled to receive social, health, and medical services [48,49]. Therefore, the municipalities are obligated to organize health checks for the unemployed. The purpose of these health checks is to advance the health, and the ability to function and work of unemployed people [50]. The initiative can come from the unemployed person, unemployment services, or the municipal social welfare administration.

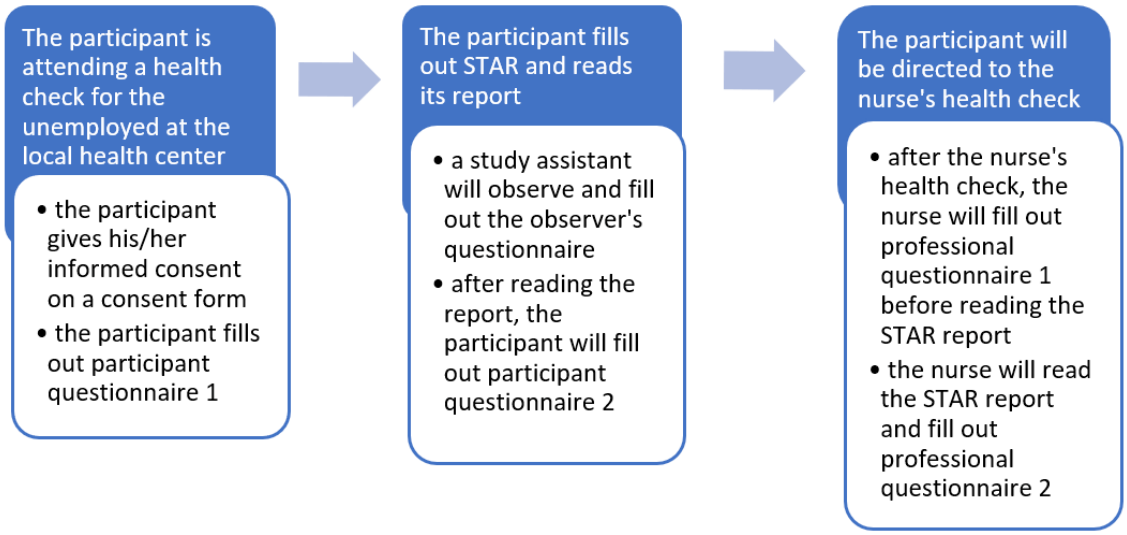
The goal is to recruit 100 participants in total. The recruitment will take place at three Finnish public health centers in Espoo, Hämeenlinna, and Tampere. Espoo and Tampere are the second and the third largest cities in Finland, with a population of 290,000 and 240,000, respectively [51]; Hämeenlinna is a slightly smaller city, with a population of 68,000. When the clients are booking their appointment, they will be informed about this study and the opportunity to participate. The participants will be asked to provide information about their cholesterol, blood pressure, and waist measurement at the appointment. A study assistant will be waiting for them at the local clinic where the health check is performed. The study assistant will ensure that the informed consent of the participants is obtained by giving them an information sheet on the study and answering any possible questions about the study. The consent form has an additional field for the participant's phone number, which will be used to perform a telephone interview 2 weeks after the essential health check portion of the study.

Study Setting

The participants will start their participation in the study after signing the consent form (Figure 1). The study assistant will give them the first questionnaire, which contains questions about the participant's background information. After filling out the first questionnaire, the participants will be asked to perform the

STAR online health examination. The study assistant will open STAR via a study email link and fill out an observer's form while observing the participant using STAR. The form has questions about the time taken to fill out STAR and read its report, and about the possible difficulties the participant experienced while using it. After filling out STAR and reading the report, the participants will fill out a second questionnaire concerning the user experience, their health confidence, how well they think STAR recognized their health challenges, and whether they would recommend STAR to a friend.

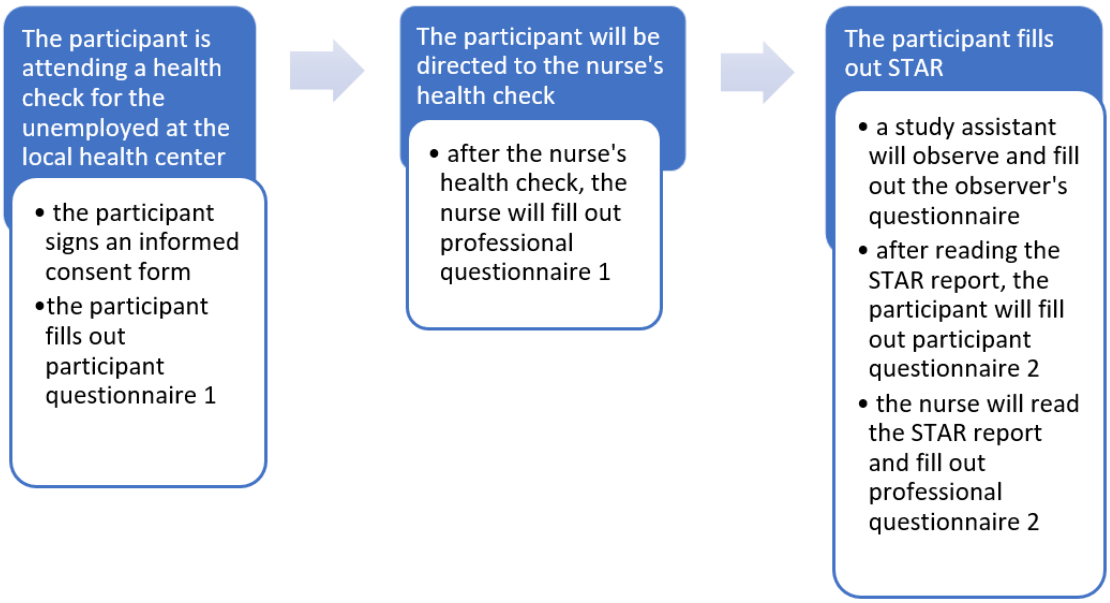
Figure 1. Flow of the study.



The participants will also attend a general health check in the nurse's office. The nurse's health check takes approximately 60 minutes to complete, including an anamnesis form; interview; and filling out evaluation forms for diabetes risk, alcohol use (audit), and depression (BDI-test). Blood pressure, weight, height, waist circumference, and BMI will also be measured. Before the health check, patients are given a referral for laboratory tests to check their blood sugar and lipids so that the results can be discussed at the health check. The health checks will be adjusted to the patient's personal needs. After the health check and before reading the STAR report, the nurse will fill out a two-part questionnaire regarding each participant's health challenges and STAR report. After filling out the first part, the nurse will read the participant's STAR report on the STAR Pro view and then fill out the second part, which includes questions about STAR's ability to recognize the participant's health challenges and whether the nurse found the STAR report to be useful from a medical professional's point of view.

To balance STAR's effect on the nurse's health check, half of the health checks will be counterbalanced; that is, the order of the STAR and the nurse's health check will be reversed after every 10 check-ups (Figure 2). The forms will be filled out accordingly. The study protocol will be piloted for 1 day at a health center before starting the data collection.

Figure 2. Counterbalanced situation.



Phone Interviews

A sample of patients who grant permission for a phone interview will be interviewed approximately 2 weeks after the health check. Semistructured interviews will be used to ask more open-ended questions about using STAR and the online training programs (an open-ended question is a question that cannot be answered with a simple "yes" or "no," and requires longer answers to explain one's point of view). The questions focus on the experiences of using the tools, and their potential to support the respondents' healthy lifestyle choices and motivation to manage their own health. The interviews will last from 30 minutes to 1 hour, and will be audio-recorded using Teams and transcribed for analysis.

Questionnaires

There are five questionnaires in total for this study: the participant questionnaires (parts 1 and 2), study assistant's questionnaire, and nurse's questionnaires (parts 1 and 2). The questionnaires include questions on the participant's background and the most significant health challenges from their own and the nurse's point of view, as well as on how well the health challenges matched the STAR report. The questionnaires also gather data on the user experience, usability, and health confidence. The first parts of the forms will be filled out before the participant uses STAR and before the nurse reads the STAR report. The second parts will be filled out after reading the STAR report. A study assistant will also fill out an observer's form containing questions about the time used and possible problems encountered while using STAR. The questionnaires are presented in Multimedia Appendix 2.

Usability will be measured by asking questions based on the Usability Metric for User Experience [52]. The client's health confidence will be measured with questions based on the Health Confidence Score [53].

Analysis Methods

The data will be analyzed with quantitative and qualitative methods.

The risk assessments and health recommendations given by the STAR report will be reviewed by determining the most crucial health risks specified by STAR among unemployed participants. The three health challenges determined by the client and the nurse's health check will be compared to the STAR report by calculating the matching percentages and their confidence intervals. These health challenges will first be classified into corresponding categories so that they can be compared to the STAR report. The new health challenges STAR found and any health challenges missed will be analyzed. The user experience and usability of STAR will be analyzed by assessing the responses from surveys.

Data from the phone interviews and open-ended questions of the survey will be analyzed using qualitative theme analysis. All phone interviews will be performed by two research group members (SK, IH), who have previous experience regarding phone interviews. The phone interviews will be recorded and transcribed verbatim. We will start to read and reread data to become familiar with what the data entail, paying specific attention to patterns that occur. The results of the first phase will create preliminary codes. The coding will be performed by all four group members. Three of the coders have previous experience in coding. After initial coding, a meeting of the coders will be held to discuss codes and categories. The final list of codes will be the result of consensus among all members of the coding group. The next steps of the thematic analysis are: (1) combining codes to themes, (2) interpretation of the codes, and (3) explanation of the contribution of each theme to understanding STAR's usability and impact on lifestyle choices and motivation.

Ethical Approval

This study was approved by the Ethics Committee of the Expert Responsibility Area of Tampere University Hospital in June 2020 (ETL Code R20067), and commenced at the start of 2021. The results of the study are expected to be published at the end of 2021.

Results

The data collection will begin in June 2021. The data collection will take approximately 3-6 months.

Discussion

Limitations and Potential Concerns

The limitations and concerns of this study involve the recruitment of the participants among the unemployed, the potential selection bias toward those better able to benefit from the intervention, and the potentially varying interpretations of "health challenges" among the unemployed and study nurses. The study material will be slow to gather, because the health centers have a loose schedule for performing health checks for long-term unemployed clients. There will be a limited number of nurses working on the health checks at the same time, and there is no certainty that the few unemployed people who are participating in a health check will agree to participate in the study. Motivating the unemployed to participate in this study may turn out to be difficult due to their individual and complex situations. However, they could be more flexible with the additional time the study takes when compared to those in the working population. Additionally, the COVID-19 pandemic has created new challenges and restrictions for public health care, which may affect the data gathering of this study. Moreover, due to social distancing, it may be harder to recruit participants, because it has been advised to avoid any unnecessary contacts, and some may categorize a general health check as such. We will take care of all appropriate COVID-19 safety measures to make the situation as safe as possible for all parties involved.

The use of a digital tool as an intervention may have an effect on the participants. There is a concern of selection bias, because people who are comfortable with digital tools will more readily agree to participate compared with those who are not familiar with such technology. People who struggle with computers and technology may refuse to participate, even though they could provide important knowledge about usability and user experience for the study. It has been reported that the users of

eHealth interventions are more likely to be highly educated and have a healthier lifestyle than average, while those who could benefit the most are not using them [31,33].

The health challenges determined by the client and the nurse could differ significantly from those highlighted in the STAR report because every individual can interpret the terms differently. We will try to solve this discrepancy by categorizing the health challenges; however, it is difficult to foresee how the health challenges determined by the participant, the nurse, and STAR will correspond.

Conclusions

As part of public health care, eHealth technologies have significant potential in solving problems regarding the current growing trend in long-term illness morbidity and multimorbidity [8-10]. Although studies on online health behavior interventions are increasing, there are few studies on online health checks and online risk calculators as part of public health care and in the area of recognizing multiple different lifestyle behavior risk factors. This exploratory research will contribute to this field as a starting point on the fieldstream of online general health check research by examining the mechanisms through which an online health check integrated into public health care may enhance the recognition of chronic disease risk and impact the health behavior of the unemployed.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
The content of Duodecim's STAR.
[DOCX File , 14 KB - resprot_v10i6e27668_app1.docx]

Multimedia Appendix 2
The questionnaires used in the study.
[DOCX File , 16 KB - resprot_v10i6e27668_app2.docx]

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Proposal

Assessing Health-Related Quality of Life, Morbidity, and Survival Status for Individuals With Down Syndrome in Pakistan (DS-Pak): Protocol for a Web-Based Collaborative Registry

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Abstract

Background: Down syndrome is the most common chromosomal disorder, with a global incidence of 1 in 700 live births. However, the true prevalence, associated morbidities, and health-related quality of life (HRQOL) of these individuals and their families are not well documented, especially in low- and middle-income countries such as Pakistan. Disease-specific documentation in the form of a collaborative registry is required to better understand this condition and the associated health outcomes. This protocol paper describes the aims and processes for developing the first comprehensive, web-based collaborative registry for Down syndrome in a Pakistani cohort.

Objective: This study aims to assess the HRQOL, long-term survival, and morbidity of individuals with Down syndrome by using a web-based collaborative registry.

Methods: The registry data collection will be conducted at the Aga Khan University Hospital and at the Karachi Down Syndrome Program. Data will be collected by in-person interviews or virtually via telephone or video interviews. Participants of any age and sex with Down syndrome (trisomy 21) will be recruited. After receiving informed consent and assent, a series of tablet-based questionnaires will be administered. The questionnaires aim to assess the sociodemographic background, clinical status, and HRQOL of the participants and their families. Data will be uploaded to a secure cloud server to allow for real-time access to participant responses by the clinicians to plan prompt interventions. Patient safety and confidentiality will be maintained by using multilayer encryption and unique coded patient identifiers. The collected data will be analyzed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corporation), with the mean and SD of continuous variables being reported. Categorical variables will be analyzed with their percentages being reported and with a *P* value cutoff of .05. Multivariate regression analysis will be conducted to identify predictors related to the HRQOL in patients with Down syndrome. Survival analysis will be reported using the Kaplan-Meier survival curves.

Results: The web-based questionnaire is currently being finalized before the commencement of pilot testing. This project has not received funding at the moment (ethical review committee approval reference ID: 2020-3582-11145).

Conclusions: This registry will allow for a comprehensive understanding of Down syndrome in low- and middle-income countries. This can provide the opportunity for data-informed interventions, which are tailored to the specific needs of this patient population and their families. Although this web-based registry is a proof of concept, it has the potential to be expanded to national, regional, and international levels.

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KEYWORDS

Down syndrome; registry; web-based registry; health-related quality of life; lower-middle income country; mobile health; patient-reported outcome

Introduction

Down Syndrome

Down syndrome, a chromosomal disorder, is caused by the presence of a complete or partial third copy of chromosome 21 [1]. Owing to the presence of extrachromosomal material, there is an amplified effect on some genes, which leads to the classic features and associated medical conditions of Down syndrome. Patients with Down syndrome commonly present with characteristic facial features, delayed development, and intellectual disability [2-4]. Down syndrome is the most common genetic cause of intellectual disability [5], with patients experiencing cognitive impairment and difficulty in learning [6]. Medically, patients are affected with various conditions such as obstructive sleep apnea, congenital heart defects, and leukemia, among others [7].

Down syndrome is prevalent in all populations, races, and ethnicities. The Center for Disease Control reported that Down syndrome is the most common chromosomal disorder, with an incidence of 1 in 700 births [8]. However, data regarding the incidence and prevalence of Down syndrome for low- and middle-income countries (LMICs) are scant. According to one study, 1 in 300 babies in Pakistan are diagnosed with Down syndrome [9]. However, for a national prevalence rate, more studies are required to compare the incidence rate in an LMIC against high-income countries.

Health-Related Quality of Life in Patients With Down Syndrome

Health-related quality of life (HRQOL) is an important parameter to assess as routine clinical assessments may not reflect the treatment burden, functional limitations, or the need for adjustment to disability that a person may experience. HRQOL assessment is complex as it requires understanding an individual's perception, experiences of their health-related issues, and perceived level of adaptation and coping.

As Down syndrome is a chronic condition, the impact of its related comorbidities is often lifelong and debilitating. Poor HRQOL has been reported in patients with Down syndrome with regard to physical, emotional, social, psychosocial, and psychological well-being [10-12]. Although this is often overlooked, it is important to acknowledge that Down syndrome affects the patient's whole family in many aspects, particularly financially and emotionally, as additional responsibilities are placed on the caregivers [13]. Multiple sociocultural factors can influence caregivers' experiences and perceptions of the patient's condition. For instance, a study conducted in Pakistan reported that parents perceived Down syndrome as a consequence of their deeds and experienced feelings of guilt regarding it [14,15]. Furthermore, a lack of understanding about the disease and its management added additional stress to these parents and hampered their ability to provide care to their child [16,17]. Early intervention, vocational therapy, and medical management are associated with improved functioning in children in terms of health and social outcomes [18,19]. Unfortunately, delayed diagnosis and management are common in LMICs, with some children being diagnosed as late as age 7 [14,15]. Owing to the various region-specific difficulties, results from studies regarding HRQOL in this population would vary from those carried out in a resource-rich setting [13].

Challenges of Down Syndrome in LMICs

The challenges faced by LMICs regarding health care delivery are unique and multifactorial. The obstacles include a lack of resources, inadequate skills and training, nonstandardized documentation, a lack of quality check frameworks, a lack of health insurance (with patients predominantly being forced to self-pay), and a lack of system infrastructure and support. Patients and their caregivers often do not feel that they have the power to verbalize what is important to them as access to any available health care becomes the predominant concern for a family. Furthermore, because of a lack of resources, there is a prevailing problem of the delayed diagnosis of Down syndrome. Pakistan, being an LMIC, has disparities in terms of health care provision. There are health care centers where antenatal monitoring is at par with developed countries; however, it is not uniformly available in the sixth most populous country. To facilitate early diagnosis, hospitals can and have started connecting with physicians and pediatricians who can enable the early diagnosis of Down syndrome. Unfortunately, no registries or formal collaborations exist to highlight these unique issues, risks, and comorbidities in Down syndrome, particularly in Pakistan.

Rationale

Disease-specific documentation in the form of a collaborative registry is crucial and serves an important purpose of understanding the disease and its associated health outcomes better. Patient-reported outcomes and patient-related experience measures have been noted as significant parameters for the implementation of the philosophy of *Value-Based Health Care*. This will be the first comprehensive registry for Down syndrome and its associated health problems in a Pakistani cohort. The information regarding individuals with Down syndrome and their families can be documented and will allow measurement of the impact of early health care interventions and routine medical follow-up on the well-being of individuals with Down syndrome and their families. Subsequently, through this registry, we can further investigate the factors affecting health care outcomes in a large cohort. This will lead to further research to improve interventions, offer novel treatment, and improve the quality of care for people with Down syndrome. To date, there are limited published data about the determinants of the well-being of young individuals with a diagnosis of Down syndrome, particularly in LMICs. Therefore, it is important to

investigate the determinants and the associated protective factors and risk factors affecting HRQOL in individuals with Down syndrome and their families.

Aim

This web-based collaborative registry aims to identify the long-term survival, morbidity outcomes, and HRQOL and the experiences in patients with Down syndrome.

Objectives

The main objectives of this study are (1) to assess the long-term survival, morbidity outcomes, and effects on HRQOL in patients with Down syndrome in Pakistan and (2) to determine predictors of HRQOL in patients with Down syndrome in Pakistan.

Methods

Study Site and Participants

This will be a prospective registry that will be conducted at the outpatient clinic of Aga Khan University Hospital (AKUH) and the Karachi Down Syndrome Program (KDSP). Patients of any age and sex with Down syndrome and their families visiting AKUH and the KDSP will be approached and invited to participate in this collaborative registry. After giving their informed consent and assent, patients will be interviewed in person or remotely via a telephone call, a Zoom meeting, or WhatsApp, as applicable. As the patients are being interviewed, the questionnaire responses will be recorded on a smart device controlled by the research assistant. According to the American Academy of Pediatrics, the health supervision of children with Down syndrome is categorized according to age [7] (Textbox 1).

Textbox 1. American Academy of Pediatrics health supervision schedule.

Birth to 1 month

- Evaluation for heart defects, feeding problems, cataracts at birth, duodenal atresia, congenital hearing loss, constipation, gastroesophageal reflux, congenital hypothyroidism, hematological problems, and apnea.

1 month to 1 year

- Previous reports reviewed and concerns addressed (existing and new).
- Tympanometry may be ordered for detection of middle ear disease.
- 0-5 months: Ophthalmology referral to evaluate nystagmus, cataracts, and strabismus [17].
- 6 and 12 months: Thyroid function and cardiac screenings.
- Signs of neurological dysfunction or seizure.

1-5 years

- Monitor growth and development of child.
- Repeat screening for hearing impairment every 6 months and vision evaluation.
- Further evaluation for specific conditions as relevant.
- Impact of early intervention (speech, occupational, and physical therapies) reviewed.

5-13 years

- Annual visits with similar monitoring of growth and development.
- Specific attention given to evaluating age-specific BMI and maintaining healthy diet to prevent obesity.
- Evaluate social function and behavioral development of the child at this stage, both at home and during school.

This routine health care surveillance is crucial for improved HRQOL of the patients and for the well-being of their families [19]. We will follow up with participants in accordance with this schedule and then schedule routine follow-ups into adulthood to assess the patients' quality of life and health status. The Pediatric Quality of Life (PedsQL) questionnaire forms have been used successfully in previous studies in Pakistan, and the patients were followed up into adulthood [20].

Web-Based Collaborative Registry

Overview

A web-based registry will be developed for data entry on the portal, with the data being stored on a cloud server. Data entry will occur in real time by the research assistant, and access to the data will be restricted to relevant study team members, physicians, or individuals involved in the care of the patient through a login ID and password. After each data entry, a PDF report will be generated, which can be printed and added to patients' medical records and viewed by the physician in real time. The collected data can provide direction for addressing the needs of the patients with Down syndrome and their families.

The main registry database will reside on a central computer at AKUH and will be managed by the study staff. A web-based dashboard will be designed to report the registry progress. All study staff will undergo basic research ethics training. Participants' information will be given a unique patient identifier code, and no personal information will be shared.

Mobile Health Digital Platform and Data Collection

The process of gathering information (variables of interest) will be executed in a systematic and digitized manner. All data will be collected on smart devices (tablets, mobile phones, etc). The data collection apps for the electronic questionnaire will be developed using the Android Software Development Kit or Open Data Kit, an open-source software package, and utilize in-house front-end software for retrievable variables. The electronic questionnaires will contain skip patterns to navigate the user to relevant questions. Electronic case report forms will also be loaded with valid values and specifications for valid ranges and range checks. It will also automatically record the start and end times of each interview, which will help monitor and manage the interview protocol. The collected data will be stored on the smart device and will be synchronized to AKUH data servers through http secure. The information from the electronic questionnaire will be uploaded to the central server for close to real-time monitoring using the dashboard interface.

Data Management

The clinical staff, under the supervision of the principal investigator and coinvestigators, will be responsible for collecting the data. The clinical team collecting the data will review them for completeness, accuracy, and visualization. The study manager or coordinator will provide guidance to the study staff on the corrections and edits that may be needed in the electronic data. The registry data manager will be responsible for the overall data management and data quality assurance. Once the data are transferred to the central registry database, the data management team will ensure completeness and validity. Only the data management staff will be authorized to make modifications to the registry database in consultation with the program manager or study coordinator with documentation of specific reasons. Identifiers will only be visible to the authorized study staff.

There are 2 unique identifiers: medical record number and registry ID number. The registry administrator and principal investigator of the study will assign access to the study according to the portfolio of the study staff and investigators. For example, physicians will have full access to clinical data and limited access to research data and vice versa for research staff. However, the principal investigator and nominated investigators of the study will have full access to the clinical and research data.

Data Security

All the devices used for collecting data will be password protected. Only designated personnel will have access to these data for monitoring and operational purposes. All data collected on handheld devices as well as during transmission will be encrypted using the Rivest-Shamir-Adleman encryption. Weekly data backup will be scheduled on a different machine, and off-site backups will occur at regular intervals. This web-based registry is an electronic portal consisting of multiple dashboards to keep track of the registry database in real time and visualize the progress of the study at a glance. It will be hosted on a Google Cloud server with multiple layers of encryption to ensure rigorous security practices against threats to the infrastructure from both internal and external factors. Access to sensitive data will be protected by advanced tools, whereas database and file storage will be protected by AES256 or AES128 encryption. This will help in guarding against unauthorized access and service interruptions.

Recruitment Process

Eligible patients with Down syndrome and their parents or guardians visiting the genetics clinic at AKUH and at the KDSP will be approached to participate in the registry. AKUH is one of the only Joint Commission International–certified tertiary care centers in Pakistan. Patients from all over the country and the international community come to receive state-of-the-art care at this leading hospital. The KDSP is a nonprofit organization formed by parents and passionate individuals interested in improving the lives of children with Down syndrome, with a focus on occupational therapy and improving their quality of life [21]. This collaboration allows an insight into not only the health care perspective but also the child's community and social support. In addition, patients who are not scheduled for a clinic visit will be approached through a telephone call, a Zoom meeting, or WhatsApp to minimize patient exposure in the light of the COVID-19 pandemic. The participants will be provided with information related to the registry. An interview slot will be allocated to interested eligible patients and their parents to schedule their interviews. Informed consent will be obtained from patients and their [22] parents both verbally and in writing when applicable, with a witness present when consent is obtained remotely, before the commencement of the interview. Participants will be offered a choice to receive that information in English or Urdu, the latter being the nationally spoken language of Pakistan. Assent will also be obtained from patients aged 7 to 18 years, with a witness being present. A copy of the informed consent and assent will be provided to the participants. The interviews will consist of a series of tablet-based questionnaires. The interviews will be conducted at the KDSP, in a designated room in the clinical trials unit at the AKUH, or remotely. When conducted remotely, the research assistant will record the participant responses on an electronic questionnaire, which will be automatically saved to the web-based registry platform.

Data Collection

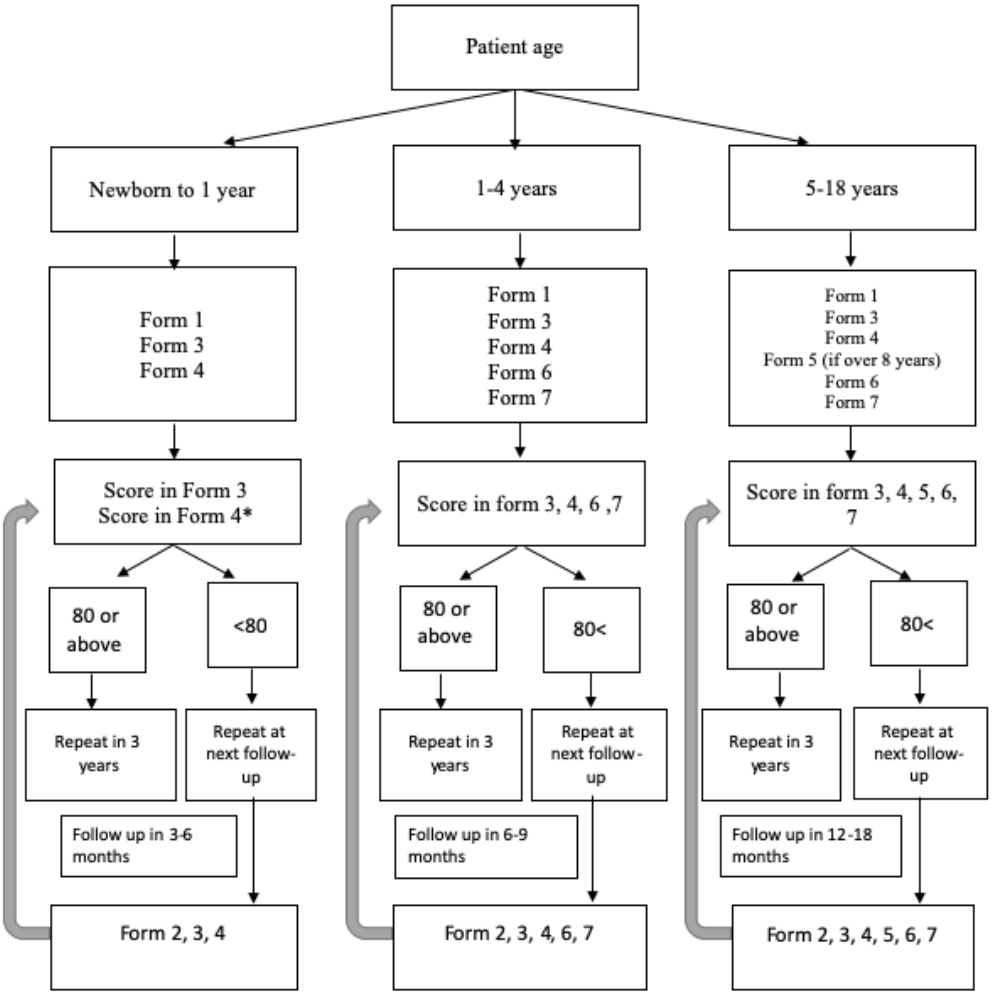
Baseline surveys regarding the sociodemographic variables, clinical history, outcomes, and health information of the patient will be administered to the patients or their caregivers by a research assistant. The baseline survey form has been developed based on the intake form used by clinicians and researchers at the National Institute of Health's Down Syndrome Registry, which is publicly available through DS-Connect [23], and Children's Hospital of Boston Down Syndrome clinic, which provided the information after an email request. The questions have been screened and modified by experts in the fields of

genetics and pediatric development. Trained staff will conduct the interviews using a tablet. Business rules, consistency checks, and skips will be incorporated, and important fields will be marked as a must to enter.

The PedsQL generic core (physical, emotional, social, psychosocial, and school or work domains), PedsQL Cognitive scale (cognitive functioning), and PedsQL general well-being questionnaires will be used to explore HRQOL. These questionnaires have been widely used in other settings to explore HRQOL [24]. The PedsQL Family Impact Module (physical, emotional, social, cognitive, communication, concerns related to the child, daily activities, and family relationship) will be used to explore the impact of Down syndrome on the family as a unit. In addition, the PedsQL Health Satisfaction Generic Module (information, family inclusion, communication, technical skills, emotional needs, and overall satisfaction) will be explored by the parents. All these questionnaires have well-established validities and reliabilities [25]. They are available for populations of different ages as well as their parents or proxies for young children (5-7 years), children (8-12 years), teenagers (13-18 years), young adults (18-25 years), and adults (>26 years). There is also a guardian or parent version only for toddlers (2-4 years), given the developmental limitations on self-reporting for children younger than 5 years.

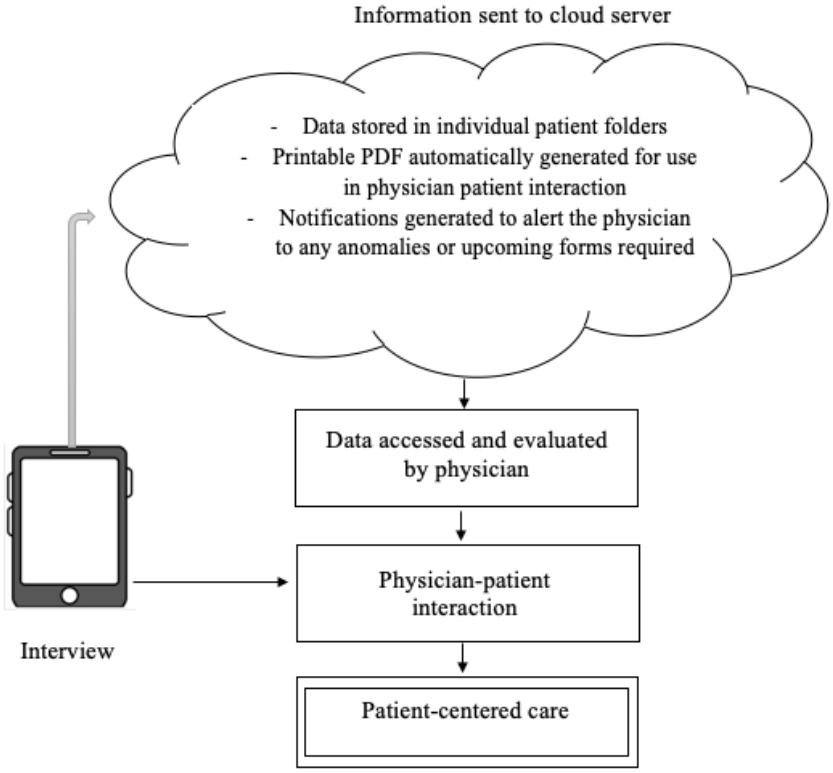
All the age-relevant questionnaires will be administered when the participants are enrolled at their initial interview. At the conclusion of a questionnaire pertaining to HRQOL, a score is generated. On the basis of a preset cutoff, the registry algorithm will alert the interviewer at the next follow-up that a particular questionnaire needs to be re-administered. If the participant's score is above the cutoff of 80, the algorithm will inform the interviewer of the need to repeat the particular questionnaire in 2 to 3 years. The scores of each questionnaire will be assessed independently. The follow-up timing of each patient depends on their age cohort (Figure 1). Follow-up appointments can continue into adulthood as there are specific PedsQL questionnaires designed for adult participants. Given the frequent follow-up appointments, financial constraints on patients and their families must be considered in a resource-constrained setting. In Pakistan, AKUH along with other nongovernment organizations are offering web-based consultations on subsidized clinical charges. Even when full charges are being received, web-based consultations allow families to save on the cost of traveling. To make it sustainable, our children's hospital has pediatric welfare funds that can help ease the financial burden.

Figure 1. Web-based registry questionnaire administration algorithm. Forms attached—Form 1: initial baseline intake form; Form 2: follow-up intake form; Form 3: family report; Form 4: health care satisfaction; Form 5: general well-being; Form 6: cognitive functioning scale; and Form 7: Pediatric Quality of Life inventory. *Assess score of each form independently and base decision of administering form again at follow-up appointment on cutoff scores.



Data will be collected in real time using a tablet-based questionnaire. The data will be collected from the patient (≥5 years), their parents or guardians (for patients aged 2-18 years), and from patient files as applicable. Once collected, the data will be uploaded to the cloud server and stored in the patient's individual folder based on their unique identification number. The stored data can be summarized in the form of an automatically generated PDF to aid with the following physician-patient interaction, and notifications regarding anomalies or upcoming forms required will be alerted (Figure 2). Details of the variables, their sources, and the questionnaires used, including sociodemographic variables, family history, birth history, immunization history, developmental history, medical history, comorbidities, medications, physical examination, health care utilization, functional status, and impact on family, are given in Table 1.

Figure 2. Web-based registry data pathway.



Permission to use the PedsQL HRQOL questionnaires has been obtained. These questionnaires were originally in English and have been translated to Urdu and then back-translated by an expert panel. Any discrepancies with the translation will be reported. The form will then be pretested for content and face validities. The final version will then be submitted to Mapi Research (PedsQL parent organization) along with the whole translation report. Differences in the Pakistani population are anticipated, and modifications to the PedsQL forms can be suggested to the parent organization following pilot testing. For patients who were already being treated at AKUH and the KDSP, the clinical notes on the file can be used retrospectively to gather more data regarding the participant.

Table 1. Variables included in quality-of-life assessment using self-developed form as a data collection tool.

Domains and domain aspects	Data source
Sociodemographic variables	
Age	Patient, parents, sibling
Education	Patient, parents, sibling
Family income	Patient, parents, sibling
Family structure, number of members	Patient, parents, sibling
Ethnicity	Patient, parents, sibling
City of residence	Patient, parents, sibling
Family history	
Consanguineous marriage	Parents
Sibling details	Parents
History of any chromosomal abnormality or disability	Parents
Birth history	
Anthropometrics, parental age, delivery details etc	Parents
Immunization history	
Birth till current immunization as per EPI[a]	Parents, immunization card
Developmental history	
Walking, feeding, speech, etc	Parents
Medical history of patient (Down syndrome)	
Down syndrome diagnosis history, chromosomal tests done, antenatal, or postnatal monitoring etc	Parents, laboratory reports
Comorbidities	
Other medical problems	Parents
Medications	
Surrogate for health status	Parents
Physical examination	
Gastrointestinal, CVS[b], CNS[c], musculoskeletal, skin, genitourinary, allergies	Physician or medical record file
Health care utilization	
Number of hospitalizations, surgical procedures, number of hospital visits, interventions, therapy, services utilized, cost of each therapy and visit, payment mode (self, insurance, philanthropist, hospital finance assistance, etc)	Parents
Functional status	
Physical, emotional, social, and psychosocial status and school or work	Patient or parent
Cognition	Patient or parent
General well-being	Patient or parent
Impact on the family	
Parental QOL[d]	Parents
Family functioning	Parents
Satisfaction with the health care received or receiving	Parents

[a]EPI: Expanded Program on Immunization.

[b]CVS: cardiovascular system.

[c]CNS: central nervous system.

[d]QOL: quality of life.

Data Analysis

The data will be exported to SPSS version 22 (IBM Corporation) for analysis. For descriptive analysis, the number of participants enrolled, mean and SD of continuous variables, and percentages for the categorical variables will be reported.

The HRQOL and health care utilization questionnaires have very similar response items and scoring. These questionnaires will capture patients' experiences in the preceding month. Both patients and parents will be asked to rate their HRQOL from 0 to 4, with 0 being "never a problem" and 4 being "almost always a problem." Responses will be reverse scored and linearly transformed to 0-100, with higher scores indicating better HRQOL. If more than 50% of the items in the scale are missing, the scale scores will be considered as missing data. The mean score of the individual domains will be calculated by adding the sum of the items to the number of items answered. The total score will be the sum of all the items over the number of items answered on all scales.

The registry will also identify the predictors of HRQOL in the patients with Down syndrome. For all predictor variables (sociodemographic and clinical parameters), the univariate analysis will be performed with the HRQOL domains. Studies have shown that in older patients with Down syndrome, poor HRQOL was reported because of health problems, limited social relationships, and restricted educational and employment opportunities [12,26]. However, although there are data regarding parent-reported HRQOL [27] and even HRQOL of parents of children with Down syndrome [27], there are very limited data regarding self-reported HRQOL in children with Down syndrome. Each predictor variable will be regressed against the HRQOL variable to assess the eligibility of a predictor variable to be included in the final model. The criteria for inclusion of a predictor variable will be set at a *P* value cutoff of .25 at the univariate analysis level. Insignificant variables that do not meet the cutoff criterion will be removed from the model at the univariate analysis level. The significant variables will then be assessed for multicollinearity. In the multivariable regression analysis stage, the cutoff for the *P* value will be set at .05. Variables will be added to the model until the overall model remains significant through the manual stepwise model-building technique. After the multivariable analysis, the interaction will be assessed among the predictor variables. The cutoff at this stage will be set at .1. For a predictor variable to have an interactive effect with another variable, the *P* value of the respective variables should be less than or equal to the set cutoff, that is, .1. Observations of the significant variables will also be vetted for outliers.

The Kaplan-Meier survival curves will be used to report survival status. Survival will be analyzed for the cohort with respect to variables such as age, sex, and comorbidities, with $P<.05$ being accepted as statistically significant.

Ethical Considerations

The registry has received approval from the ethics review committee at AKUH, Pakistan. Informed consent will be obtained from patients and their parents both orally and in writing, and participants will be offered a choice to receive that information in English or Urdu. Assent will also be obtained from patients aged 5 to 18 years. The study participants will have a unique identifier to maintain patient confidentiality. Original and backup files will be archived in password-protected computers or servers at AKUH. Data confidentiality will be maintained at all times. No personal identifiers will be used in any reports or publications of this study. No individual identifiers such as names of participants or areas of location will be shared. Although the risks associated with this study are negligible, it is possible that participants may become distressed while telling their story. In this instance, we will follow the participant distress protocol developed for this study. Data confidentiality and archiving will be maintained according to the Good Clinical Practice Guidelines. Data findings will be disseminated through peer-reviewed publications and presentations at national and international conferences.

Results

This study was approved by the AKUH Ethics Review Committee (Reference ID: 2020-3582-11145). Currently, no funding is available, but opportunities are being explored. Furthermore, we are preparing to begin pilot testing of the registry by September 2021.

Discussion

Benefits of a Patient Registry

In recent years, the utilization of technology has profoundly impacted and benefited patient care. The dearth of information available at a moment's notice allows the practice of evidence-based medicine and provides the ability to monitor trends and patterns. A significant source of this information is from biobanks and data registries, and with the use of technology and web-based designs, these data can be accessed in real time. The true beneficiaries of data registries are the patients as the increased information allows for patient-centered care and real-time decisions that can impact patient lives [28]. A majority of registries are formed and operated in high-income countries, where there is the presence of established health care systems to ease patients with respect to costs and follow-up appointments and the invaluable use of electronic health records. However, although they face unique challenges and obstacles [29], a number of registries are being successfully operated in LMICs [30,31], and the data obtained have a great impact on patient care and further research in a setting where there is a lack of availability of organized data.

Limitations

At its conception, this registry was reliant on regular patient follow-ups at the AKUH and KDSP. However, in Pakistan, the majority of patients do not have health insurance. This results in out-of-pocket payments for doctors' appointments, testing, and procedures, which are often too taxing on the patient's family. Furthermore, because of a scarcity of resources, there are few tertiary care centers where the needs of children with Down syndrome can be addressed. This results in further expenses as families need to travel far distances to receive care. Together, these problems create a large pool of patients who

are lost to follow-up. In light of the COVID-19 pandemic, we further anticipate that patients will be reluctant to visit hospitals for interviews or regular checkups. We have used technology to bridge these deficits, with web-based consultations being carried out at a reduced fee at the KDSP with AKUH doctors to ensure that patients can be evaluated regularly from remote areas. Furthermore, the option for interviews via telephone calls or video calls is available, which we anticipate will make interviews more accessible to patients and their families. Concerns that arise from telephone interviews, such as a lack of facial cues regarding a patient or their family's comfort level, are intended to be mitigated by the use of video call tools as well.

Strengths

Being the first registry for patients with Down syndrome in Pakistan, the project offers insight into the demographics, morbidity, mortality, and economic burden for this patient cohort. This information is rarely available in LMICs, as cases are underreported and undertreated. These data can create an opportunity for region-specific interventions and changes that can address the specific problems faced by this population. Furthermore, through the web-based design, the registry offers a unique opportunity for physicians to receive real-time data regarding the patient's HRQOL, development, and general health based on extensive questionnaires. Often, this information could be missed in a regular patient consultation because of time constraints. With this information, physicians can implement immediate interventions to reduce any difficulties or stressors experienced by the patient and their family, creating true patient-centered care.

Conclusions

With the development of a Down syndrome registry, the opportunity to study Pakistan-specific trends in patients with Down syndrome presents itself. Given the vast differences in culture, social, and economic situations, discrepancies are expected between the quality of life of patients in LMICs and high-income countries. However, the assessment of HRQOL and patient-reported outcomes will allow us to see how this condition affects patients, how they and their families view their condition, and what their specific concerns are. This will allow the implementation of patient-centered care, a concept that is highly acclaimed yet often lacking in LMICs. This information will prove invaluable for implementation and influencing decisions for other patient populations with demographics similar to those seen in Pakistan. Although this study is currently limited to 2 centers in a major city of Pakistan, with the collection of data and initiation of this project, we are confident in the ability to procure funding soon to expand the project to regional, national, and eventually international levels.

Acknowledgments

This project would not be possible without the support of our collaborators, the KDSP. Their work in community building and ensuring the provision of social support to this cohort meets our aims of improving the quality of life of children with Down syndrome. Through this collaboration, we can ensure holistic care is provided to these patients.

Conflicts of Interest

None declared.

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Abbreviations

AKUH: Aga Khan University Hospital
HRQOL: health-related quality of life
KDSP: Karachi Down Syndrome Program
LMIC: low- and middle-income country
PedsQL: Pediatric Quality of Life

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Protocol

Using a Tailored Digital Health Intervention for Family Communication and Cascade Genetic Testing in Swiss and Korean Families With Hereditary Breast and Ovarian Cancer: Protocol for the DIALOGUE Study

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Abstract

Background: In hereditary breast and ovarian cancer (HBOC), family communication of genetic test results is essential for cascade genetic screening, that is, identifying and testing blood relatives of known mutation carriers to determine whether they also carry the pathogenic variant, and to propose preventive and clinical management options. However, up to 50% of blood

relatives are unaware of relevant genetic information, suggesting that potential benefits of genetic testing are not communicated effectively within family networks. Technology can facilitate communication and genetic education within HBOC families.

Objective: The aims of this study are to develop the K-CASCADE (Korean–Cancer Predisposition Cascade Genetic Testing) cohort in Korea by expanding an infrastructure developed by the CASCADE (Cancer Predisposition Cascade Genetic Testing) Consortium in Switzerland; develop a digital health intervention to support the communication of cancer predisposition for Swiss and Korean HBOC families, based on linguistic and cultural adaptation of the Family Gene Toolkit; evaluate its efficacy on primary (family communication of genetic results and cascade testing) and secondary (psychological distress, genetic literacy, active coping, and decision making) outcomes; and explore its translatability using the reach, effectiveness, adoption, implementation, and maintenance framework.

Methods: The digital health intervention will be available in French, German, Italian, Korean, and English and can be accessed via the web, mobile phone, or tablet (ie, device-agnostic). K-CASCADE cohort of Korean HBOC mutation carriers and relatives will be based on the CASCADE infrastructure. Narrative data collected through individual interviews or mini focus groups from 20 to 24 HBOC family members per linguistic region and 6-10 health care providers involved in genetic services will identify the local cultures and context, and inform the content of the tailored messages. The efficacy of the digital health intervention against a comparison website will be assessed in a randomized trial with 104 HBOC mutation carriers (52 in each study arm). The translatability of the digital health intervention will be assessed using survey data collected from HBOC families and health care providers.

Results: Funding was received in October 2019. It is projected that data collection will be completed by January 2023 and results will be published in fall 2023.

Conclusions: This study addresses the continuum of translational research, from developing an international research infrastructure and adapting an existing digital health intervention to testing its efficacy in a randomized controlled trial and exploring its translatability using an established framework. Adapting existing interventions, rather than developing new ones, takes advantage of previous valid experiences without duplicating efforts. Culturally sensitive web-based interventions that enhance family communication and understanding of genetic cancer risk are timely. This collaboration creates a research infrastructure between Switzerland and Korea that can be scaled up to cover other hereditary cancer syndromes.

Trial Registration: ClinicalTrials.gov NCT04214210; https://clinicaltrials.gov/ct2/show/NCT04214210 and CRiS KCT0005643; https://cris.nih.go.kr/cris/

International Registered Report Identifier (IRRID): PRR1-10.2196/26264

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KEYWORDS

HBOC; proportion of informed at-risk relatives; coping; communicating; decisional conflict; cultural and linguistic adaptation; implementation; RE-AIM; mobile phone

Introduction

Background

In 2018, there were approximately 2.1 million breast cancer diagnoses and more than 600,000 associated deaths worldwide [1,2]. The worldwide average breast cancer incidence is 74.2 per 100,000 women [3], with approximately 25% of cases occurring in women younger than 50 years and in women with a family history of cancer [4,5]. Approximately 5%-10% of breast cancer and 20% of ovarian cancer cases occur due to germline pathogenic variants associated with hereditary breast and ovarian cancer (HBOC) syndrome, most commonly observed in the *BRCA-1* and *BRCA-2* genes (hereafter *BRCA*). The prevalence of germline pathogenic variants differs among ethnic groups [6]; however, Switzerland and Korea have a similar prevalence ranging from 23% to 26% [7,8].

The availability of genetic services (counseling and testing) for actionable hereditary cancer syndromes such as HBOC enables population-level cancer prevention [9]. Blood relatives of HBOC cases have a 12.5%-50% probability of inheriting the same pathogenic variant and can be tested with 100% accuracy. Chemoprevention, prophylactic surgery, and intensive surveillance can lower cancer risks for relatives who test positive, whereas those who test negative are excluded from these interventions [10-12]. The Centers for Disease Control and Prevention Office for Public Health Genomics recommend genetic testing in cancer-free individuals with a known HBOC family history and in patients with cancer who have strong indications of HBOC syndrome (eg, ovarian cancer) [13]. Cascade genetic screening is a systematic effort to identify and test all blood relatives of HBOC cases to determine whether they also carry the same pathogenic variant [10]. The CASCADE (Cancer Predisposition Cascade Genetic Testing) Consortium in Switzerland promotes cascade genetic screening for HBOC [14,15], whereas the Korean Hereditary Breast Cancer (KOHBRA) network identifies the prevalence of HBOC-associated pathogenic variants in the Korean population [16,17].

Despite calls to action for HBOC cascade genetic testing, there are systemic barriers to its implementation. Privacy laws worldwide, including Switzerland and Korea, restrict health care providers from revealing genetic information to anyone except the tested individual, who has the right not to disclose this information, despite implications for relatives' health

[18-20]. The potential benefits of genetic testing are not being effectively communicated through family networks, leading to more than 50% of at-risk individuals not using genetic services and not receiving important information from a credible source [21-23]. Second-degree and male relatives, those living further away, and those with an estranged relationship with the mutation carrier are most likely not to be informed about genetic testing [24,25]. Despite these difficulties, a family-based approach in communicating hereditary cancer risk is advantageous because it may reach relatives through the social bonds and functions already existing within the family network, and it is not limited to those in contact with the health care system [26].

Interventions that support mutation carriers during the disclosure of genetic test results can reduce psychological distress and provide relatives with accurate and credible information about cascade genetic testing. Technology-enabled education is not inferior to face-to-face genetic consultations [27,28], but it increases access to services and cost-effectiveness [29-32]. The Family Gene Toolkit [33] is a web-based intervention designed to increase prerequisites for HBOC cascade testing, that is, active coping, open family communication, and informed decision making. The prototype Family Gene Toolkit was tested in the United States for acceptability and patient satisfaction with excellent results, confirming its value for these families. However, it is not available in other linguistic and cultural contexts. Adapting existing interventions, rather than developing new ones, takes advantage of the previous valid experiences without duplicating efforts.

In summary, HBOC cascade genetic testing, meaning the identification and testing of blood relatives, provides risk management options for those with a germline pathogenic variant and excludes confirmed noncarriers (ie, negative testing when there is a known pathogenic variant in the family) from intensive surveillance and risk-reducing measures. Due to privacy laws, mutation carriers have the sole responsibility to inform blood relatives about genetic test results and advocate for genetic services. Digital health platforms can support mutation carriers during the disclosure process and provide relatives with accurate and credible information.

Objectives

The DIALOGUE study will build a bilateral research infrastructure to support collaboration and multidisciplinary initiatives around HBOC in Switzerland and Korea. The specific aims are to develop the K-CASCADE (Korean–Cancer Predisposition Cascade Genetic Testing) cohort in Korea by expanding an existing research infrastructure developed by the CASCADE Consortium in Switzerland; develop a digital health intervention to support open communication and cascade genetic testing in HBOC families, based on the linguistic and cultural adaptation of the Family Gene Toolkit; evaluate the efficacy of the digital health intervention on primary (communication of genetic test results to relatives and cascade genetic testing) and secondary (psychological distress, genetic literacy, coping, and decision making) outcomes; and explore the translatability of the platform using the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) framework.

Methods

Design

The DIALOGUE study will use a cohort design to establish the K-CASCADE in Korea and a randomized controlled trial (RCT) design to test the effects of digital health intervention in the Swiss and Korean contexts. The study will measure clinical and process outcomes in real-world conditions, including different settings, participants, and resources [34,35].

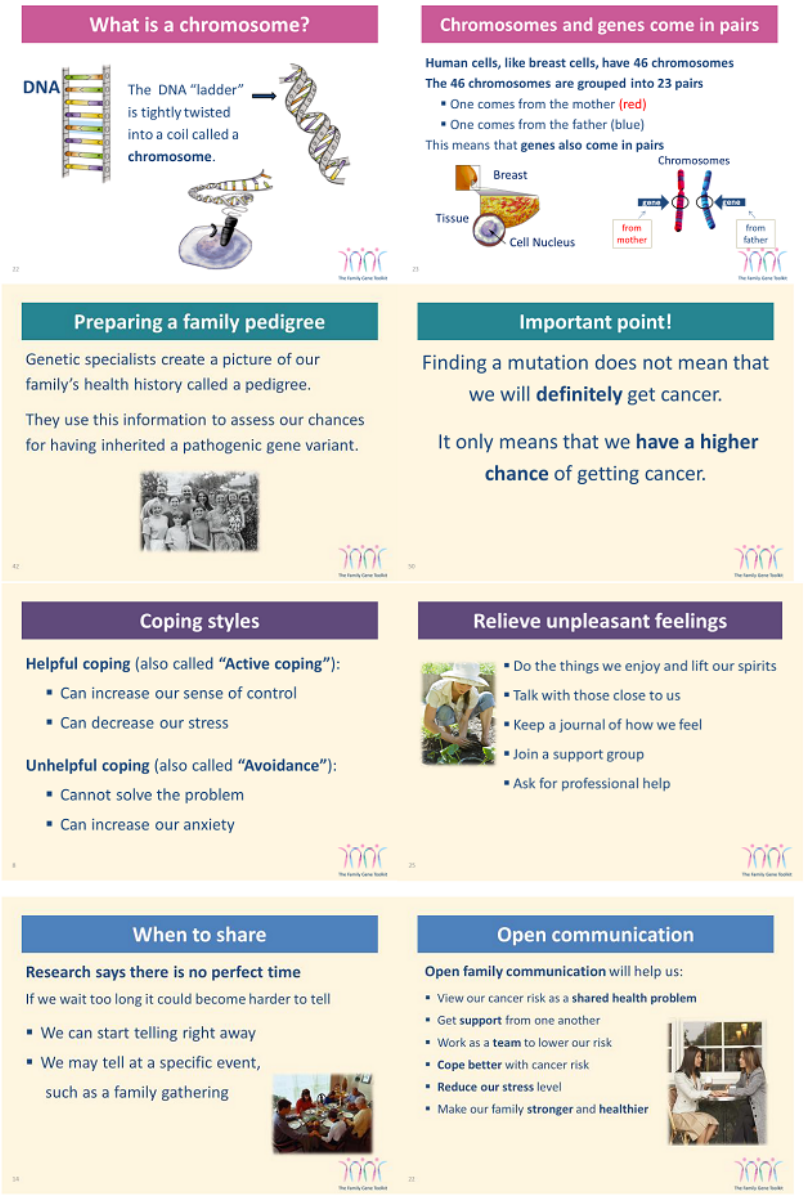
Aim 1: Develop the K-CASCADE Cohort

The K-CASCADE cohort will identify and survey mutation carriers and blood relatives as its archetype, the Swiss CASCADE cohort, using similar design, assessments, and procedures for sample identification and data collection [14]. Adult Korean men and women with *BRCA* pathogenic variants will be invited to the K-CASCADE cohort. They will also be asked to invite their first- and second-degree relatives and their first cousins for cascade genetic screening. Similar to the Swiss CASCADE, it is envisioned that the K-CASCADE cohort will include known mutation carriers, untested relatives with unknown mutation status, and relatives who tested negative for the pathogenic variant.

Aim 2: Adapt the Digital Health Intervention

The content of the Family Gene Toolkit is driven by theory [36] and supported by empirical findings [37-41]. It is designed to address challenges related to the quantity and complexity of genetic information mutation carriers are asked to communicate with family members [42,43]. Understanding HBOC (eg, probability of mutation, prognosis, prevention, and treatment) and the accuracy of genetic testing are important for decision making. Inherited cancer risk requires ongoing management and, thus, active coping with health challenges. Mutation carriers' personal values and communication skills are important for the disclosure of genetic cancer risk. The Family Gene Toolkit embraced the above challenges and included 4 modules designed to increase knowledge of cancer genetics (module 1), provide decisional support for genetic testing to untested relatives (module 2), increase active coping with common challenges faced by HBOC families (module 3), and provide skills-building communication training (module 4; Figure 1). The adapted Family Gene Toolkit will include the 4 original modules and a fifth module about the management of cancer risk based on recommendations from the National Comprehensive Cancer Network [44].

Figure 1. Examples from the Family Gene Toolkit.



The research team will create tailored messages based on the linguistic and cultural adaptations of the modules. Tailoring is a process that *fits* the message to meet one's personal needs and characteristics, rather than targeting group criteria [45,46]. Tailored messages improve whether and how one listens to a message and its impact on behavior change. Shallow tailoring involves elements of appearance (eg, female or male mutation carriers), whereas deep tailoring involves more complex elements of relevance (eg, coping style). Adaptation of the Family Gene Toolkit involves elements of both shallow and deep tailoring based on preintervention assessments of participants' characteristics such as sex, affected with cancer versus cancer-free, and tendency to rely more on a specific coping style. The research team will use readily available e-learning products with different tailored messages, multiple interactions and assessments, and a device-agnostic interface for the adaptation of the Family Gene Toolkit. Messages will be developed in English and translated at the eighth-grade reading level while considering Swiss and Korean legislation, health insurance policy, cultural values, and national languages. Swiss and Korean stakeholders will review the content of the adapted Family Gene Toolkit and identify the required modifications by providing feedback on word choices, sensitivity of messages, and appearance. Mini focus groups and individual interviews with clinicians involved in genetic consultations will evaluate the prototype of each module and the tailoring elements. Focus groups with Swiss and Korean HBOC mutation carriers and relatives will provide suggestions to enhance the comprehensibility, usefulness, acceptability, and feasibility of the intervention. Feedback from clinicians and HBOC families will help in further refining each module and the tailored messages.

Assessing the usability of the adapted Family Gene Toolkit involves task-oriented assignments about the most important functions and features of the website as well as the ease and user-friendliness of navigation. Participants will *think aloud* while navigating each module and complete each task [47].

They will also evaluate the tailored messages for readability and comprehension.

Swiss and Korean participants will complete the 5 modules at their own pace, but within a timeframe of 4 weeks after they first engage with the platform. The 4-week interval enables information assimilation and adequate time to reflect and act based on tailored messages while providing a controlled learning environment. Feedback will be based on baseline responses, including tailored advice about improvements that can be made.

Consistent with testing real-world alternatives [48], the DIALOGUE study will provide a comparison website with targeted (generic) information. The comparison website will mimic the structure and functions of an existing website [49]. The adapted Family Gene Toolkit and the comparison website will be technically implemented in the same system that will collect baseline and follow-up data, randomize participants, deliver the intervention and the comparison website, track access and use of the platform, and provide a user-friendly experience to participants.

Aim 3: Evaluate Intervention Efficacy on Primary and Secondary Outcomes

A cluster RCT will evaluate the magnitude of intervention effects as compared with the comparison website. Randomization will occur at the family level, that is, after baseline data collection, the digital health intervention will randomly assign mutation carriers to either intervention arm, stratifying for country. Invited relatives will be automatically directed to the same arm as the mutation carrier. All study participants will complete a survey at baseline (T_1) before the intervention and again at 2 months (T_2) and 6 months (T_3) after the intervention. The 2- and 6-month follow-up time points will assess the short-term and long-term effects in line with our previous studies [33,50].

Aim 4: Explore Intervention Translatability

The implementation and dissemination of the adapted Family Gene Toolkit will be evaluated based on the constructs of the RE-AIM framework [51] at the individual and organizational levels.

Settings

The DIALOGUE study involves oncology and genetic testing centers of the Swiss CASCADE Consortium from 3 linguistic regions of Switzerland (German-, French-, and Italian-speaking) and similar settings in Korea, eg, Severance Hospital, Seoul, and the National Cancer Center, Goyang. Settings ensure diversity in hospital characteristics (eg, general or advanced level) and geographic location to increase sample representativeness and generalizability.

Sample and Sample Size

The DIALOGUE study targets individuals who have been identified through genetic testing as carrying a *BRCA* pathogenic variant (proband) and their blood relatives. Textbox 1 describes the inclusion criteria for the probands and relatives. Eligible probands will be females and males (expected female-to-male ratio=4:1) and their first- and second-degree relatives (parents, siblings, offspring, aunts, uncles, nieces, nephews, and grandparents) and their first cousins. Participants may have a cancer diagnosis (expected breast-to-ovarian cancer ratio=5:1) or they may be cancer-free. Individuals who tested positive for a variant of uncertain significance and mutation carriers without any blood relatives, spouses, and partners are excluded because cascade genetic testing does not apply to them. We also exclude individuals who tested positive for a non-*BRCA* pathogenic variant because of the current variation in the implementation of panel testing among the different sites, which will likely influence the recruitment of participants with non-*BRCA* mutations. The study will only include adults because hereditary cancer risk assessment is not recommended for children. The study will also exclude vulnerable participants, such as critically ill patients and those living in nursing homes, to avoid increasing the subject burden and provide surveillance recommendations to participants who are not able to follow through the program.

Textbox 1. Inclusion criteria.

Switzerland

- Probands
  - Has tested positive for a BRCA pathogenic variant
  - ≥1 first- or second-degree relative or first cousin
- Probands and relatives
  - ≥18 years old
  - German, French, Italian, and English
  - Swiss resident
  - Mentally able to provide written consent
  - Access to computer, tablet, or smartphone

Korea

- Probands
  - Has tested positive for a BRCA pathogenic variant
  - ≥1 first- or second-degree relative or first cousin
- Probands and relatives
  - ≥19 years old
  - Korean and English
  - Korean resident
  - Mentally able to provide written consent
  - Access to computer, tablet, or smartphone

K-CASCADE Cohort

Estimates of sample accessibility follow consultations with the medical directors of clinical sites and assume average HBOC prevalence rates of 5% for both countries. There are approximately 90 new mutation carriers per year from the clinical centers affiliated with the Swiss CASCADE Consortium. Data from the Swiss CASCADE cohort indicate that it is feasible to recruit approximately 50% of the probands from each clinical site. Each proband is willing to invite an average of 4 relatives, with a response rate of 50% among relatives. In Korea, with 5 participating hospitals, 540 individuals are expected to enter the K-CASCADE cohort over 3 years (6 individuals per month×12 months×3 years×5 hospitals, 50% participation rate).

Intervention Adaptation

A purposeful sample of 20-24 participants (10-12 mutation carriers and 10-12 relatives) per linguistic region will participate in individual interviews and/or mini focus groups in each country. There will be homogeneity within members of each focus group, but the samples will be diversified in terms of demographics (eg, sex) and clinical history (eg, affected with cancer vs cancer-free) among groups. Mini focus groups or interviews will be conducted with a convenience sample of 6-10 expert clinicians involved in genetic consultation in each country. Mini focus groups allow more time to share experiences and encourage greater in-depth information and insights. The adapted Family Gene Toolkit will be tested for usability and acceptability with 5 new mutation carriers and/or relatives per linguistic region [52,53].

Intervention Efficacy

The cluster RCT will invite 114 probands to have a total of 104 evaluable subjects (52 for each website). This sample size would allow detecting whether using the adapted Family Gene Toolkit or the comparison website would increase the proportion of informed relatives by 25% with a statistical power of 80%, a significance level of 5%, and a dropout rate of 9.6% (11/114). We estimated the distribution of the proportion of relatives and dropout rates from our previous studies [14,50]. Less than 10.5% (12/114) of potential participants have no relatives, and less than 10.5% (12/114) have no access to a computer, tablet, or smartphone, making them ineligible for the study. We expect to recruit and retain the final sample of 114 probands over 18 months.

Intervention Translatability

This step involves assessing the potential for implementing the adapted Family Gene Toolkit in real-world conditions. RE-AIM dimensions will be assessed from participating and nonparticipating mutation carriers, relatives, and providers throughout the study.

Recruitment and Procedures

K-CASCADE Cohort

The opportunity to participate in the K-CASCADE cohort will be advertised through the KOHBRA network, the Ovarian Cancer and Genetics study group, and other clinical sites. Recruitment procedures for Korean probands and relatives will follow steps and procedures similar to those outlined for the Swiss CASCADE cohort [14]. In short, index cases (first person in the family with the pathogenic variant) identified in participating centers will be invited to participate in the study by collaborating clinicians and through patient advertisements posted in the clinics. Potential participants will also be able to view information on the study website. Individuals carrying a *BRCA* pathogenic variant, and if they have at least one eligible relative based on pedigree data, will meet study recruiters to ask questions and provide written consent. To alleviate ethical concerns associated with contacting blood relatives without their explicit consent, the K-CASCADE cohort will approach them through probands, targeting only relatives the proband is willing to contact. This recruitment method is used by the Swiss CASCADE cohort and in previous family-based studies with very good recruitment outcomes [39,54]. Relatives agreeing to participate will also provide written consent. In the consent form, probands and relatives will indicate their willingness to invite additional relatives to the K-CASCADE, be contacted once a year for 5 years and provide updated information about their health, participate in a focus group or individual interview for the adaptation of the Family Gene Toolkit in Korean, and participate in an RCT for testing the effects of the adapted Family Gene Toolkit. Probands and relatives may participate in all or some of the study steps previously described.

Probands and relatives will provide baseline assessments via a URL link to the digital health intervention and a unique passcode. A second prompt will be sent 2 weeks later. If there is no response to the second contact, study recruiters will contact the participants by phone. Relatives will also provide written consent, and they will receive a URL with a unique passcode. The Swiss CASCADE platform will facilitate data collection in both countries to maintain the consistency and accuracy of data entry, data management, and analyses. Korean respondents will log on as K-CASCADE participants to provide survey data.

Intervention Adaptation

Participants will be recruited through the Swiss CASCADE cohort and through flyers posted in the affiliated Korean institutions and clinics. After obtaining consent, focus groups or individual interviews will be organized at an easily accessible site and in participants' language. Focus groups will be coded by 2 members of the team in each country and linguistic region and will be audiotaped with participants' explicit consent. Participants will be asked to *think aloud* while viewing electronic mockups of the intervention and while navigating a final version of the digital health intervention. The latter sessions will be videotaped.

Clinicians involved in genetic consultations will be identified through the CASCADE Consortium in Switzerland; through the Schweizerischen Arbeitsgemeinschaft für Klinische Krebsforschung, Network for Cancer Predisposition Testing and Counseling in Switzerland; and through the KOHBRA network in Korea. They will be recruited via email and/or invitation letters and will also provide consent. Semistructured exploratory questions will elicit their opinions on structural barriers to HBOC cascade genetic testing. At a later stage, they will also view a nearly final version of the digital health intervention and will provide feedback. Sessions will be audiotaped and videotaped with clinicians' consent.

Intervention Efficacy

After they complete the baseline questionnaires (T_1), probands (index case) in both countries who agree to participate in an RCT and test the effects of the adapted Family Gene Toolkit will be emailed a unique URL link and passcode allowing them access to the digital health intervention. Furthermore, they will be able to log in and review the intervention modules multiple times using the same URL link and passcode. The system will randomize participants in a 1:1 ratio to either the digital health intervention or the comparison website. Stratification by country (Switzerland vs Korea) will be facilitated with different URL links for participants from each country. Participants will receive weekly email or text alerts, encouraging them to visit the website and complete viewing of the contents of the digital health intervention within 4 weeks. They will also receive email or text alerts to complete a knowledge quiz, an exercise for value clarification related to genetic testing, and a family communication rubric that will be included in the content of the different modules. Participants randomized to the comparison website will receive 1 email alert 2 weeks after they engage with the website. Relatives will be allocated to the same study arm as the respective proband and will also receive a URL link and a unique passcode. Relatives will first be asked to complete a consent form and then to complete the baseline survey, after which they will have access to either the adapted Family Gene Toolkit or the comparison.

Primary and secondary outcomes will be assessed at 2 months (T_2) and 6 months (T_3) after the intervention. We selected the 2- and 6-month follow-up time points to measure the short-term and long-term intervention effects, in line with our previous studies [33,50]. To minimize the attrition rate, if a response has not been received within 2 weeks from the time participants receive the URL link to the follow-up survey, then the study personnel will make 3 attempts to contact them by email or phone and encourage them to complete the survey.

Measures and Outcomes

K-CASCADE

The core questions of the Swiss CASCADE cohort [14] constitute the basic measurements for the K-CASCADE. Instruments are purchased (if not available for free) and will be translated into Korean (if not available) following the World Health Organization's translation guidelines. The baseline survey covers cancer diagnoses and surveillance, use of and experience with genetic testing (for testers and nontesters), communication with health care providers, and satisfaction with cancer genetic services. It assesses information about prophylactic surgeries; epidemiological data about personal,

reproductive, and family history of breast and ovarian cancer; and modifiable lifestyle risk factors (smoking, drinking, physical activity, etc). The baseline survey also assesses demographic characteristics and psychosocial variables, for example, the fear of cancer recurrence and self-efficacy to use services, which constitute the basis for creating the tailored messages provided by the adapted Family Gene Toolkit. These instruments are listed in Table 1. The Korean survey will be pilot tested with 10 study participants for comprehension and accuracy.

Table 1. Demographics and psychosocial characteristics.

Variables	Instruments	Cronbach α	Test-retest reliability	Assessment	
				Baseline	Follow-up
Demographics, personal, and family cancer history	Self-report [55]	—[a]	—	✓[b]	
Tailoring variables					
Degree of relationship between proband-relatives (eg, first degree)	Self-report	N/A[c]	N/A	✓	
Fear of cancer recurrence (for patients)	Concerns About Recurrence Scale [56], 4 items, 7-point Likert scale	.93	0.91	✓	
Self-efficacy dealing with cancer (for patients)	Self-efficacy–HBOC[d]-related cancer [57], 14 items, 7-point Likert scale	.80	0.71	✓	
Self-efficacy using genetic services	1 item, 7-point Likert scale	N/A	N/A	✓	
Family support	Family Support in Illness [58], 10 items, 7-point Likert scale	.86	0.83	✓	
Family hardiness	Family Hardness Index [59], 20 items, 7-point Likert scale	.90	0.82	✓	
Satisfaction with genetic counseling (for tested individuals)	Multidimensional Impact of Cancer Risk Assessment [60], 19 items, 7-point Likert scale	.81	—	✓	
Barriers and facilitators for genetic services	Barriers and facilitators for genetic services [61], 11 items, multiple choice	N/A	N/A	✓	

[a]Not available.

[b]The variable will be assessed at the specific time frame.

[c]N/A: not applicable.

[d]HBOC: hereditary breast and ovarian cancer.

Intervention Adaptation

A trained moderator will ask focus group participants to answer semistructured exploratory questions designed to elicit their opinions on the most pressing issues for family communication, using appropriate probe questions to explore potential cultural interpretations. The interview guide explores issues around family communication that took place during the genetic consultation, decision making related to the disclosure of test results to relatives, and attitudes toward using digital health platforms. Participants will also rate their satisfaction with the content, format, and appearance of the website. Assessing intervention feasibility also involves assessing the number of modules accessed, time spent on each module, and the utilization of links, which are automatically recorded on the website.

Intervention Efficacy

Data to evaluate the magnitude of intervention effects will be assessed using the instruments listed in Table 2. These have strong psychometric properties and have been used in previous studies on patients with cancer. Most of these instruments have been translated into and validated in German, French, and Italian and will be translated into and validated in Korean. Primary and secondary outcomes are assessed at the 2-month and 6-month follow-up surveys. Satisfaction with the intervention and acceptability will be assessed at the 2-month follow-up with questions about intervention usefulness, ease of use, clarity, appropriate length, level of detail, relevance, and interest with a 7-item survey (Likert scale ranging from 1=low to 7=high) [62,63].

Table 2. Instruments to assess primary and secondary outcomes.

Concepts	Instruments	Cronbach α	Test-retest reliability	Assessment	
				Baseline	Follow-up
Primary outcomes					
Proportion of informed relatives	Website data	N/A[a]	N/A	✓[b]	✓
Intention to inform relatives	Informing Relatives Inventory [64], 68 items, 7-point Likert scale	.86	—[c]	✓	✓
Intention for genetic testing (untested relatives)	1 item, 7-point Likert scale	N/A	N/A	✓	✓
Secondary outcomes					
Psychological distress	Profile of Mood States [65], 37 items, 7-point Likert scale	.86	—	✓	✓
Genetic literacy—genetic affinity	Risk Factor Knowledge Index [39], 17 items, true, false, and do not know	.89	0.85	✓	✓
Genetic literacy—cancer genetics	Breast Cancer Genetics Index [66], 12 items, true, false, and do not know	.82	0.81	✓	✓
Coping with stressful events	Brief Cope [67], 25 items, 7-point Likert scale	.81	0.78	✓	✓
Decision making—untested individuals	Decisional Conflict Scale-HBOC[d] Genetic Testing [68], 16 items, 7-point Likert scale	.96	—	✓	✓
Decision making—tested individuals	Decisional Regret-Genetic Testing [69], 5 items, 7-point Likert scale	.87	—	✓	✓
Intervention evaluation					
Acceptability, detail, usefulness, relevance, and satisfaction	Intervention Evaluation [62,70], 16 items, 7-point Likert scale	—	—		✓

[a]N/A: not applicable.

[b]The variable will be assessed at the specific time frame.

[c]Not available.

[d]HBOC: hereditary breast and ovarian cancer.

Intervention Translatability

Textbox 2 outlines RE-AIM outcomes to be assessed, which will help in evaluating the potential for a broader implementation and dissemination of the digital health intervention.

Textbox 2. Reach, effectiveness, adoption, implementation, and maintenance outcomes assessed in the study.

Reach (individual)

- Response rate of mutation carriers and relatives
- Number of probands and relatives accessing the website
- Demographic, linguistic characteristics, and region
- Response rate to K-CASCADE (Korean–Cancer Predisposition Cascade Genetic Testing)

Effectiveness (individual)

- Assess the number of times participants accessed each module
- Assess the number of relative invites initiated through the website
- Evaluate the acceptability, interest, usefulness, level of detail, relevance, and satisfaction follow-up survey

Adoption (setting, staff, and organization)

- Number of clinicians and new settings willing to participate in the study
- Diversity (geographic, linguistic, etc) in participating settings

Implementation (setting, staff, and organization)

- Monitor referrals of mutation carriers from different clinical sites
- Evaluate the cost for adapting modules for other hereditary cancer syndromes (eg, Lynch syndrome)

Maintenance (individual and setting)

- Assess resources needed to maintain the website
- Assess the number of visits per month per year

Data Management and Data Analyses

K-CASCADE Cohort

Korean participants' data entered in the Swiss CASCADE platform will be available for descriptive and comparative analyses, using epidemiological and psychosocial data along with coded and nonidentified clinical data. Existing clinical data from Severance Hospital, stored in the Clinical Research Analysis Portal, will also be accessed for participants who provide additional consent. At year 4, the accrued data from Korean women will be used in conjunction with clinical data for comparative analyses with the Swiss CASCADE cohort.

Intervention Adaptation

The mini focus groups or interviews with HBOC families and clinicians will be audiorecorded with participants' consent and transcribed verbatim, using codes to protect individual identification. Transcripts will be reviewed by the research team, and content will be analyzed using an iterative process of reading transcripts, coding, and comparing the data to identify salient themes. Two members of the research team in each country will also review the videotapes obtained from usability testing and the *think aloud* protocol. They will confirm that there are no functional errors on the website, color schemes and graphical images are well received, participants can navigate through various sections of the website with ease, the layout accurately conveys information, and the program works as expected. Data regarding acceptability will be analyzed using descriptive statistics.

Intervention Efficacy

The efficacy cluster RCT will use pre- and postintervention data from baseline (T_1) and follow-up (T_2 and T_3) surveys. Data values will be checked for validity (within the appropriate range) using histograms and box plots and corrected whenever possible. Many items are a part of multi-item scales and are anticipated to correlate with each other. Scales will be tested for internal consistency reliability with Swiss and Korean participants using principal component analysis and Cronbach α coefficients. Scales with Cronbach α values of .71 and higher will be used. Multiple imputation or other techniques will address missing data if they exceed 5% of observations and if they are less than 25% for each specific scale. Data from participants who withdraw will be kept to ensure internal validity.

Primary outcomes will be calculated with the Wilcoxon-Mann-Whitney test to compare the proportions of informed relatives per study arm. Other primary and secondary outcomes and metadata from the automatic recording of website activity will be analyzed using descriptive statistics. Descriptive analyses will include calculating the means and frequencies of key variables and subject descriptors (eg, genetic testing). This will include tabulating counts and frequencies of variables, including demographics and personal cancer history. Bivariate analyses (using the chi-square test for differences in proportions and *t* test for differences in means) will assess the associations between demographic factors and clinical characteristics. The following comparisons will be made: between probands and relatives, between men and women, between patients with cancer and cancer-free individuals, between participants with

children and those with no children, between different age groups, and between patients with different cancer diagnoses. A detailed methodology for summaries and statistical analyses will be documented in a statistical analysis plan. This plan will be finalized before database closure and will be under version control at the Clinical Trial Unit, University Hospital Basel. All analyses will be conducted using the statistical software R [71], using *two-sided* statistical tests and confidence intervals with confidence levels α=5% and (100%−α)=95%, respectively. Deviations from planned analyses are not foreseen. The study statistician will review and approve any deviations from the original statistical plan.

Intervention Translatability

Data exploring the RE-AIM of the digital health intervention will be analyzed using qualitative and quantitative methods. Narrative data obtained from mini-interviews will be audiorecorded, transcribed verbatim, and analyzed for common themes. Descriptive analyses will include calculating the means and frequencies of the key variables and subject descriptors. Bivariate analyses (chi-square test for differences in proportions and *t* test for differences in means) will compare key variables between participants and nonparticipants.

Results

The DIALOGUE study, including the development of the K-CASCADE cohort in Korea, was funded in October 2019. It is projected that data collection will be completed by January 2023, and results will be published in fall 2023.

Discussion

Principal Findings

The need to enhance family communication around HBOC has been documented in the literature since mid-2000 [72-74], followed approximately 10 years later by scientific calls to enhance cancer predisposition cascade genetic testing [75-77]. The DIALOGUE study is a resource-effective international research platform that proposes building a tailored, interactive website to reach a large number of HBOC families and enhance cancer predisposition cascade genetic screening, presumably requiring only a fraction of the cost and required clinician time compared with previous approaches. Developing the K-CASCADE cohort will link together the expertise of an eminent network of HBOC scholars and clinicians that will benefit both countries and serve as a model for potential expansion to other countries and in other language contexts. The cross-cultural adaptation of the Family Gene Toolkit will help explore the similarities and differences in communication practices among HBOC families in the Swiss and Korean contexts, potentially providing important information about the Korean and Swiss contexts that affect HBOC discourse [78]. This comparison will also reveal context-specific characteristics regarding the influence of the health care system, insurance coverage, and socioeconomic aspects on the application of genetic knowledge that can provide useful information for adapting other digital health solutions within the Swiss and Korean contexts. The goal of the adapted Family Gene Toolkit is to attend to the needs of diverse families, including the function of different members, and cultural and linguistic backgrounds. It is thus important to consider digital health technologies as sociocultural products with a need for an adaptation to specific local contexts and a critical reflection about how they may affect local perceptions of illness [78]. The final product will likely be more cost-effective and will expedite scaling-up, dissemination, and implementation, given the existing strong clinical partnerships within each country.

Conclusions

The adaptation and implementation of culturally sensitive, digitally based health interventions that enhance the understanding of genetic cancer risk are extremely timely and relevant, given the expansion of genetic testing technology, the falling costs of genetic testing, and the increased pressure for the integration of genetic knowledge in routine clinical care. Genetic testing for hereditary susceptibility to disease has received increasing attention among the health care community and at the individual, familial, and international levels. The DIALOGUE study will contribute to the development of high-quality comprehensive support systems that enhance the counseling process and facilitate informed decision making by minimizing conflict and distress and making resources available in culturally appropriate ways. Ultimately, the study contributes to a broader dissemination of genetic information and helps in expanding the public health understanding of the impact of new technologies on risk stratification and disease management.

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Conflicts of Interest

None declared.

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Abbreviations

CASCADE: Cancer Predisposition Cascade Genetic Testing
HBOC: hereditary breast and ovarian cancer
K-CASCADE: Korean–Cancer Predisposition Cascade Genetic Testing
KOHBRA: Korean Hereditary Breast Cancer
RCT: randomized controlled trial
RE-AIM: reach, effectiveness, adoption, implementation, and maintenance

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Protocol

Supporting Clinicians to Use Technology to Deliver Highly Personalized and Measurement-Based Mental Health Care to Young People: Protocol for an Evaluation Study

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Abstract

Background: Australia's mental health care system has long been fragmented and under-resourced, with services falling well short of demand. In response, the World Economic Forum has recently called for the rapid deployment of smarter, digitally enhanced health services to facilitate effective care coordination and address issues of demand. The University of Sydney's Brain and Mind Centre (BMC) has developed an innovative digital health solution that incorporates 2 components: a highly personalized and measurement-based (data-driven) model of youth mental health care and a health information technology (HIT) registered on the Australian Register of Therapeutic Goods. Importantly, research into implementation of such solutions considers education and training of clinicians to be essential to adoption and optimization of use in standard clinical practice. The BMC's Youth Mental Health and Technology Program has subsequently developed a comprehensive education and training program to accompany implementation of the digital health solution.

Objective: This paper describes the protocol for an evaluation study to assess the effectiveness of the education and training program on the adoption and optimization of use of the digital health solution in service delivery. It also describes the proposed tools to assess the impact of training on knowledge and skills of mental health clinicians.

Methods: The evaluation study will use the Kirkpatrick Evaluation Model as a framework with 4 levels of analysis: Reaction (to education and training), Learning (knowledge acquired), Behavior (practice change), and Results (client outcomes). Quantitative and qualitative data will be collected using a variety of tools, including evaluation forms, pre- and postknowledge questionnaires, skill development and behavior change scales, as well as a real-time clinical practice audit.

Results: This project is funded by philanthropic funding from Future Generation Global. Ethics approval has been granted via Sydney Local Health District's Human Research Ethics Committee. At the time of this publication, clinicians and their services were being recruited to this study. The first results are expected to be submitted for publication in 2021.

Conclusions: The education and training program teaches clinicians the necessary knowledge and skills to assess, monitor, and manage complex needs; mood and psychotic syndromes; and trajectories of youth mental ill-health using a HIT that facilitates a highly personalized and measurement-based model of care. The digital health solution may therefore guide clinicians to help young people recover low functioning associated with subthreshold diagnostic presentations and prevent progression to more serious mental ill-health.

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KEYWORDS

mental health service delivery; youth mental health; model of care coordination; transdiagnostic; health information technology; education; training; adoption into clinical practice; Kirkpatrick evaluation

Introduction

Australia's mental health care system has long been fragmented and under-resourced, with services falling well short of demand [1]. Mental health consumers often receive inconsistent and sporadic treatment delivered by independent services, with little collaborative decision making or multidisciplinary continuous care [2]. At particular risk are young people who do not respond to brief interventions and are unable to access continuous care [3], and those who deteriorate under care [4-6]. Coordination between crisis and ongoing care providers is also poor, with medical staff in emergency departments expressing clear learning needs in developing care plans for patients presenting with mental health problems [7]. The advent of a novel coronavirus and its resulting global COVID-19 pandemic has added additional strain to Australia's mental health services with increasing demands for crisis support and intervention [8-11], highlighting the need for a revolution of current mental health service delivery [12].

The World Economic Forum has recently called for the "…rapid deployment of smarter, digitally-enhanced health services…" as a means of potentially addressing demand issues and facilitating effective care coordination [13]. The recent Australian Productivity Commission's inquiry into mental health also recommends that technology should play a larger role by improving access to the right services at the right time [14]. Moreover, it has been proposed that digital solutions may be a viable method of delivering personalized and measurement-based care to young people, transcending the often-narrow focus on symptom or risk reduction [15]. While there are ethical, data security, and privacy challenges that must be addressed in relation to the implementation of technology-based solutions [13], it has been noted that staff resistance to change and perceived technological complexity frequently present as barriers to the uptake of health information technologies (HITs) [16]. Consequently, education and training that foster engagement and address the use of HITs in practice are essential for successful adoption and optimization of technology-enabled solutions in clinical practice [17]. This increasing need for training and upskilling of clinicians working in digitally enhanced mental health services has not been addressed in the existing literature, which has previously been limited to training specific to clinicians' disciplines, treating specific diagnoses, or intervention modalities [18-20]. As such, there is an urgent need for education and training in the effective use of digital health solutions to meet the increase in demand for mental health services and facilitate effective care coordination across a multidisciplinary workforce.

Researchers at The University of Sydney's Brain and Mind Centre (BMC) have developed the Youth Mental Health (YMH) and Technology Program, which adopts an innovative digital health solution to prevent further progression of mental ill-health for young people in care [21]. This digital health solution includes two key components. The first is the *BMC Youth Model*, a highly personalized (ie, treatment targeted to address individual needs) and measurement-based (ie, data-driven) model of care generated from over 10 years of longitudinal research led by the BMC to assess multiple clinical and functional domains in young people presenting for mental health care and treatment [22,23]. This cohort includes 6743 young people aged 12 to 30 years, which was analyzed to uncover initial underlying neurobiology of mental ill-health in young people [24]. Findings were reported through a supplement of research articles that explore the associations between the multiple clinical and functional domains, neurobiological measures, as well as clinical, social, and functional outcomes [22]. The BMC Youth Model explicitly aims to prevent the progression of emerging and mixed syndromes into more complex and severe forms of illness and to facilitate symptomatic and functional recovery. The second is an HIT — such as the InnoWell Platform, which is listed on the Australian Register of Therapeutic Goods — that is a customizable digital toolkit to assist assessment, monitoring, and management of mental ill-health and maintenance of well-being by collecting, storing, scoring, and reporting personal and health information back to consumers and their health professionals to promote collaborative care partnerships [25]. Though we reference the InnoWell Platform as an exemplar HIT, it is important to note that the BMC Youth Model can be facilitated via any HIT so long as its design has been guided by similar clinical and scientific concepts to provide highly personalized and measurement-based care.

The education and training program has been designed to encourage the adoption of highly personalized and measurement-based care in clinical practice, to ensure young people get the right treatment at their first point of entry into care. Specifically, the program focuses on teaching youth mental health professionals how to assess, monitor, and manage complex needs and illness pathways. The education and training program now delivers information via multimodal tools, including online seminars, case study webinars, and in-service workshops. The HIT is referred to throughout the training, as it aids in facilitating highly personalized and measurement-based care (including assessment of clinical stage, pathophysiological mechanisms, and multidimensional needs) and supports the choice of treatment options while tracking a young person's progress.

This paper briefly describes the education and training program and outlines a protocol for an evaluation study to assess the effectiveness of education and training on the adoption and optimization of use of the digital health solution in service delivery.

Methods

Education and Training Program

The education and training program has been designed to be accessed in-person or online. This has been done to provide access to standardized, high-quality training delivered by experienced clinician-researchers from the BMC. This is particularly important for reaching out to those services that would not ordinarily have access to such opportunities, such as health services in regional Australia. The program is currently comprised of online seminars, case study webinars, and in-service training workshops.

The online seminars introduce the theoretical, clinical, and scientific underpinnings of the YMH and Technology Program that provide the background knowledge necessary for clinicians to understand the digital health solution and begin to apply it to their own clinical practice. To date, 6 seminars delivered by experienced clinician researchers (authors ES and IH) have been recorded covering approximately 60 minutes each (see Textbox 1) and are freely accessible through the BMC Youth Mental Health Research YouTube Channel.

Textbox 1. Modules of the education and training program.

1. A highly personalized and measurement-based model of care to manage youth mental health
2. Combining clinical stage and pathophysiological mechanisms to understand illness trajectories in young people
3. A comprehensive assessment framework for youth mental health care
4. Using the Brain and Mind Centre (BMC) Youth Model to personalize care options – right care, first time!
5. A youth mental health service delivery model to support highly personalized and measurement-based care
6. Maximizing the use of digital health solutions in youth mental health care

These online seminars are further enhanced by case study webinars, which detail practical application of the digital health solution and help to translate newly acquired knowledge into clinical skills [26]. Two such case study webinars spanning an hour each have been recorded to date and cover 3 cases, their initial presentation, and the tracking of their syndromes over time demonstrating the value of the digital health solution.

In-service training workshops will be delivered by BMC clinician-researchers and focus on the practical application of the BMC Youth Model into the specific youth mental health service. The workshops typically include case studies common to the participating service. These workshops can be conducted either face-to-face or online. To date, 2 regional *headspace* services in Northern New South Wales have attended in-service training workshops.

In order to encourage and reward participation in all components of the education and training program, continuing professional development points are available for psychiatrists, psychologists, mental health nurse practitioners, social workers, and occupational therapists. To further encourage engagement, additional specialized supplemental webinars (eg, applying the BMC Youth Model to understand the relationship between circadian rhythms and mental health and applying the BMC Youth Model to enhance psychological therapy for individuals with anxiety and other mood disorders) and case studies will be released, demonstrating how the BMC Youth Model can be applied to specific disorders and complex cases.

An Evaluation Framework

The importance of a standardized and consistent framework for evaluation of education and training programs has previously been highlighted [27,28]. Evaluations often only focus on participants' reactions and acquired knowledge and tend to neglect the assessment of behavioral change or impact on client outcomes, which are both critical factors in determining effectiveness [27].

This study will utilize the Kirkpatrick Evaluation Model, which includes 4 levels of training evaluation including: Reaction, Learning, Behavior, and Results [29] (see Table 1). This evaluation framework is ideally suited to a mixed methods approach combining quantitative and qualitative methods, as each level of evaluation requires the implementation of appropriate methodology that is complementary to, but independent of, the other levels. Aspects of the Kirkpatrick Evaluation model have been successfully used in mental health training, for instance in suicide prevention [30].

Table 1. Applying the Kirkpatrick Evaluation Model as an evaluation framework for the education and training program.

Level	Key question
Level 1: Reaction	What are the reactions of clinicians to the digital health solution?
Level 2: Learning	Have clinicians learned the relevant knowledge relating to the digital health solution?
Level 3: Behavior	Have clinicians transferred and applied their knowledge of the digital health solution to standard clinical practice?
Level 4: Results	What has been the impact of the digital health solution on service performance, such as efficiency, clinical safety, and clinical outcomes?

The Kirkpatrick Evaluation Model [29] also highlights the importance of ongoing education and training, as the majority of learning is acquired through practice. In order to sustain education and training, the Kirkpatrick model encourages

monitoring, reinforcing, encouraging, and rewarding. For this study, monitoring and reinforcing will be completed at 3 months, 6 months, 9 months, and 12 months post-initial education and training, with individual progress reports being provided in order to encourage and reward their adoption of the YMH and Technology Program.

Measures

Participant Profile

Before commencing the education and training program, clinicians will be asked to complete a participant profile. This profile includes questions regarding their educational background, professional background, years of clinical experience, and reasons for participating in the education and training program.

Online Seminar, Case Study Webinar, In-Service Workshop Evaluation Form

This form assesses clinician reaction (Level 1) to the education and training program, including satisfaction, engagement, and relevance. This form consists of 20 items, of which the first 15 are rated on a 5 - point Likert scale ranging from "1 = totally disagree" to "5 = totally agree," and the remaining 5 questions represent an open-ended format. Clinician satisfaction will also be measured using the Training Satisfaction Rating Scale, an existing scale with good content validity [31]. This scale is a 12-item questionnaire assessing participant agreement to objectives and content (eg, "In my opinion, the planned objectives of the [online seminar/ case study webinar/ in-service workshop] were met."), method and training context (eg, "The [online seminar/ case study webinar/ in-service workshop] enabled us to take an active part in training."), and usefulness and overall rating (eg, "The education and training received is useful for my personal development."). In addition to the existing scale, 3 items will be used to evaluate the quality of facilitation (eg, "The facilitator(s) were knowledgeable about the education and training topics."). Lastly, participants will be invited to provide qualitative feedback on the education and training program regarding most liked and disliked aspects, major learnings, and expected results of the training (eg, "What aspects of the training could be improved?").

Knowledge Questionnaire

This questionnaire assesses clinician learning (Level 2) of key concepts of the digital health solution through the online seminars. This questionnaire consists of 30 multiple-choice questions relating to multidimensional assessment and outcomes, clinical staging and illness trajectories, social and biological development, real-time monitoring, and technology-enabled practice. Clinicians must select correct answers out of a list of answers that includes equally plausible distractors. In order to keep the questionnaire brief and reduce the chances of participants learning the answers through repetition, clinicians will be asked to complete 5 randomly selected questions at each time point (ie, at baseline, 3 months, 6 months, 9 months, and 12 months). Furthermore, at each time point, participants will be asked to identify which webinars and case studies they have watched in order to be able to link training engagement with outcomes.

Skill Development Scale

This scale assesses confidence in clinical skills (Level 3) central to the BMC Youth Model using 8 visual analogue scales coded as values "0" to "100." Marks to the left represent low confidence in development of skills, and marks to the right indicate high confidence in development of skills. The 8 items relate to multidimensional assessment, clinical staging, case formulation and treatment planning, shared decision making, intervention skills, outcome monitoring, and care continuity and coordination. Respondents are asked to reflect on each of these areas and rate how well they feel they perform these tasks in clinical practice.

Behavior Change Scale

This scale assesses clinician change in behavior (Level 3) using a scale consisting of 9 items that ask how frequently they utilized new knowledge and skills related to multidimensional assessment, clinical staging, intervention matching, shared decision making, monitoring, responding to increased suicidality, and continuity of care. Clinicians rate how often they employed a skill in their standard clinical practice in the past fortnight on a 5-point Likert scale ranging from "1 = not at all (with no clients)" to "5 = always (all of the time, for all clients)." For each item, clinicians can also indicate that the particular skill is not applicable to their service (0 = N/A).

Clinical Practice Audit

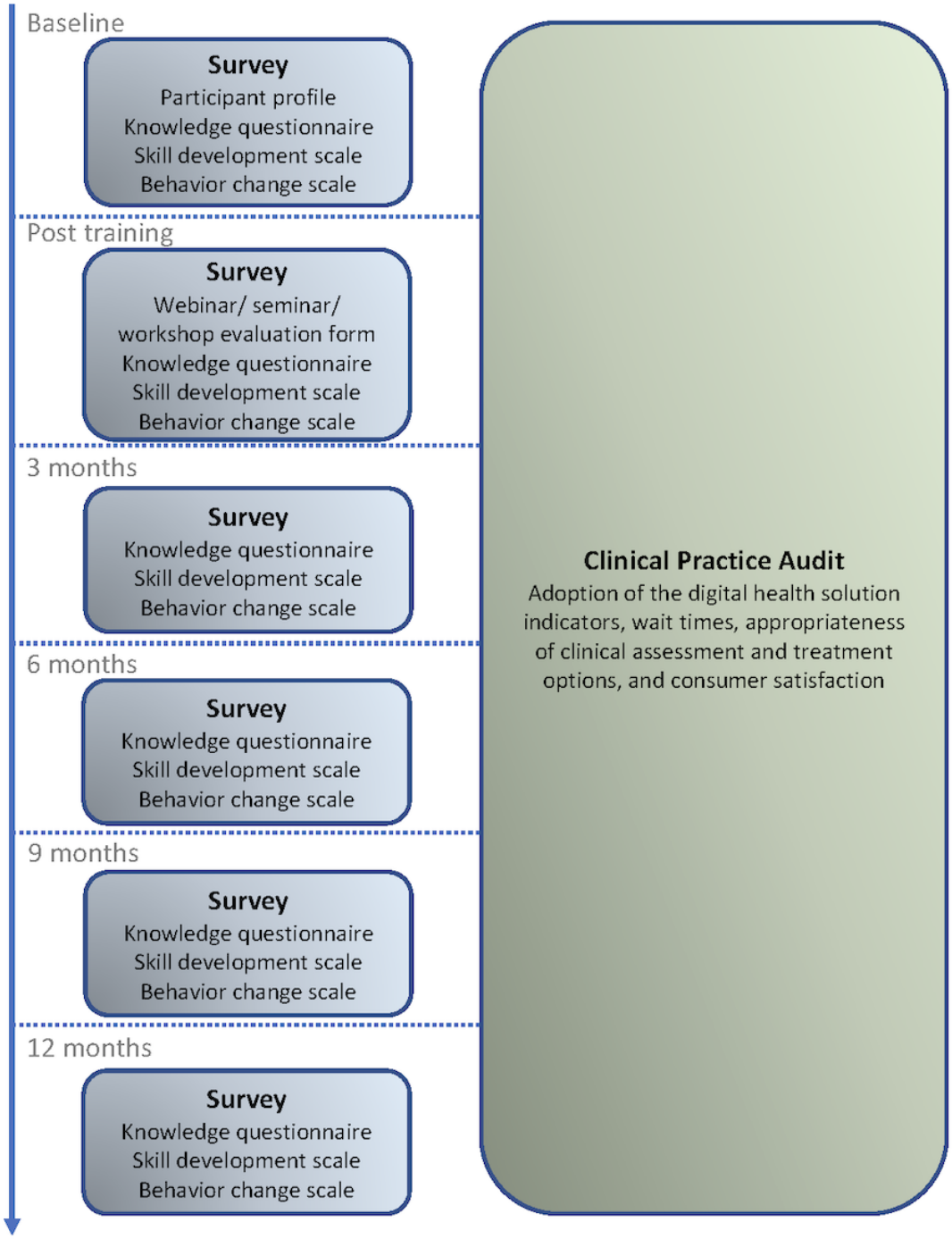
Change in clinician practice (Level 3) and impact on client outcomes (Level 4) will be assessed using real-time and aggregated data from the InnoWell Platform [32]. Indicators of adoption of the digital health solution include, for example, the frequency with which clinicians access the platform and time spent on the platform, accuracy of clinical staging assignment, and the recommendation of treatment options. Indicators of impact on client outcomes include, for example, efficiency (eg, time to first assessment and wait time for clinical intervention), clinical safety (eg, notifications for suicide thoughts and behaviors and average time to respond to notifications), and clinical outcomes (eg, changes over time in psychological distress as well as social and occupational functioning).

Procedure

The timeline of procedures is summarized in Figure 1. Before commencing the online education and training components, clinicians will complete the participant profile and a baseline knowledge questionnaire, skill development scale, and behavior change scale. A baseline clinical practice audit will also be completed. On completion of the 6 online seminars, the 2 case study webinars, and the in-service workshops, participants will be asked to complete a posttest knowledge questionnaire as well as the skill development and behavior change scales. Importantly, participating clinicians will additionally be contacted after 3 months, 6 months, 9 months, and 12 months and asked to complete the posttest knowledge questionnaire, skill development scale, and behavior change scale as a means to monitor and reinforce knowledge, skills, and behavior [29]. Together with real-time data from the InnoWell Platform (pre-education and training and then every 3 months posteducation and training), participants will privately receive

a progress report to encourage and reward their adoption and optimization of the digital health solution [29]. Finally, after each online seminar, case-study webinar, or in-service workshop, clinicians will be asked to complete the evaluation form.

Figure 1. Flow chart of evaluation methods pre- and post-education and training.



Participants

Participants will be drawn from 11 participating headspace services in Australia who have previously agreed to implement the HIT. The services include 5 from Sydney, 5 on the North Coast of New South Wales, and 1 in South Australia. Participants will include mental health professionals (eg, psychologists, social workers, mental health nurses, occupational therapists) and service managers. The sample size will be determined by participating services, with all health professionals and service managers being invited to participate in the education and training program.

Statistical Analyses

In order to assess participants' reactions to the training, a mixed methods approach will be utilized, specifically a Triangulation

Design, Validating Quantitative Data Model [33]. This design would allow the for the quantitative findings (eg, objectives and content, method and training context, usefulness, and quality of facilitation) to be validated and expanded on by including a few open-ended qualitative questions (eg, most liked and disliked aspects, major learnings, and expected results of the training).

Descriptive statistics will be used to analyze quantitative data gathered from the combined evaluation form data, as well as individually for the online seminars, case study webinars, and in-service workshops. A thematic analysis will be conducted to analyze qualitative data collected via the evaluation forms to identify patterns or themes within the data [34]. Procedurally, thematic analysis entails (1) becoming familiar with the data, (2) generating initial codes, (3) searching for themes, (4) reviewing themes, (5) defining and naming themes, and (6) reporting the final thematic concepts. The data will be coded using NVivo by a minimum of 2 different researchers in order to assess interrater reliability. These resulting thematic concepts can then be used to validate and embellish the quantitative survey findings.

In order to assess Learning, Behavior, and Results, pre- and postsurveys and clinical practice audit data will be compared using paired *t* tests to understand short-term impacts, and repeated measures analysis of variance will be used to understand long-term changes in knowledge, skill, behavior, and client outcomes.

Ethics and Dissemination

Ethics approval has been granted via Sydney Local Health District's Human Research Ethics Committee (Protocol No X18-0499 & HREC/18/RPAH/715). Research findings will be disseminated through peer-reviewed journals and scientific conference presentations. Participant data will be nonidentifiable and aggregated.

Results

As of September 2020, clinicians and their services were being recruited to this study. Data collection is expected to be completed and the first results to be submitted for publication in 2021. Results will then be disseminated to the participants, the public, and researchers through publications in journals and presentations at conferences.

Discussion

This paper details a comprehensive protocol for an evaluation study to assess the effectiveness of the education and training program on the adoption and optimization of use of the digital health solution to provide the knowledge and skills to assess, monitor, and manage the complex needs of young people presenting with mental ill-health problems.

Evaluations of education and training programs within mental health generally focus on the perceived usefulness of such programs, increased knowledge, and confidence in using acquired skills, but frequently neglect assessing the impact on changing clinician knowledge, skills, behaviors, and client outcomes [35]. By using the Kirkpatrick Evaluation Model [29], this study will assess the effectiveness of the education and training program in meeting the learning needs of clinicians (*Reaction*), increasing clinicians' knowledge of youth mental health (*Learning*), clinicians adopting the digital health solution in standard clinical practice (*Behavior*), and improving service performance (eg, efficiency, clinical safety, and clinical outcomes; *Results*).

While the evaluation protocol will produce valuable insights, there are limitations that should be noted. First, the measures of knowledge and skill rely on self-rating, which are subjective and may be influenced by the participant's level of self-awareness [36,37]. Second, it is generally recognized as being quite difficult to objectively measure the competence of mental health practitioners [37]. Last, the Kirkpatrick model is not without its flaws; for example, it has received criticism for being overly simplified and lacking an ability to provide information about *how* training can be improved [38]. Nevertheless, the Kirkpatrick model has been successfully utilized in prior mental health training [30] and will provide data in a way that can guide further research.

The research protocol presented here is the first of its kind to explore the education and training of mental health professionals in the use and benefits of technology-enabled solutions. As such, it has the potential to have a significant impact on determining how mental health professionals are trained as technology becomes more integrated into their practice [13,14]. The quantitative and qualitative data obtained from this study will be used to iteratively adapt and improve the education and training program in order to ensure that young people get the right care the first time and to prevent further progression of mental ill-health while in care. These results will also guide the creation of additional education and training resources to keep participating clinicians engaged and to the ensure sustainability of the digital health solution. Future resources may include a case study workbook and the creation of a community of practice that could provide a shared context for practitioners, enabling dialogue between practitioners who might not ordinarily have the chance to interact [39]. Further, our education and training team is currently exploring a more sophisticated online interactive platform to promote ongoing customized learning with participating youth mental health services.

Ultimately, this research will help teach mental health professionals how to facilitate a highly personalized and measurement-based model of care. This may therefore guide clinicians to help young people recover from low functioning associated with subthreshold diagnostic presentations and prevent progression to more serious mental ill-health.

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Conflicts of Interest

IH was an inaugural Commissioner on Australia's National Mental Health Commission (2012-18). He is the Co-Director, Health and Policy at the BMC University of Sydney. The BMC operates an early-intervention youth services at Camperdown under contract to headspace. He is the Chief Scientific Advisor to, and a 5% equity shareholder in, InnoWell Pty Ltd. InnoWell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the AU $30-million Australian Government-funded Project Synergy (2017-20; a 3-year program for the transformation of mental health services) and to lead transformation of mental health services internationally through the use of innovative technologies. TD is now Director (Research and Evaluation), Design and Strategy Division, Australian Digital Health Agency. Other authors on this paper have no conflicts of interest to disclose.

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Abbreviations

BMC: Brain and Mind Centre
HIT: health information technology
YMH: Youth Mental Health

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Protocol

Exploring Nurse and Patient Experiences of Developing Rapport During Oncology Ambulatory Care Videoconferencing Visits: Protocol for a Qualitative Study

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Abstract

Background: Telehealth videoconferencing has largely been embraced by health care providers and patients during the COVID-19 pandemic; however, little is known about specific techniques for building rapport and provider-patient relationships in this care environment. Although research suggests that videoconferencing is feasible and can be effective for some types of care, concerns about the impact of technology on provider-patient relationships exist across health disciplines. Suggestions for adapting some in-person rapport techniques, such as the use of small talk, eye contact, and body language to facilitate trust, personal connection, and communication during videoconferencing encounters, have been discussed in the popular press and clinical commentaries. Notably, evidence regarding the effects of these strategies on rapport and clinical care outcomes is lacking. Understanding how to establish rapport in videoconferencing visits is especially important in oncology nursing, where rapport with patients enables nurses to become a source of emotional support, helping patients adapt and navigate the cancer journey.

Objective: This study aims to investigate the nature of nurse-patient rapport in ambulatory cancer care videoconferencing visits. The objectives include exploring how patients with cancer and nurses describe experiences of rapport and strategies for cultivating rapport in videoconferencing visits and similarities and differences identified by patients with cancer and nurses between experiences of rapport in videoconferencing and in-person visits.

Methods: Semistructured narrative interviews of patients with cancer and nurses will be conducted to understand the experience of rapport building in videoconferencing visits. Nurses and patients will be interviewed separately to facilitate an understanding of the perspectives of both types of participants. Interviews will be conducted on a secure videoconferencing platform. This qualitative descriptive study will describe participant experiences in a manner that, although not without interpretation, is as close to the data as possible. The research team will meet regularly to discuss, define, and document codes, categories, and themes, and the team will maintain a detailed audit trail of analytical decisions. In addition, member checking will enhance the rigor of the study. Nurse and patient interviews will be analyzed separately using identical procedures and may be explored side by side in the final analysis to provide a comparative analysis. Data management and analysis will be performed using NVivo 12.

Results: Data collection will begin during summer 2021, with results from the data analysis anticipated by winter 2021. A research team trained in qualitative methodology will use conventional content analysis to analyze the data using first- and second-level codes derived directly from the transcribed text data.

Conclusions: This study aims to determine what behaviors, communication techniques, and relational practices need to be adapted in videoconferencing telehealth visits, setting the foundation for future development of interventions and evidence-based practice guidelines for relationship building during videoconferencing telehealth visits.

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KEYWORDS

nursing; oncology ambulatory care; provider-patient relationship; rapport; telehealth; videoconferencing visits

Introduction

Background

When the replacement of ambulatory in-person visits with videoconferencing suddenly became essential for persons with cancer because of the COVID-19 pandemic, providers had little experience or existing research to support this change in practice [1,2]. Some oncology ambulatory care centers went from all in-person visits to more than 50% of patient visits on videoconferencing [3]. Although videoconferencing has been broadly embraced by providers and patients during the pandemic, little is known about specific techniques for building rapport and provider-patient relationships in this care environment.

Review studies of videoconferencing in telehealth, although often focused on feasibility and acceptability for patients who are geographically underserved, show that this computer-mediated modality has utility and even comparable outcomes with in-person care for patients with a variety of chronic diseases and mental health challenges [4-7]. A systematic review of 15 studies conducted in oncology suggests that videoconferencing is feasible and can be effective in the care of some cancers [8]. More recent studies have focused on videoconferencing for palliative care consultation and support to patients, family caregivers, and community-based care providers [9-11]. These studies indicate that videoconferencing is feasible and often preferable for palliative care consultations [11,12], hospice family meetings [13,14], and support groups [15].

Knowledge Gaps

Although research suggests that videoconferencing is feasible and can be effective for some types of care, concerns about the impact of technology on provider-patient relationships exist across health disciplines. Nurses, physicians, and mental health providers have expressed concern that the two-dimensional interactions in video conferencing coupled with the loss of physical proximity, presence, and touch depersonalizes care and inhibits the providers' ability to best understand the patient and demonstrate care [16-19]. In palliative care studies, providers have indicated a reluctance to initiate emotional topics, feeling a need to be physically present with the patient to provide necessary support [20,21]. Reluctance has also been described because providers cannot be sure that patients have adequate privacy in videoconferencing visits [14]. Suggestions for adapting some in-person rapport techniques such as the use of small talk, eye contact, and body language to facilitate trust, personal connection, and communication during videoconferencing encounters have been discussed in the popular press and clinical commentaries [1,22-24]. However, few studies seem to have evaluated these modalities [25-28] or more advanced relational skills such as presence [29], conveying caring [30], empathy [31], and person-centered care [32]. Even in telepsychology, where research is more robust [33], providers remain concerned about the impact of videoconferencing on therapeutic alliance and nonverbal communication channels [16,34] and are uncertain about how best to adapt techniques.

Importance of Nurse-Patient Rapport

Rapport has been defined as a connection established with another person based on respect, acceptance, empathy, and a mutual commitment to engagement [35,36]. Interpersonal interventions that cultivate rapport between patients and providers have the potential to improve patient health outcomes and satisfaction [37,38]. For persons with cancer, feeling known personally and connected with nurses and health care providers on a level beyond their disease process reduces suffering and improves satisfaction, health outcomes, and quality of life [39-41]. Being known beyond their disease includes acknowledging the roles that patients have outside of being a person with cancer, including their personal and professional roles, and interacting with them as people rather than as patients [39,42]. Research suggests that rapport makes a trusting and therapeutic relationship more likely [43,44] and, in turn, enables providers to become a source of emotional support, helping patients adapt and navigate the cancer journey [35,45-47]. The cancer journey is often a prolonged experience that spans diagnosis, treatment, and years of survivorship with ongoing care and multiple comorbidities [48]. Having a nurse who is not only knowledgeable but who can also provide a whole-person approach to care is essential. Ambulatory oncology nurses play a pivotal role in a patient's cancer journey by helping patients and families integrate new information and build the capacity and skills to adapt and address care challenges [47,49]. For example, a patient with cancer who lives alone or has a baseline mobility impairment may require a very different plan of care to successfully manage common side effects such as nausea, vomiting, and diarrhea. As such, nurse-patient rapport facilitates the trusting relationship necessary to ensure holistic assessment of needs, personalization of care, and adaptive work [39,50-52].

Critical Need for Research

Studies suggest that relationship development and communication in videoconferencing encounters, although similar to in-person interactions, present unique challenges that can affect rapport, diagnostic accuracy, and treatment compliance when not addressed [25,28]. For example, camera placement and the ability to visualize the self during videoconferencing platforms create both a downward gaze [53] and excessive levels of gaze [54] that are unnatural when compared with in-person encounters. In addition, video and audio lapses that result in overlapping conversations or uncomfortable periods of silence interfere with communication [28]. Studies comparing in-person and videoconferencing encounters have found that providers use less empathetic, supportive, and facilitating statements [31] in virtual encounters, and there is less information exchange, with the presentation of fewer problems [55]. Of note, evidence regarding the effects of these findings on rapport and clinical care outcomes is lacking.

Research Aim and Questions

The purpose of this qualitative descriptive study is to explore the nature of nurse-patient rapport in ambulatory cancer care videoconferencing visits. The use of videoconferencing in telehealth nursing is relatively new, especially in oncology ambulatory care. With little existing research to build on, prioritizing studies that provide a foundation for future inquiries is essential. This gap requires a descriptive, exploratory study to increase our understanding of nurse-patient rapport in such a context. Knowledge gaps include an understanding of the attributes of videoconferencing experiences for nurses and patients, along with antecedents, facilitators, barriers, and outcomes. The proposed study will address (1) how patients with cancer and nurses describe experiences of rapport and strategies for cultivating rapport in videoconferencing visits and (2) similarities and differences identified by patients with cancer and nurses between experiences of rapport in videoconferencing and in-person visits.

Methods

Overview of the Study Design

Nurses and patients will be interviewed separately to ensure that both can speak freely about their experiences and to facilitate understanding of the perspectives of both types of participants. Semistructured interviews will be conducted on Zoom (Zoom Video Communications), a secure videoconferencing platform. Narrative interviewing guidelines will be used, providing participants with the opportunity to describe their experiences before the researcher asks any probing questions. This approach aligns with our qualitative descriptive methodology by focusing on how participants describe their experience of rapport using everyday language to provide insight on videoconferencing [56]. As suggested by Sandelowski [56,57], a descriptive qualitative approach focuses on participants' descriptions of their experiences while limiting the interpretation of meaning to only what is directly reported by the participant. Unlike a phenomenological approach, which deeply explores a few homogenous participants' lived experiences, this study will include enough participants to comprehensively describe the experiences of nurse-patient rapport in the new context of videoconferencing in ambulatory oncology [56,57]. Qualitative descriptive research provides rich, in-depth descriptions of experiences that are not feasible with quantitative approaches [58]. This study aims to uncover patterns and themes concerning how rapport is experienced during videoconferencing visits to provide a foundation for the development of practice guidelines.

Participants and Setting

The study recruitment, consent process, and data collection will be conducted remotely because of COVID-19 restrictions. Stratified purposive sampling will be used to recruit participants from an academic ambulatory oncology center in the northeastern United States. Providers at this center have had recent experiences with videoconferencing visits to provide rich data about these encounters. Stratification will include the number of telehealth videoconferencing visits that patients and nurses have experienced. The literature suggests that the level of experience influences ease of use and perceptions of telehealth videoconferencing visits [4]. Patients will be stratified into 2 groups (ie, ≤2 and >2 videoconferencing visits). Nurses will be stratified into 2 groups (ie, 10-20 and >20 videoconferencing visits). Further stratification may be added to ensure that the sample is diverse, with various perspectives from participants of different ages, backgrounds, and experiences. Participants will be asked to share self-identified information, including age, gender identity, race, ethnicity, household income (patients), education, length of time receiving care (patients) or duration of employment (nurses) at the ambulatory care clinic, and the estimated number of telehealth videoconferencing calls that they have participated in as patient or nurse during the last 12 months. The exact size of the final sample will depend on data saturation in each of the 4 stratified groups and be large enough to capture the rich experiences of nurses and patients but small enough to permit a thorough analysis of the data [59]. Recruitment will end when no new themes related to the research questions are identified, indicating data saturation [60]. Participants who do not have access to technology and adequate broadband width to support videoconferencing will be excluded from the study. As this proposed study aims to analyze the experiences of individuals who have this technology and experience, future studies that will focus on patients with limited technology access are planned.

Inclusion and Exclusion Criteria

The inclusion criteria for patients are (1) adults (aged ≥18 years), (2) able to read and converse in English, (3) receiving care and undergoing active treatment at the identified oncology ambulatory care center, (4) have participated in at least one videoconferencing visit with a nurse from the identified oncology ambulatory care center within 3 months before the interview, and (5) enrollment in the oncology ambulatory care center's secure web-based platform with the necessary technology to conduct the videoconferencing interview. Patients with a medical diagnosis related to cognitive impairment (eg, Alzheimer disease or related dementias) will be excluded. The inclusion criteria for nurses are (1) licensed registered or advanced practice nurses employed at the oncology ambulatory care center for at least a year after orientation and (2) participation in videoconferencing visits with patients at the identified oncology ambulatory care center.

Ethical Considerations

The institutional review board (IRB) application for this study is currently under review. The Center for Research in Nursing and Patient Care Services within the cancer center supports the facilitation of this study. The applicant's university IRB will also review the proposal after it has been approved by the cancer center. Approval from both participating IRBs will be received before beginning the study. Written informed consent will be obtained from all participants before data collection.

The research methods, including qualitative interviews and asking for demographic information, involve minimal risk to participants. A study information sheet, which includes the study purpose and activities as well as the primary researcher's contact information, will be provided electronically to

participants. This will allow participants to contact the research team directly. This information will also be shared verbally during the consent process and included in the informed consent form. Participants will be informed that their participation is voluntary and can be stopped or rescheduled at any time. Participants will also be informed that they can withdraw from the study at any time without any impact on their care or employment. The researchers will maintain open and honest communication throughout the process and create an environment of trust and safety by answering all questions and allowing participants as much time as necessary. Patients will be allowed to include their informal caregivers in this process because the literature suggests that such inclusion may reduce the burden of the recruitment process for patients with cancer [61]. However, informal caregivers will not be interviewed and will be asked to allow the patient to answer all the interview questions independently.

Care will be taken to contextualize any data that could potentially threaten the confidentiality and privacy of participants. For example, exemplar quotations will simply refer to participants by number or pseudonym when presenting the results. Data collected from participants will be deidentified and used only for research purposes and associated dissemination. Participants will be assigned unique identification numbers that will be used on all data collection forms and data files (ie, interviews, transcripts, and demographic questionnaires). Electronic files, including the key for the unique identification numbers and corresponding participant names, will be stored on the researchers' computers on a secure password-protected hard drive or server with firewall protection and multifactor authentication. Any hard copies of transcripts or field notes will be stored in a double-locked location. Only members of the research team will have access to the electronic and printed files. Interviews will be conducted on Zoom, the institution-approved secure videoconferencing platform with approved data management and security features that allow secure recording and storage without recourse to third-party software. Zoom security measures include user-specific authentication, real-time encryption, and the ability to back up recordings to the aforementioned secure password-protected server.

Participation in this study offers no direct benefits to the nurses or patients who participate. However, participants may find it beneficial to discuss and reflect on their encounters and the nurse-patient relationship. They may also feel a sense of satisfaction from contributing to the advancement of knowledge and future practice implications attributed to the study. Nurses and patients will be invited to attend the presentation of the study results. Evidence demonstrates that both patients with cancer [61] and nurses [62] often gain a sense of fulfillment when participating in research.

Recruitment

Conducting interviews on the institution-approved platform will allow recruitment and data collection to proceed even as social distancing is maintained during the ongoing pandemic. Recruitment of participants will be carried out at the oncology clinics at the ambulatory care center where nursing videoconferencing is currently part of the care process. Nurses and patients will be recruited through a combination of efforts, including announcements at nursing staff meetings, postings on a web-based study recruitment message board, and the distribution of study brochures. Nurses will be recruited into the study first, and they will be invited to share the study information sheet with eligible patients. Interest in, and support for the study has been obtained from the cancer center's nursing leadership, who will foster opportunities for the research study to be presented to nursing staff. Nurses will self-identify and be asked to share the study brochures with patients who may be potential participants in the study. Information about the study in web-based research bulletins will also allow patients to self-identify. Participants interested in participating in the study will be screened and provided information on the study and informed consent by the researchers through telephone or email. A time for the interview will also be agreed upon. The written consent and demographic data collection will be carried out through Research Electronic Data Capture at the time of the interview. All patient and nurse interviews will be conducted on the institution-approved videoconferencing platform to ensure a secure encounter. Patients will be allowed to include their informal caregivers in this process because the literature suggests that this reduces the burden of the recruitment process for patients with cancer [61]. Although the concern for adding burden to patients with cancer is legitimate, evidence suggests that patients with cancer often find meaning in the disease process by participating in research [61,62]. No subjects will be excluded from the study based on age, self-reported gender identity, race, or ethnicity, except where necessary to meet the inclusion and exclusion criteria.

Data Collection Procedures

Individual nurses and patients will be interviewed separately. Interviews will be conducted on Zoom, the institution-approved platform, which is used by the ambulatory care center. Using the institution-approved platform will ensure that the participants are familiar with the technology and will also prompt memories of their experiences of rapport in videoconferencing encounters. Videoconferencing has been shown to be a feasible and acceptable vehicle for collecting qualitative data, with both researchers and participants reporting high levels of satisfaction [63], and a comparison of in-person interviews with videoconferencing interviews found little difference in the development of interviewer rapport [64]. Interviews will be audio recorded and transcribed to allow analysis of these text-based data. Data analysis will be ongoing and occur concurrently with data collection.

Interview guides for nurse and patient participants are under development by the research team to direct the semistructured interviews. Seminal research by Radwin [46] and Thorne [41] on the perceptions of patients with cancer of clinical care are guiding the development of the interview guide. The interviews will use a narrative format with 4 phases: initialization, main narrative, questioning, and closure [65]. During the initialization phase, participants will be asked to confirm their understanding that the interview is being recorded. The purpose of the interview will be described as, "This is an opportunity to share your experiences of having videoconferencing visits with your

oncology nurse." A grand tour question will be used to initiate the interview: "Please describe your thoughts and feelings about having visits with your oncology nurse via videoconferencing." Per narrative interviewing guidelines, participants will be given an opportunity to tell their complete story (main narrative phase) about their experiences before the interviewer asks any probing follow-up questions [65]. In the questioning phase of the interviews, participants will be asked to describe their experiences of rapport in nurse-patient interactions during both in-person and videoconferencing encounters. Follow-up questions will be used to probe more deeply after the initial responses to provide rich, detailed descriptions. For example, participants will be asked to reflect on how experiencing rapport in videoconferencing visits was similar to, or different from, their in-person experiences. In addition, a broad question will be used to explore whether the participants felt that strategies or contextual issues (ie, technology challenges, two-dimensional nature of the relationship, ability to detect facial features or body language, lack of touch or other sensory stimulation) may have affected their experience of rapport in videoconferencing visits either positively or negatively. Questions for nurses and patients, although similar, will be slightly modified, given their differing roles. Before concluding, the interviewer will ask participants if there is anything else that they want to share. The guide for patients can be found in Textbox 1.

Textbox 1. Patient interview guide.

Grand Question (Start Here): Please Describe Your Thoughts and Feelings About Having Videoconferencing Visits With Your Nurses

- Follow-up probing questions
  - How would you describe rapport?
  - How do you experience rapport with your nurse in a videoconferencing visit? For example, what does it look like and how does it feel? How does it feel and look when you do not have rapport with your nurse?
  - How do you go about developing rapport with your nurse in a videoconferencing visit?
  - How does the experience of rapport with your nurse in a videoconference visit compare with a traditional in-person encounter? What are the differences in your visits when videoconferencing is used? Is it easier to establish rapport in-person?
  - How does having a videoconference visit affect your ability to communicate with your nurse?
  - What factors do you think may be influencing or have an impact on your ability to build rapport with your nurse in videoconferencing visits?
  - Would you want to continue videoconferencing visits once the COVID-19 pandemic is controlled? Why or why not?
  - Is having rapport important to you and if so, why or why not?
  - Is there anything else you would like to share with me?

Data Management and Analysis

Overview

Conventional content analysis will be used to analyze the qualitative data collected in this study. This approach is useful in exploring areas where little is known and robust descriptive data are needed to better understand the research questions [66,67]. The purpose of this study is to understand how rapport is described and evolves within the context of this new clinical setting by focusing on manifest content rather than symbolic meaning (latent content). By focusing on manifest content, the analysis is firmly placed in the realm of content analysis rather than thematic analysis or other approaches, such as narrative, discourse, or semiotic analysis [67,68]. Codes will be derived directly from the transcribed text data, keeping the coding close to the participants' descriptions [56,67]. Nurse and patient interviews will be analyzed separately using identical procedures. The content analysis management process described by Elo and Kyngäs [66] will be used to organize the analysis process. This management process includes 3 phases: preparation, organization, and reporting.

Preparation Phase

With each interview representing the unit of analysis for this study, data preparation will include reading through each entire transcript while listening to the entire interview and noting important topics in the margin. The data preparation phase allows for immersion in the text data and for the researchers to become familiar with each case as a whole [66]. After reading each transcript, a summary analytic memo will be initiated to capture overall impressions, a holistic view of the interview, contextual information that might have influenced the interview, and any personal perceptions [69]. The data preparation phase will also make transparent any research team member beliefs or experiences elicited by the data that require bracketing [69].

Organizational Phase

The goal of the organizational phase is to label and condense the data into meaningful units, allowing patterns and relationships within the units to emerge. Initially, research team members will go line by line through the transcript, applying meaningful codes [67]. An inductive approach that allows the codes to emerge from the data will be used. Coding is often divided into 2 levels [69]. First-level coding methods assign codes to data units as they are read line by line again. There are many first-level coding methods, but based on this study's aim to capture the interpersonal experiences of nurses and patients who participate in videoconferencing visits, the coding method will likely involve both process and emotional coding [69]. Process coding captures interactions and outcomes, whereas emotional coding is useful for descriptions of intrapersonal and

interpersonal experiences [69]. In addition, codes using the participants' own words, also called in vivo coding, may provide rich labels that are authentic to participants' experiences [69]. To support the exploration of the data, team members will consider codes that answer questions (ie, what, who, how, when, where, why), capture actions (eg, watching, listening, advocating), and describe characteristics of the experience (eg, supportive, encouraging, warm, interested). This first-level coding approach is purposefully selected to represent the manifest content of the data rather than its symbolic meaning [69].

Second-level coding will explore relationships and patterns in the data, resulting in categories and themes [66]. This process will be intentionally iterative to keep the analysis as close as possible to the participants' accounts, encompassing the experiences of all the participants interviewed, with ideas emerging to either confirm data already analyzed or provide new data that need verification [56,70]. Analyses will include creating, defining, and recording codes, categories, and themes and matching the themes with exemplar quotations. After separate analyses of patient and nurse data have been completed, a comparison of the data will allow the exploration of similarities and differences. This analysis may result in additional themes for the final reporting phase [66].

Code names, definitions of codes, and exemplar quotes will be constructed in a codebook using the data analysis management tool NVivo 12.0 (QSR International Pty Ltd). During the initial weeks of the analysis, the authors will individually code the same cases and meet as a team to compare and define codes. Once all research team members agree on the coding of 20% of the transcripts, a codebook will be created to guide coding of the remaining transcripts. The team will continue to meet to discuss new codes and revise the codebook as needed. As the codebook evolves and agreement between team members becomes consistent, team members will code different cases. Bimonthly scheduled coding meetings will be used to discuss and clarify the coding of uncertain data segments. Suggested codebook revisions will always be discussed until an agreement is reached. Changes will be documented in analytical memos to ensure documentation of the process and clear, consistent data coding. Any revisions in codes will require revisiting the previous coding to ensure the integrity of the analysis.

Reporting Phase

The final phase of the analysis process is reporting. Exemplar quotes from the participants will be used as evidence of the findings [66,67]. As nurse and patient interviews will be analyzed separately, data reporting will reflect themes for each group separately but may be presented side by side to illustrate a comparative analysis. The findings will be evaluated within the context of related theories and evidence-based research [66,67]. A narrative of the final analysis will create a story of the data, adding insight and new knowledge [66,71].

Plan for Ensuring Rigor or Trustworthiness of Findings

The study's rigor, also described as trustworthiness in qualitative research [60,70], will be enhanced by (1) conducting all analyses as a research team (ie, a nursing doctoral student well versed in qualitative research and a nurse faculty researcher with 15 years of qualitative research experience), with weekly coding meetings to discuss and define all codes, categories, and themes; (2) collecting and analyzing the data concurrently, listening carefully while remaining open to the emergence of unexpected findings, and being willing to let go of poorly supported ideas [70]; (3) using detailed memos to create an audit trail of analytical decisions [60,72]; (4) confirming that the categories represent expansive and diverse experiences with exemplar quotations from multiple participants [60,73]; and (5) using member checking techniques by asking participants clarifying questions during the interviews [60]. The Consolidated Criteria for Reporting Qualitative Research checklist will be used to guide the reporting of the study results [74].

Risks for bias in general include the effects of the researcher on the participants; the effects of the participants on the researcher; and the researcher's own perspectives, experiences, assumptions, values, and beliefs. More specific risks for bias include the influence of COVID-19 as the context that increased the use of videoconferencing, level of experience of the participants with videoconferencing, and the use of nurses to help with recruitment. In qualitative research, the researcher is the instrument [60], and this is reflected in the strategies used to enhance the rigor and trustworthiness described previously. In large measure, rigor will be enhanced with reflexivity strategies that include ongoing memos with researcher self-reflections. This transparency will also enhance the research team's capacity to remain receptive to new emerging findings during the analysis process [60]. The interview guide, developed by the researchers, is based on a systematic review of the literature, and the narrative interview approach involves starting with a grand question that is designed to allow the participant's experience to guide the interview. In addition, stratified purposive samples will be used to ensure collection of data from participants who have multiple perspectives, and the nurses who assist in recruitment will be asked to offer the study information to all their patients who meet the study criteria. This will reduce the risk of nurses only telling a particular group of patients about the study (ie, patients with whom they share a good rapport). Finally, a presentation of the findings will be set within the context of the pandemic.

Results

Study Status

IRB approval will be obtained before beginning data collection. Data collection will begin during summer 2021, with analysis expected to be completed by winter 2021.

Anticipated Results

Few studies have focused exclusively on rapport building in videoconferencing [21]; however, rapport is often mentioned in research conducted on telehealth videoconferencing visits. These incidental findings provide some clues to our expected results. For example, studies often highlight how the visual component of videoconferencing makes relationship building easier compared with telephonic consultation [21,75-77]. Other studies suggest that adjustments to the background, camera

positioning, and volume, along with the increased use of verbal confirmations during the interaction, are useful [21,29,75,78]. Helping patients navigate technology with a positive attitude, including the use of in-person support to provide the caring touch and hands-on technical assistance, has been reported to enhance rapport [29,54,79,80].

Unique barriers to rapport in videoconferencing visits have also been reported as secondary findings, and they include uncertainty around patient privacy [9,12,21,79], loss of sensory input owing to the limited view of the peripheral space and full visualization of body language [14,54,81], loss of physical connectedness [21,29,79], and patients being left out in provider exchanges [82,83]. Finally, technology failures have been described as having a negative impact on rapport [29,81].

By focusing our exploration exclusively on patient-nurse rapport in oncology ambulatory videoconferencing visits, this study seeks to fully describe this experience from both nurse and patient perspectives. The study will also seek to understand the unique challenges, facilitators, and barriers to developing and experiencing rapport in these computer-mediated encounters. This investigation may validate some of the incidental findings from other studies or uncover new considerations.

Discussion

Study Significance

A strong and supportive nurse-patient relationship is especially important for persons with cancer. Looking at how the movement toward videoconferencing visits during the COVID-19 pandemic affects the nurse-patient relationship and the capacity to maintain high quality, supportive cancer care is essential, given the likelihood that telehealth videoconferencing visits will become an enduring component of cancer care. Although caring within the videoconferencing technological environment may require adapting our practices, it must not detract from the essential nature of nursing. One view of caring in a technological medium is described by Locsin and Purnell [19] in their theory, Technological Competency as Caring in Nursing. This midrange theory views technology as a complementary opportunity that can facilitate knowing and connection [19]. The nurse's technological competency is seen as another way of caring [19,84]. From this vantage point, videoconferencing visits can be a way to maintain human connectedness during the pandemic or even beyond. Technological Competency as Caring in Nursing describes the human connection and communication between the nurse and patient as a *cocreated moment* essential to protecting humanness and preventing patients from becoming objects of care in technological environments [19].

Conclusions

The pandemic makes this exploration of rapport in telehealth videoconferencing with nurses and patients timely. The rapid and successful use of videoconferencing visits, coupled with potential benefits to patients, providers, and health care systems, suggests that patient care using this technology will likely continue to be a significant component of oncology ambulatory care even after the pandemic has subsided [2,85-87]. This research will help determine what behaviors, communication techniques, and relational practices need to be adapted to advance effective nurse-patient rapport in oncology videoconferencing visits. This study will set the foundation for developing interventions and evidence-based practice guidelines for developing a nurse-patient therapeutic relationship during videoconferencing telehealth visits.

Authors' Contributions

PDK and JCDG designed the study protocol. PDK drafted the initial manuscript, and JCDG contributed to critical reviews and revisions of the manuscript. All authors approved the final manuscript and agreed to its publication.

Conflicts of Interest

None declared.

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Abbreviations

IRB: institutional review board

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Protocol

Directly Observed Therapy to Measure Adherence to Tuberculosis Medication in Observational Research: Protocol for a Prospective Cohort Study

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Abstract

Background: A major challenge for prospective, clinical tuberculosis (TB) research is accurately defining a metric for measuring medication adherence.

Objective: We aimed to design a method to capture directly observed therapy (DOT) via mobile health carried out by community workers. The program was created specifically to measure TB medication adherence for a prospective TB cohort in Western Cape Province, South Africa.

Methods: Community workers collect daily adherence data on mobile smartphones. Participant-level adherence, program-level adherence, and program function are systematically monitored to assess DOT program implementation. A data dashboard allows for regular visualization of indicators. Numerous design elements aim to prevent or limit data falsification and ensure study data integrity.

Results: The cohort study is ongoing and data collection is in progress. Enrollment began on May 16, 2017, and as of January 12, 2021, a total of 236 participants were enrolled. Adherence data will be used to analyze the study's primary aims and to investigate adherence as a primary outcome.

Conclusions: The DOT program includes a mobile health application for data collection as well as a monitoring framework and dashboard. This approach has potential to be adapted for other settings to improve the capture of medication adherence in clinical TB research.

Trial Registration: Clinicaltrials.gov NCT02840877; https://clinicaltrials.gov/ct2/show/NCT02840877

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KEYWORDS

tuberculosis; directly observed therapy; treatment adherence and compliance; medication adherence; mobile applications

Introduction

A major challenge for prospective clinical tuberculosis (TB) research is accurately defining a metric for measuring medication adherence [1,2]. Accurate measurement of adherence is imperative to correctly capture a medication's impact and guide best dosing, including the thresholds for missed doses and exposure impact on toxicity [3]. Inaccurate adherence characterization can lead to the misinterpretation of study findings, including those of drug efficacy [4]. From self-report to direct observation, researchers grapple with weighing cost and privacy with efficiency and accuracy when considering methods for adherence capture.

Medication adherence and preventing loss to follow-up in TB treatment are critical for individual favorable treatment outcomes, preventing recurrence, and stopping forward transmission [5]. Directly observed therapy (DOT) has been central to TB treatment programs since the World Health Organization (WHO) adopted the directly observed therapy, short-course (DOTS) strategy in 1994 [6]. Since the initiation of the 2015 End TB Strategy, the WHO has highlighted the potentially important role that digital solutions can play in supporting medication adherence [7]. The adherence technologies currently available on the market have been summarized elsewhere [8]. Although these approaches, such as electronic drug monitoring, have been widely trialed for HIV and have been increasingly implemented programmatically for TB, application in prospective TB research has been limited [9].

Electronic approaches to adherence monitoring are not without their challenges in the context of TB treatment. Recently, electronic drug monitoring has been studied for TB treatment adherence. 99DOTS, an adherence program launched in India in 2016, has shown mixed results [10-13]. Medication Event Monitoring Systems has also been associated with mixed reliability and efficacy [14-16], and video-observed therapy and wirelessly observed therapy [17,18] may face implementation challenges in low-resource settings. Another ongoing project in India, Operation ASHA, uses biometric fingerprint scanning at centralized TB treatment centers to confirm adherence, but preliminary qualitative results indicate positive adherence behavior change in only about half of patients [19]. Given the limitations of certain electronic adherence monitoring approaches (eg, Medication Event Monitoring Systems) and the cost and challenges of implementing strategies such as video-observed therapy in resource-constrained settings, we sought to combine the approaches of in-person adherence monitoring and electronic monitoring to facilitate accurate measurement of medication adherence in the research setting.

The Tuberculosis Treatment Outcomes and Alcohol Use Study (TRUST; R01AI119037) [20] is a prospective cohort study which aims to investigate the association between problem alcohol use and TB treatment response, controlling for medication adherence. A critical component of the study design is high-quality measurement of adherence in order to enable accurate measurement of the relationship between alcohol exposure and treatment response. Here we present the design and methodology of a mobile health (mHealth)–based DOT program developed for the purpose of measuring anti-TB medication adherence for TRUST participants.

Methods

Study Setting

The TRUST study recruits newly diagnosed TB patients receiving treatment at a primary health clinic in Worcester, the fourth largest city in South Africa's Western Cape Province. The subdistrict from which the study recruits from has one of the highest TB burdens in the region (2016 incidence rate of 933 per 100,000 population; D Theron, personal correspondence to K Jacobson, 2017) and concurrent high rates of alcohol use [21-23]. The standard of care for anti-TB medication adherence monitoring at the study clinic is a variant of DOT in which patients choose a family member or friend who commits to observing their daily dose and signing a small card as confirmation. Patients bring this card to their monthly follow-up visit to be reviewed by a clinic nurse and documented within the medical record. This approach is highly vulnerable to falsification and misreporting. To improve this, TRUST developed and implemented the following program.

TRUST DOT Program Overview

The TRUST DOT program operates fully independent of the clinic's TB program and current DOT activities. A team of professional community workers (DOT workers) is overseen by TRUST's dedicated DOT coordinator and community liaison. Our program's innovation is that DOT workers collect adherence data on smartphones, submitting forms for each of their assigned participants back to an encrypted central server each weekday (see details in Mobile Data Collection Application). DOT workers scan a unique quick response (QR) code affixed to the participant's medication box at each encounter to confirm being in the presence of the participant. The date, time, and GPS coordinates of the encounter are captured each time a form is submitted. A separate form is submitted at the beginning of each week to capture self-reported adherence for the preceding Saturday and Sunday.

DOT workers live within the study clinic's catchment area and are assigned participants who live in the same neighborhoods as themselves for ease of conducting daily visits. DOT workers are organized into "neighborhood groups," allowing for case sharing within each group through the mobile app. Participants are initiated on DOT within 1 week of starting TB treatment. At the initiation visit, the DOT coordinator and assigned DOT worker visit the home of the participant, register them to the system, and review participant expectations. The DOT worker then visits the participant every weekday until either treatment completion or end of study participation, whichever comes first.

Program Definitions

DOT workers observe dosing Monday through Friday (defined as "DOT days") with participants self-reporting their weekend adherence data. Routine adherence and program monitoring focuses on DOT days, with periodic data audits addressing weekends. Participants currently enrolled in the study and on treatment are considered active cases. Optimal adherence to

anti-TB medication is often cited as 90% [24]. This measure has been used in multiple studies to classify good or optimal adherence [25-28]. Informed by this threshold, we defined 3 adherence tiers to capture the degree to which the participant has diverged from optimal adherence (Table 1). DOT workers record both observed and self-reported adherence on DOT days. Observed adherence is defined as a DOT worker or other study team member (eg, study nurse) personally observing the participant take their medication. Self-reported adherence is defined as the participant reporting that they took their medication. A participant is classified as nonadherent on a day when they cannot be located or reached or if they report not taking their medication.

Additionally, we defined 3 participation tiers to describe the degree to which a participant is engaging with the DOT program. This is assessed by looking at the proportion of DOT days in which adherence was self-reported versus observed, with a higher proportion of days in which adherence was self-reported indicating diminishing participation in the study (Table 1).

Table 1. Directly observed therapy adherence tiers for program participation monitoring.

Tiers	Green	Yellow	Red
Adherence tiers	Adherent on ≥90% of DOT[a] days	Adherent on 75%-89% of DOT days	Adherent on <75% of DOT days
Participation tiers	Reported adherence on <20% of DOT days	Reported adherence on 20%-39% of DOT days	Reported adherence on ≥40% of DOT days

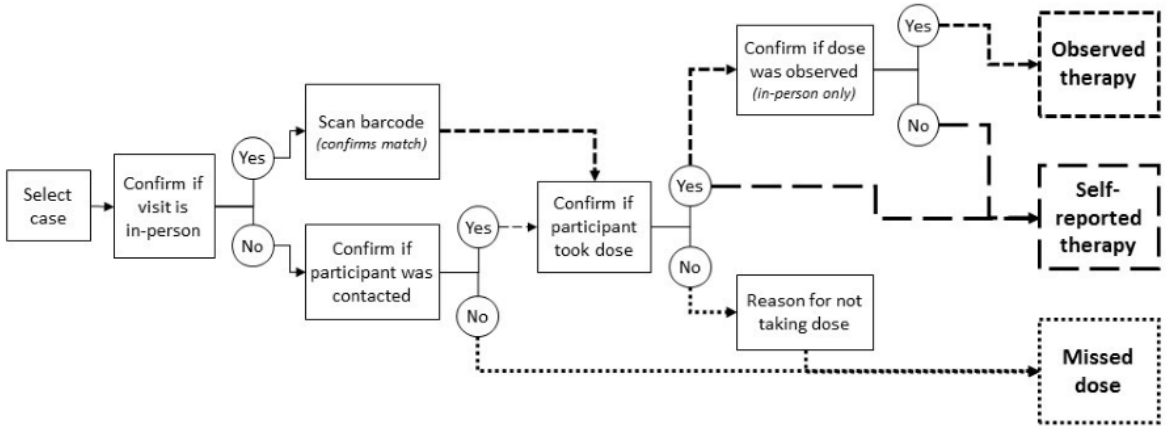
[a]DOT: directly observed therapy.

Mobile Data Collection App

Daily DOT data are collected and submitted on basic smartphones carried by each DOT worker. The TRUST DOT data collection app was built using CommCare, an open source mHealth platform for electronic data collection and case management [29] and is outlined in Multimedia Appendix 1. DOT workers log in and submit data through unique user accounts. Every DOT worker in a given neighborhood group can access all active cases registered within that group through their active case list. The DOT coordinator and each study staff member can access all active cases across all neighborhood groups from their own user account.

The app structure is described in Figure 1. When conducting a daily visit, DOT workers confirm that they are with the participant by using the app to scan a unique QR code that study staff affix to the participant's medication box. A new QR code sticker is affixed to each box of medication dispensed by the TB program at monthly clinic visits. The app cross-checks the scanned QR code against the QR code registered for the given participant in the system and only proceeds if a match is confirmed. The DOT worker then indicates whether the participant took their medication and whether the dose-taking was observed (ie, the DOT worker may meet with a participant in-person, but the participant could have taken their dose before the DOT worker arrived). The DOT worker may proceed through the app without scanning a QR code, but observed adherence is not considered validated unless a QR code has been scanned. Alternatively, the DOT worker may select that they were not with the participant and then indicate whether they received an indirect report that the participant took their medication.

Figure 1. Flow diagram of data collection app for directly observed therapy days (Monday through Friday). Small dashed lines denote pathways to observed therapy. Large dashed lines denote pathways to self-reported therapy. Dotted lines denote pathways to a missed dose classification.



Adherence and Program Monitoring Indicators

For purposes of systematically monitoring the DOT program, we defined indicators to assess both individual participant-level adherence as well as program-level adherence and program function (Textbox 1).

Textbox 1. Indicators for the directly observed therapy program and participant performance and engagement.

Participant-level adherence monitoring indicators

1. What adherence tier does the participant fall into?
2. What participation tier does the participant fall into?
3. Has the participant been nonadherent on 2 or more days of their last 5 directly observed therapy (DOT) days?
4. Has the participant had no observed therapy for 2 or more of their last 5 DOT days?

Program-level monitoring indicators

1. What proportion of participants fall into each adherence tier?
2. What proportion of participants fall into each participation tier?
3. What proportion of DOT workers observed therapy for ≥80%, 60%-79%, and <60% of their participants in the last 5 DOT days?
4. What proportion of each DOT worker's participants have observed therapy for ≥90%, 75%-89%, and <75% of the DOT days?

Individual Participant-Level Indicators

Participant-level adherence indicators assess both recent and cumulative trends in adherence and DOT program participation for each study participant. Suboptimal adherence (whether recent or cumulative) or an increase in self-reported adherence alert study staff to a participant's decreased engagement and potential risk of missing further doses and subsequent loss to follow-up. When assessing recent adherence, we look at DOT days as continuous from Monday to Friday.

Program-Level Indicators

We also developed indicators to examine program-level trends. At the program level, we assess the proportion of participants falling into each adherence and participation tier. At the DOT worker level, we assess adherence trends of all participants assigned to a given DOT worker and compare trends across DOT workers. Variability across DOT workers alerts study staff to potential issues in worker performance. Trends across all study participants alert staff to program functionality or adherence trends across the study population.

Data Monitoring and Visualization

We created a dashboard in Microsoft Excel (Microsoft Corporation) to display data against participant- and program-level indicators and which is provided in Multimedia Appendix 2. The study's data dashboard is linked to the CommCare server and, when opened while connected to internet, actively pulls and updates all data submitted up until the day prior. Reflective of the aforementioned monitoring indicators, the dashboard is organized into 2 tabs: (1) participant monitoring and (2) DOT worker monitoring. Both tabs are filterable by date.

Participant Monitoring Tab

In the participant monitoring tab, data for active cases are aggregated and displayed at the participant-level. Participants are selected based on their unique study ID and registered case name from a scrolling list. For each participant, adherence information from the last 7 consecutive DOT days is displayed in a table along with cumulative adherence and cumulative percent of adherence observed. Multiple sorting buttons allow the user to subset the list of those participants with a cumulative adherence ≤75%, those with a cumulative self-reported adherence on ≥40% of DOT days, those who missed 2 or more of their last 5 DOT days, and those who had no observed therapy for 2 or more of their last 5 DOT days.

DOT Worker Monitoring Tab

In the DOT worker monitoring tab, data are aggregated by worker. A table displays the number and proportion of participants in each adherence tier by DOT worker. When a cell displaying a given adherence tier for a specific DOT worker is selected, all participants that fall into that cell are displayed within a scrolling menu. When a participant is selected from this menu, their adherence for the last 7 consecutive DOT days is displayed in a table.

Program Implementation

Before implementation, DOT workers undergo hands-on training on using the mobile app, engaging with participants, and conducting good clinical practice. DOT workers are trained to remain impartial to whether or not a participant takes their medication and are instructed to focus on encouraging the participant to meet and communicate with them in person, regardless of adherence. Follow-up on suboptimal adherence is the responsibility of the study's DOT coordinator and the clinic. As per agreement with the clinic, information on participant adherence is reported back to the clinic nurses who decide the appropriate course of action. The study's goal is to collect adherence accurately, not to change or improve medication adherence patterns.

At the initial study visit, the study nurse schedules a DOT initiation visit for each participant within 1 week of their enrollment. The study nurse places a unique QR code on the participant's pillbox that has the participant's unique study ID embedded within it. This is scanned by the DOT worker at each DOT visit to confirm they are with the participant. Participant details and the scheduled DOT initiation date are communicated to the DOT coordinator, who assigns a DOT worker to the participant based on where the participant lives and the current caseloads of the DOT workers.

At the DOT initiation visit, the DOT coordinator meets the assigned DOT worker at a location agreed upon with the participant, typically the participant's home. At this time, the

DOT coordinator goes over the expectations of the participant and the DOT worker together. A routine time and place for DOT is scheduled, and the participant is registered as an active case on the DOT worker's phone.

As mentioned previously, DOT workers are each assigned to 1 of 3 neighborhood groups. DOT workers communicate regularly with one another and the DOT coordinator so that should one worker be unavailable, cases can easily be reassigned to ensure visits are not missed. For instance, if a participant needs to be admitted to the hospital, the DOT coordinator can submit forms for all active cases across all neighborhood groups.

DOT workers are required to submit 1 form per participant per weekday. If they are unable to meet or contact a particular participant on a given day, they submit a form indicating so and the participant is categorized as nonadherent on that day. No weekday adherence data are submitted retrospectively.

When a participant completes treatment or ends study participation, whichever comes first, DOT visits end and the DOT coordinator closes the participant's case through the app.

Preventing Data Fabrication

Data fabrication is a risk faced by all field research; we implement numerous measures to prevent this. First, reporting observed adherence requires the DOT worker to scan a QR code on the participant's pillbox, which stays in the possession of the participant. Second, the phone's GPS coordinates are automatically recorded by the app each time a form is submitted. Although the exact location of DOT visits may vary, trends and outliers may indicate falsification of data. If there is concern that a DOT worker may be fabricating data, these GPS coordinates can be cross-referenced against where the DOT worker is expected to be at the time of a DOT visit. Third, routine and regular monitoring of submitted data through the dashboard and through larger data audits allows for identification of trends of nonadherence and trends of perfection, which when clustered with a specific DOT worker and inconsistent with the programwide trends, may indicate falsified data.

DOT workers attend a weekly meeting with the study DOT coordinator, where they discuss challenges and receive feedback based on data submitted. Ongoing refresher trainings are conducted at these regular meetings. Finally, the DOT coordinator conducts regular scheduled and unscheduled observations of DOT workers during their daily visits.

Ethical Considerations

This project is approved by the Boston University/Boston Medical Center Institutional Review Board (protocol no. H-34970; approved March 17, 2016) and the ethics committees of the South African Medical Research Council (protocol no. EC011-5/2016, approved July 5, 2016), Stellenbosch University (protocol no. SU-BEE17-0001; approved May 5, 2017), and University of Cape Town (protocol no, 497/2016; approved July 13, 2016). The study is also approved by the South African Western Cape Department of Health.

Results

Recruitment and Enrollment

The study began recruitment on May 16, 2017, and recruitment is ongoing. As of January 12, 2021, a total of 236 TB patients have been enrolled into the TRUST cohort. Of these participants enrolled, 206 remained enrolled in the study throughout the duration of TB treatment. A total of 21 were not followed up through treatment completion due to withdrawal from the study (n=7, 33.3%), moving out of the study catchment area (n=5, 23.8%), treatment failure (n=1, 4.8%), death (n=2, 9.5%), or unspecified reasons (n=5, 28.6%). A total of 20,789 forms recording medication adherence have been submitted via the mobile app.

Planned Analyses

Following the closing of enrollment and conclusion of participant follow-up, investigators will perform primary analyses to model predictors of time to mycobacterial culture positivity—a marker of treatment response—and treatment outcomes, while controlling for adherence. Additional secondary analyses with adherence as the primary outcome will be performed to assess the performance of this DOT program and patterns of adherence and to better understand TB treatment adherence overall. Details on the assessment of the study endpoints are described further in the published study protocol [20].

Discussion

We describe an mHealth-based DOT program to collect anti-TB medication adherence information in the context of a prospective cohort study. Accurate measurement of medication adherence as part of prospective clinical research is paramount to successfully conducting quality research on mechanism and effect. Due to inaccurate and nonstandardized measurements in clinical research, we do not know the accurate impact of TB medication adherence on treatment response. With poor capture, adherence remains an unmeasured potential confounder of other factors associated with poor outcomes. As mHealth interventions gain popularity for improving TB outcomes, an improved knowledge of TB medication adherence and a gold standard method to capture adherence data are needed to assess these interventions [7,30].

We recognize a limitation of our approach is the reliance on self-reported adherence for weekends. Binge drinking, particularly on weekends, is the main pattern of alcohol consumption within our study population [23]. Adherence on weekends during heavy drinking episodes may be lower and therefore vulnerable to the weaknesses of self-reporting. Another limitation is considering a missed day as a missed dose. Because participants remain in possession of their medication, they may take their medication on days when a DOT worker is unable to connect with them, including on holidays when our DOT workers do not work, or during periods of community violence or disruption, leading to underestimation. Additionally, while the scanning of a QR code confirms colocation of the study participant and DOT worker, it does not ultimately confirm that

the medication was swallowed. This is a limitation that strategies such as video-observed therapy attempt to overcome. It is important to note that the DOT workers employed by this study are in no way incentivized by their assigned participants' adherence and are instead encouraged to record accurately whether a dose was taken or not: the intervention for nonadherent patients is the responsibility of the study nurses, not the DOT workers. Scalability of this outlined program would depend on the resources available to a given project and the geographical catchment area of a given study.

We present a model for how to leverage mHealth technology to maximize efficiency and validity of community-based DOT in prospective clinical TB research. Additionally, real-time adherence and engagement monitoring may empower study teams to act swiftly to prevent disengagement or loss from care and potential treatment failure due to medication nonadherence. The details in this approach have the potential to be adapted for other prospective TB research studies in order to improve capture of medication adherence outside of a hospitalized setting.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Outline of the CommCare directly observed therapy mobile phone app.
[DOCX File , 18 KB - resprot_v10i6e24510_app1.docx]

Multimedia Appendix 2
Microsoft Excel directly observed therapy data dashboard.
[ZIP File (Zip Archive), 311 KB - resprot_v10i6e24510_app2.zip]

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Abbreviations

DOT: directly observed therapy
DOTS: directly observed therapy, short-course

mHealth: mobile health
QR: quick response
TB: tuberculosis
TRUST: Tuberculosis Treatment Outcomes and Alcohol Use Study
WHO: World Health Organization

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Protocol

Engaging Sexual and Gender Minority Youth in HIV Interventions Through Gay Dating Apps: Recruitment Protocol

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Abstract

Background: HIV continues to disproportionately impact sexual and gender minority youth (SGMY) in the United States. Public health efforts have increasingly focused on developing efficacious interventions to curb the spread of HIV among SGMY and help those living with HIV achieve and sustain viral suppression. However, recruiting and engaging SGMY in prevention and care interventions is challenging.

Objective: During the past decade, gay dating apps have quickly emerged as popular web-based spaces in which SGMY congregate. Although the recruitment of SGMY through these apps has been commonly reported, advertisement is the typical modality used, and direct recruitment approaches are not adequately described. This study aims to describe the process for developing a direct recruitment protocol for use in gay dating apps.

Methods: The Adolescent Medicine Trials Network Comprehensive Adolescent Research and Engagement Studies is a community-based research program consisting of 3 interrelated studies testing scalable behavioral interventions to improve HIV prevention and care engagement among youth aged 12-24 years in Los Angeles and New Orleans. To supplement our in-person recruitment approaches for Comprehensive Adolescent Research and Engagement Studies, the New Orleans site formed a gay dating app recruitment team. In April 2018, the team developed a loosely structured protocol that included study-specific profiles and sample language to guide initial recruitment efforts. Two self-identified Black, gay cisgender male field recruiters field-tested the protocol on the popular gay dating app Jack'd. During the field test, the recruitment team met weekly to discuss the recruiters' experiences and user reactions. For example, we learned the importance of addressing concerns about study legitimacy and identifying appropriate ways to describe the study. We iteratively incorporated these lessons learned into the final protocol and developed a training program and tracking procedures before moving to full-scale implementation at both sites.

Results: Adhering to this protocol yielded 162 enrollments in New Orleans (332 total enrollments across the two sites) throughout the recruitment period (April 2018 to August 2019). Most of these participants were sexual minority cisgender males (91%), and

the remainder were identified as members of gender minority groups. We outlined step-by-step instructions on training staff, engaging users, and scheduling and tracking recruitment activities.

Conclusions: This paper provides a practical guide for researchers and community-based providers to implement a gay dating app recruitment protocol. Our experience indicates that gay dating app recruitment is feasible and fruitful when the staff members are knowledgeable, flexible, honest, and respectful to the user. Perhaps the most salient lesson we learned in approaching gay dating app users is the importance of setting clear and transparent intentions without judgment. As gay dating apps continue to increase in popularity, researchers need to stay vigilant to changing formats and develop systematic approaches to harness their potential as invaluable recruitment strategies for SGMY.

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KEYWORDS

HIV/AIDS; adolescents; recruitment; dating apps; msm; mHealth; gender; gay; behavior interventions; mobile phone

Introduction

In the United States, sexual (ie, gay, bisexual, nonheterosexual identity, attraction, and behavior) and gender (ie, transgender, gender nonbinary, and gender identity incongruent with the sex assigned at birth) minority youth (SGMY), particularly youth of color, continue to be disproportionately affected by HIV. In 2018, 92% of all new HIV cases among youths aged 13-24 years were sexual minority cisgender males [1]. Although HIV data on gender minority youth are limited, young transgender women have been heavily impacted and have a high HIV prevalence [2]. For instance, current estimates suggest that 44% of Black or African American, 26% of Latina, and 7% of White transgender women live with HIV [3]. It is not surprising that public health efforts have increasingly focused on developing efficacious interventions to curb the spread of HIV among SGMY and help those living with HIV achieve and sustain viral suppression.

However, recruiting and engaging SGMY in prevention and care interventions has been challenging. It has long been accepted that one of the most effective recruitment approaches is meeting participants where they congregate. In the late 90s and the early 2000s, community venues such as clubs and bars were fruitful places for recruiting SGMY. This era also saw the advent of the internet as an increasingly popular social space, in which a number of studies leveraged internet chatrooms to recruit members of sexual minority groups [4,5]. Owing to their widespread use as dating and socializing sites, geolocation social networking (GSN) apps, such as Grindr, Jack'd, Scruff, and other social networking platforms are rapidly becoming the dominant recruitment venues for SGMY. The location features of these apps allow users to connect with other users from a broad geographic area and identify those nearby and easily accessible for dates or casual sexual encounters. By identifying users in close proximity to research staff, the geolocation features of these apps can also be harnessed to facilitate targeted SGMY recruitment efforts.

During the past decade, researchers have utilized GSN apps in a variety of ways to recruit sexual and gender minority participants for HIV research. Many studies have relied on passive methods, such as advertising banners and popup ads or posting a study-specific profile with contact information [5-13]. Others have used more active approaches to engaging with GSN users for study recruitment by having research staff create profiles and initiate conversations with users [14-17]. However, we could not find a single study that adequately described the actual procedures or steps used to recruit participants directly. Given the relative success and increasing utility of GSN recruitment, researchers should provide a clear step-by-step description of their recruitment processes and suggestions for overcoming obstacles inherent in using these apps for recruitment purposes.

In this paper, we describe our process for developing a direct recruitment protocol for use in gay dating apps that we implemented for a cooperative program project called Comprehensive Adolescent Research and Engagement Studies (CARES), which is one of 3 program projects and a coordinating center that comprises the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN; ClinicalTrials.gov NCT03134833) [18].

Methods

Study Description

CARES is a community-based research program consisting of 3 interrelated studies (ATN 147, ATN 148, and ATN 149) testing scalable behavioral interventions to improve HIV prevention and care engagement among youth aged 12-24 years in Los Angeles and New Orleans [19]. Although we initially developed the protocol outlined in this manuscript to recruit youth at risk for HIV into ATN 149 in New Orleans, it was later integrated into recruitment efforts in Los Angeles [20].

We recruited 1494 youths for ATN 149 from May 2017 to August 2019, of whom 1052 were SGMY. Eligible youth had to (1) be between 12 and 24 years of age, (2) test HIV seronegative on a fourth-generation Alere test, and (3) be at risk of acquiring HIV as determined by their responses on a brief behavioral risk factor screener. After providing written informed consent, participants completed a baseline behavioral assessment, were tested for HIV and sexually transmitted infections, and randomized to one of four technology-based interventions of varying intensity. Participants completed a behavioral assessment and were tested for HIV and sexually transmitted infections at 4-month intervals for 2 years.

Venue-Based Recruitment Strategies

For the first year of the study, we used traditional venue-based recruitment directly approaching youth at youth-focused community venues and agencies and popular community events. Other methods we used included distributing palm cards, posting study flyers at targeted venues, agencies, and events, and obtaining referrals from providers and study participants. These efforts, though successful in identifying a number of youth who reported multiple HIV risk behaviors, did not yield sufficient numbers of SGMY to meet recruitment targets.

To bolster SGMY enrollment, we targeted Pride events, college Gender and Sexuality Alliance activities, Parents and Friends of Lesbians and Gays meetings, bars and clubs popular among SGMY, and events hosted by other SGMY-serving organizations. We encouraged referrals by incentivizing SGMY participants for each successfully enrolled referral from within their networks. Cognizant that these approaches were only reaching youth willing to engage in community events and frequent popular venues, we decided to recruit SGMY through social networking sites, particularly gay dating apps.

Gay Dating App Recruitment Protocol Development

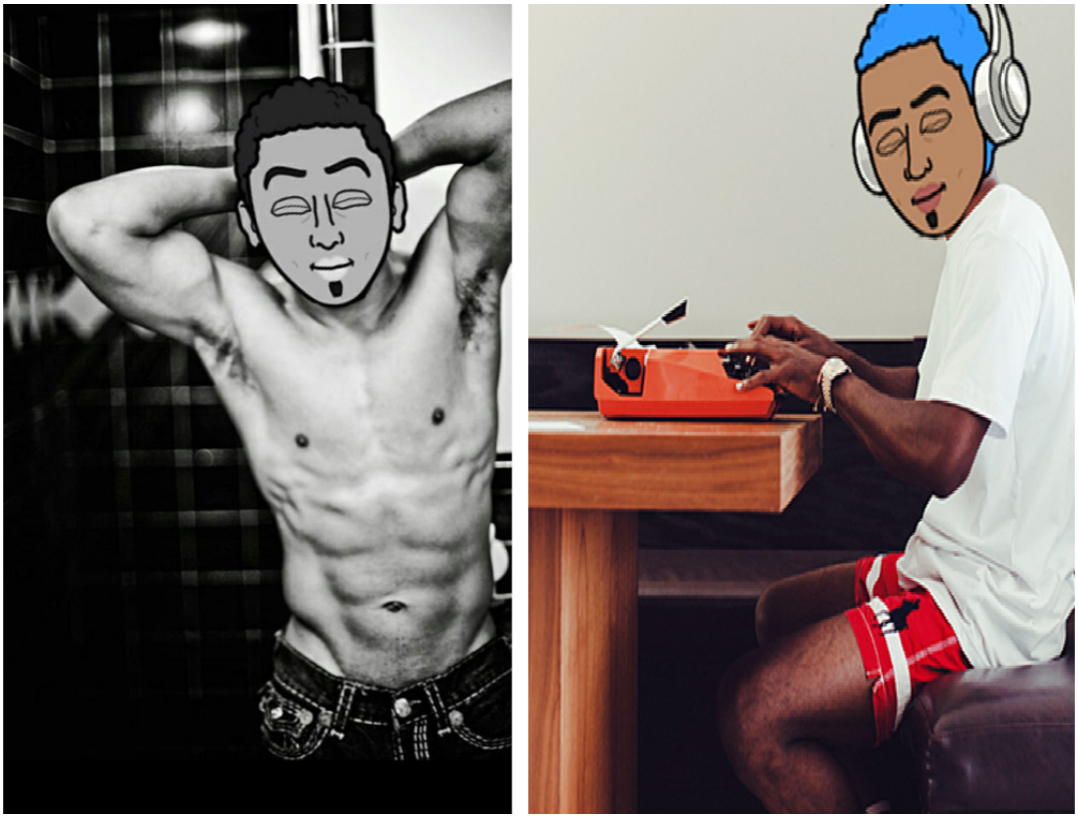
Initial Field Test

In April 2018**,** we formed a social media recruitment team in New Orleans comprising the project director, a Latinx gay cisgender male, and 2 self-identified Black, gay cisgender male field recruiters. The team decided to first target Jack'd, a social networking smartphone app that uses geospatial technology to connect users based on geographic location, because it is one of the most popular gay dating apps among Black or African American sexual minority cisgender males in the South [21]. The team developed a loosely structured protocol that included study-specific profiles and sample language to guide the initial recruitment efforts and met weekly to discuss experiences and iteratively modify the protocol as needed. To determine the most productive recruitment periods, the team developed weekly schedules that varied by time of day and day of the week and monitored the yield. We adjusted the recruiters' schedule to accommodate recruitment during *nontraditional* work hours, especially during evenings and weekends. Once we gained experience recruiting via Jack'd, we followed the same procedures to recruit other social networking apps, including Scruff and Grindr, with similar results. We tried recruiting Adam4Adam but were immediately blocked from using the app. The initial field test lasted 6 weeks, and we kept a series of ongoing notes and memos describing the process, recruiters' experiences, and user reactions.

Profiles

Recruiters created their own study-specific profiles for use in apps. The characteristics of each profile reflected those common among app users. For example, we described ourselves as 20 or 21 years old; Black or African American man; versatile; and *looking for friends*, *networking*, *fun*, and other descriptors found in user profiles. Sample photos are illustrated in Figure 1. One profile used a bitmoji character superimposed on a photo of a field recruiter. This character, called *Nolan*, became our unofficial mascot that was created in response to the popularity of bitmojis. The other profile used a stock photo of a cisgender male who was described as attractive by the team.

Figure 1. Sample profile photos.



Sample Language

We provided recruiters with scripted language to assist in initiating and maintaining conversations with users. Recruiters were encouraged to adapt the language as needed and share adaptations during our weekly meetings. Recruiters also kept ongoing records of the adaptations and user responses that we used to iteratively modify the suggested language, as shown in Textbox 1.

Textbox 1. Scripted language for conversations.

Introductions and Rapport Building

- Hey wassup, I'm <NAME>. How are you doing tonight/today?
- What's your name?
- It's nice to meet you.
- Where are you from? I'm from <PLACE>.

More Information About Participation

- I work at [BLANK] for a community health program. We offer services to improve the sexual health of young guys under 24. Let me know if you're interested and I can tell you more about it.
- I work for a health program at [BLANK] that is trying to help young guys under 24 to improve their sexual health. Your participation could be really helpful in finding ways to improve the health of our community. If you want to learn more, here is our website [INSERT LINK].
- It's pretty simple. All you'd have to do is come in to get tested for sexually transmitted infections [& HIV] and answer a short survey about once every 4 months. You also learn about how to have fun, safe sex. You get paid every time you come in.
- The program goes on for 2 years and by the end of it, you stand to get a total of $350 over the whole program. We also offer free testing for HIV, syphilis, gonorrhea and chlamydia.

Inappropriate Messages or Sexual Advances

- I understand this app is used to hook up, which is OK. My goal is to connect you to information on our study and how to be involved. Click here for more info: [INSERT LINK].
- Have you read my bio? I'm on here to promote a study offering HIV & sexually transmitted infections testing. Is that something you would be interested in learning about?

Lessons From the Initial Field Test

After completing the initial field test, the entire New Orleans CARES team met weekly to review the findings, discuss recruiters' experiences, and make further revisions to the protocol. In this section, we summarize the main challenges faced during the initial field test.

Repeated Interactions

When approached, some users said that they had previously been contacted by our recruiters, leading some to discontinue the conversations abruptly. Other users blocked our profiles because they had already been *hit up*. In reviewing these interactions, we realized that because our recruiters lived within 5 miles of each other, there was overlap in the users they could approach within their geospatial recruitment area. Although this is an artifact of GSN apps, it resulted in recruiters approaching the same users. We brainstormed strategies to minimize this possibility but quickly realized that documenting all of the recruiters' user interactions would be a formidable, labor-intensive task for a number of reasons. First, users can change various aspects of their profiles (photos and text descriptions), making it difficult to track each user. Recruiters noted that this happened often. Second, the added effort necessary to document information on every user with whom the recruiters interacted would be time-consuming. We determined that the most viable approach when this occurred was to apologize and thank the user for their time.

Finding the Right Moment to Introduce the Study

We compared two approaches—stating intent upfront versus building rapport through casual conversations before introducing the study. Neither was perfect. At times, upfront intent leads to unresponsive users. When using the second approach, some users felt deceived or *catfished* given the time and *build-up* to mention the study. We opted to introduce the study as early as possible in the conversation to minimize perceptions of deceit.

Being Respectful and Following Users' Wishes

We attribute part of our success in not being blocked from using the apps to our recruiters' respectful tone, adherence to the wishes of the users, and understanding of the requirements of the app. For instance, recruiters did not send an excessive number of messages to multiple users within a given day. When a recruiter was *ghosted* (ie, abruptly discontinued a conversation), we did not immediately try to reconnect.

Inappropriate Messages or Sexual Advances

Given the nature of Jack'd, our recruiters were often contacted with sexually explicit photos or unwarranted sexual advances. Although we had anticipated and role-played some possible responses, some user reactions were unanticipated. For instance, a user asked our recruiter if, in addition to working on the study, they were also looking to *hook up*. When our recruiter responded, *only working!* the user was offended, said they felt judged, and blocked our profile. Reflecting upon the interaction, we concluded that the user might have perceived judgment from

the use of an exclamation point. This heightens the importance of being mindful of subtle cues that users could misinterpret.

Establishing Legitimacy

One of our biggest challenges was convincing users that our recruiters were legitimate New Orleans' CARES representatives. Although recruiters used scripted language to describe the study and sent a link to the ATN CARES website [22], some users remained skeptical and asked pointed questions without agreeing to be screened. Others discontinued the conversation but did not usually block our profile. This was surprising given that our website described CARES, linked to our Instagram account, and included information on community events we hosted and a contact form for additional information. To address these concerns, we made repeated attempts to revise the scripted language, which proved to be somewhat effective, and recruiters even sent pictures of their university ID and a team photo. We added an *Our Team* page to the website that included photos and bios from the team. Although these modifications were helpful, in rare instances, we continued to encounter users who questioned the study's legitimacy.

Importance of Alternating Recruitment Periods

Throughout the initial field test, we varied the duration (2-5 h), day of the week, and time of each recruitment (5 PM to 2 AM) period. As anticipated, recruitment during *regular* workdays (9 AM to 5 PM) was not productive. The most fruitful recruitment periods, those that yielded the highest volume of engaging conversations with potential participants, spanned from Thursday evening through Sunday afternoon.

Scheduling Appointments

There was variation in the ease with which recruiters were successful in scheduling appointments. Recruiters urged interested users to schedule their screening and enrollment appointments as proximal to the time they were first engaged as possible. On rare and fortuitous occasions, users would ask to come in immediately, which we accommodated if feasible. However, it was more common for recruiters to communicate with users multiple days before securing an appointment. Many of these conversations would occur sporadically for multiple weeks or months before the users would commit to scheduling an enrollment visit. As recruiters often had dozens of conversations each week, we requested permission to *favorite* these users so we could easily reinitiate conversations rather than scrolling through the apps' message log to find the user.

Other Considerations

Although a number of participants would provide their phone numbers to coordinate travel for their enrollment appointments, many would stay connected to the app until they walked through the door. The popularity of *Nolan*, our bitmoji profile photo, was noteworthy. Some potential participants asked for *Nolan* at their initial appointment, although they had been given the recruiter's actual name.

Brainstorming in Real Time

As we could not anticipate all possible scenarios, recruiters would engage the project director and each other in real time when they faced *roadblocks* and were unsure how to respond, such as when users would make sexual advances or challenge the study's legitimacy. Real-time brainstorming allowed recruiters to maintain user engagement and address their concerns seamlessly. It also improved recruiters' abilities and skills in executing the protocol.

Protocol Refinement

When the initial field test was completed, we reviewed the field notes, discussed the recruiters' experiences and user reactions, and used them to refine and finalize the protocol described in the *Results* section. We also developed a training program and tracking procedures before moving to full-scale implementation.

Results

Overview

In this section, we provide step-by-step instructions to guide researchers and community-based providers in implementing the gay dating app protocol we developed. Adhering to this protocol yielded 162 enrollments in New Orleans (332 total enrollments across the two sites) throughout the recruitment period (April 2018 to August 2019). Most of these participants were sexual minority cisgender males (91%), and the remainder were identified as members of gender minority groups.

Step 1: Select Gay Dating Apps Popular With the Target Population

As the popularity of gay dating apps varies by region and target population, it is critical to identify the most popular apps used by the target population in the selected areas. With the aid of a community advisory board, key stakeholders, scientific literature, and research staff who are members of the target population, we developed a list of apps and cross-referenced the data to identify the most popular apps. Jack'd emerged as the most popular, and, with time, we expanded to other popular apps (Grindr and Scruff). Before making the final selections of apps, it is important to conduct an initial review of the terms of access and use governing each app to ensure that the research procedures align with the terms and conditions of the app. As the terms of use may change, it is a good idea to monitor the terms and conditions regularly. We recommend purchasing premium accounts rather than using the free version of the apps because the premium versions have expanded capabilities that maximize efficiency in recruitment, such as unlimited messaging and filtered searches (age, race or ethnicity, location, online or offline status, and HIV status). On the basis of our experience, our advice is to recruit on multiple apps, if possible. Not only does this allow different recruiters to target the same geographic area, but it also reduces the chances that recruiters approach the same user on the same day on the same app.

Step 2: Train Staff

There are a number of concepts and skills that the staff members need to master to become effective recruiters on gay dating apps. In addition to having a solid command of the research protocol, including appointment scheduling and sample language, the staff members need to understand the guiding principles for effective interactions on the web and be proficient in using the lingo, symbols, and rapid exchanges typical of the

medium. Furthermore, they must be cognizant, sensitive, and understanding of the sociocultural and contextual issues of the target population. Thus, the training program should incorporate didactic sessions, group discussions, modeling, and practice with coaching and feedback. A typical training period spans between 2 and 4 weeks, depending on the skill and experience of the staff. During the first few days of training, we focused on content and processes such as mastering the protocol, learning the lingo (eg, bareback and pnp), and gaining a deeper understanding of the target population. For the rest of the training period, we shifted toward skill acquisition and refinement through real-time observations and practice with coaching and feedback.

Although there are different approaches for gaining the requisite skills, after staff had mastered content and process, we paired an experienced social media recruiter with a trainee under the supervision of the project director. Initially, the trainee watched, took notes, and asked questions during recruitment events as the experienced recruiter engaged users in real time on the app. The trainees then engaged users on the apps with the guidance and supervision of the experienced recruiter. The team met regularly to discuss trainees' progress, identify issues, and resolve emerging challenges. This process continued until the project director determined that the trainee had achieved competence in recruiting on their own. Our experience dictates that effective social media recruiters are not required to be members of sexual or gender minority groups but must be engaging, respectful, and willing to master the intricacies of the medium.

Step 3: Create User Profile

Our young sexual minority cisgender recruiters were front and center in designing profiles that would appeal to potential participants. They were asked to create profiles with eye-catching photos and text descriptions that were easy to read and transparent in describing who we were and our intentions. These recruiters then met with the project director to discuss the profiles together and make refinements before initiating recruitment with the profile.

Step 4: Develop and Manage Recruitment Efforts

To leverage the geospatial capabilities of the dating apps to recruit youth at the highest risk, we initially targeted zip codes with the highest HIV incidence among our target population and worked our way down to zip codes with fewer cases when the potential pool of users in an area was saturated. This was possible because the premium functionality of the apps allowed for searches at the zip code level and/or the ability to pinpoint an area on a map. We developed a schedule of recruitment periods that varied by time of day and day of the week, ensuring that we had maximal coverage across the periods. Although we had initially identified Thursdays through Sundays as being particularly high volume for user engagement, we wanted to make sure that we reached users who were active outside of those days and times. Thus, some shifts were scheduled as early as 7 AM and ended as late as 2 AM each day of the week. To ensure recruiters could balance their other study-related duties, recruitment shifts spanned from 2 to 4 hours and flexible work hours were instituted to accommodate their schedules. For instance, recruiters working late-night shifts were not expected to be at the office first thing the next morning.

At the end of each recruitment period, recruiters completed a tracking form that was used to monitor the yield of the recruitment period, identify patterns in engagement, and document the quantity and quality of the interactions. Specifically, recruiters tracked the number of (1) conversations in the shift, (2) scheduled appointments, (3) nonresponses, and (4) users engaged but who did not have an appointment scheduled. Recruiters could also add pertinent information about the conversations, such as things that worked well, challenges encountered, or any other information (Textbox 2). Although we tried to track conversations by users, we found this challenging because identifiable aspects of user profiles can be modified, including photos and text descriptions, and we could not devise a system to track communications with a large number of users, especially in ways that could be easily referenced by all recruiters.

Textbox 2. Sample of final dating app user engagement tracking sheet data points.

Label and Description

- Time: interviewers added the date, start time, and end time of that shift.
- Location: the zip code that the interviewer used for their search within that given shift.
- Number of confirmed appointments: interviewers would enter the number of users with whom they were able to schedule an in-person study visit.
- Number of refusals: the number of users who asked not to be contacted anymore, blocked the interviewer, or explicitly stated disinterest in the study.
- Number ignored: the number of users to whom the interviewer sent a message but received no response.
- Number too far to participate: the number of users that were ineligible because not living in the area.
- Total number contacted: all contact attempts within the shift.
- Notes: interviewers add notable experiences (eg, not many age-eligible users and user questioned legitimacy).

Step 5: Engage Users and Schedule Appointments

Although each recruiter developed their own unique engagement approach and script, being more free-flowing and less scripted in our conversations yielded the most promising results. Recruiters were free to use their own words, but constant copying and pasting from a predetermined script sounded too robotic and turned off users. Our most successful recruiters were those who kept the natural flow of the conversation while describing the study and motivating the user to schedule a screening appointment. Introducing the study earlier in the exchange rather than later was also important for some users not to feel deceived or led on. With some users, recruiters asked the user to read their profiles early in the rapport-building process. With other users, they wove the study description naturally into the conversation. After sending an introductory message, if recruiters encountered a minimally responsive user (long delays in responses) or a completely nonresponsive user, recruiters would move to directly describe the study and include their study phone number and email in the message. This would allow the user to make an informed decision about contacting the research team at a later time convenient for them. For users with whom conversations spanned multiple days or weeks, recruiters would ask to add the user as a *favorite* to easily reengage with them in the future. Being honest and respectful of the user at all times is essential, as it allows recruiters to follow the natural flow of the conversation and motivates the user to schedule a study appointment.

Step 6: Hold Regular Meetings to Monitor Recruitment and Sustain Motivation

We held weekly meetings during which we used the tracking forms to review progress, discuss challenges, and revise the protocol and recruitment schedule. Recruiters shared their experiences and problem-solved difficult situations. If possible, we recommend having a senior recruiter on call to help resolve the most challenging issues in real time. We also made sure to celebrate recruitment successes and would encourage friendly competition between recruiters by acknowledging the recruiter who attained the most enrollments in a given month. This was key to building a mutually supportive environment and sustaining motivation.

Discussion

This is one of the first studies to provide a detailed protocol for directly recruiting on gay dating apps. Our experience indicates that gay dating app recruitment is feasible and fruitful when the staff is knowledgeable, flexible, honest, and respectful to the user. Although internet-based recruitment has been commonly reported by many HIV researchers, advertisements are the typical modality used [5-11]. The recruitment procedures have not been well described in the few papers that discuss direct recruitment [14-17]. It is important to note that our protocol development process relied heavily on the expertise of our sexual minority cisgender male staff. Their voices were central in crafting the profile pictures and language and leading the training with other recruiters.

Contrary to what some might say, successful recruiters do not have to be members of sexual minority groups. Although the familiarity with navigating these apps is useful, it is not essential because these skills can be taught. Our structured training approach partnered trainees with experienced recruiters to provide first-hand exposure to the entire process and real-time coaching and feedback as they developed proficiency in navigating the app. We also found tremendous value in maintaining constant communication among the recruiters and the project director to collaboratively and instantaneously problem-solve issues that emerged.

Perhaps the most salient lesson we learned in approaching gay dating app users is the importance of setting clear and transparent intentions without judgment. As researchers, we must be aware of the impact our presence has on the spaces we enter. Virtual venues are perhaps the only spaces where many users, particularly those who are more isolated and stigmatized, connect and engage with others in their communities [23]. Gay dating apps allow users to connect on a variety of levels that can range from simple conversation to *hooking up*. We may be an unwelcome distraction and respect their time and intentions to use the app. Profiles and messages should be clear in describing who we are and our reasons for engaging with them. Furthermore, we must scrutinize the content of our communication and be mindful of the use of symbols and punctuation. For instance, users may misinterpret capitalization as screaming or a misplaced exclamation point as a judgment.

Although gay dating app recruitment was instrumental in helping us to meet our enrollment targets, it requires considerable time and effort and can be complicated when recruiters are engaged in multiple tasks. In our case, recruiters conducted other research activities, including participant assessments, retention, and follow-up visits. Balancing the demands of gay dating app recruitment with staff's other study-related responsibilities requires ongoing monitoring and scheduling adjustments. Thus, both staff and management had to be flexible, adaptable, and willing to adjust their duties and responsibilities as needed. We recommend that researchers assign dedicated staff to gay dating app recruitment if feasible.

In recent years, gay dating apps have become more stringent in conditions for app usage, specifying that the apps are for private, noncommercial use. Currently, this may limit opportunities for direct recruitment methods for research, but app developers are becoming more interested in expanding their existing sexual health initiatives; thus, direct recruitment may be a possibility in the future. Grindr, for example, provides a comprehensive sexual health resource center and consistently has popup and banner ads for access to HIV prevention services (eg, pre-exposure prophylaxis and HIV testing) [24]. Our success with direct recruitment methods could indicate another avenue for connecting users to these resources. Furthermore, research has shown that young sexual minority males find direct communication and outreach of sexual health resources and services through gay dating apps acceptable [17]. New apps are continually being developed and may not impose similar restrictions on researchers.

In this manuscript, we described our experiences and provided step-by-step instructions that other researchers interested could follow and refine in recruiting through gay dating apps. This protocol can also be adapted by researchers engaging in social media recruitment in other types of apps. This protocol represents a first step that can be improved by targeted and rigorous research. For instance, studies examining different elements of profiles and pictures used by recruiters could yield data to improve engagement [25]. Qualitative studies to garner user perspectives and reactions to recruitment efforts could also be valuable. Using an implementation science framework could provide more insight into user experiences to refine communication approaches and tracking methods. Gay dating apps continue to increase in popularity. Researchers need to stay vigilant to changing formats and terms of service and develop systematic approaches to harness the potential of gay dating and other social networking apps as invaluable recruitment strategies for SGMY.

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Conflicts of Interest

None declared.

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Abbreviations

ATN: Adolescent Medicine Trials Network for HIV/AIDS Interventions
CARES: Comprehensive Adolescent Research and Engagement Studies
GSN: geolocation social networking
SGMY: sexual and gender minority youth

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Protocol

Monitoring Beliefs and Physiological Measures Using Wearable Sensors and Smartphone Technology Among Students at Risk of COVID-19: Protocol for a mHealth Study

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Abstract

Background: The COVID-19 pandemic has significantly impacted lives and greatly affected the mental health and public safety of an already vulnerable population—college students. Social distancing and isolation measures have presented challenges to students' mental health. mHealth apps and wearable sensors may help monitor students at risk of COVID-19 and support their mental well-being.

Objective: This study aimed to monitor students at risk of COVID-19 by using a wearable sensor and a smartphone-based survey.

Methods: We conducted a prospective study on undergraduate and graduate students at a public university in the Midwest United States. Students were instructed to download the Fitbit, Social Rhythms, and Roadmap 2.0 apps onto their personal smartphone devices (Android or iOS). Subjects consented to provide up to 10 saliva samples during the study period. Surveys were administered through the Roadmap 2.0 app at five timepoints: at baseline, 1 month later, 2 months later, 3 months later, and at study completion. The surveys gathered information regarding demographics, COVID-19 diagnoses and symptoms, and mental health resilience, with the aim of documenting the impact of COVID-19 on the college student population.

Results: This study enrolled 2158 college students between September 2020 and January 2021. Subjects are currently being followed-up for 1 academic year. Data collection and analysis are currently underway.

Conclusions: This study examined student health and well-being during the COVID-19 pandemic and assessed the feasibility of using a wearable sensor and a survey in a college student population, which may inform the role of our mHealth tools in assessing student health and well-being. Finally, using data derived from a wearable sensor, biospecimen collection, and self-reported COVID-19 diagnosis, our results may provide key data toward the development of a model for the early prediction and detection of COVID-19.

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International Registered Report Identifier (IRRID): DERR1-10.2196/29561

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KEYWORDS

college students; COVID-19; global pandemic; mental health; mHealth; pandemic; risk monitoring; wearable sensors; well-being

Introduction

Background

A global pandemic affecting over 100 countries has created great uncertainty, disruptions, and imposed tight restrictions on movement. This unparalleled time has required individuals to adapt to new routines, such as self-isolation, quarantine, and careful health behaviors (eg, mask-wearing, hand-washing, and self-reporting of respiratory symptoms) to protect not only one's own health but also the health of the broader community. These routines have made it more difficult for young adults, such as college students, to see their friends and family as they were used to before the pandemic [1]. College students who are facing these unexpected changes and those who are now physically separated from friends and family are more prone to developing mental health issues in the absence of social support [1]. An additional concern is the degree to which students have had their close friends and family affected by the COVID-19 pandemic (eg, job loss, illness, and death). Accordingly, this has placed college students at a significant risk of decline in mental health and subjective well-being [1].

Having originated in Wuhan (Hubei Province, China) in the beginning of December 2019, SARS-CoV-2 was identified as the cause of an outbreak of COVID-19 [2]. As of February 2021, the virus had spread to 210 countries with more than 100 million confirmed cases [3,4]. Among those millions of cases, 76% of the confirmed cases included adults younger than 65 years, with 18-29-year-old people constituting a large proportion of the infected population [5]. This disease is usually transmitted through inhalation of or contact with infected droplets, and the incubation period ranges from 2 to 14 days [6]. Common symptoms include fever, cough, sore throat, and fatigue, among others [6]. While the illness has been mild for most people, in some—usually those with comorbidities—it progresses to pneumonia, acute respiratory distress syndrome, or multiorgan dysfunction [6]. Many people are asymptomatic but are still capable of spreading the disease, which contributes to the complexity of the disease [6,7].

During this unprecedented global pandemic, the return of students to campus has been heavily contemplated by colleges nationwide. While younger adults with COVID-19 and no other underlying health conditions are at a minor risk of severe health outcomes, colleges nationwide are making maximum efforts to halt the spread of the disease [8]. College campuses have implemented numerous COVID-19 prevention practices, including an increased testing capacity and requirements for mask-wearing and physical distancing. With these practices in place, college students are now expected to adapt to a "new normal." This unpredictability, in conjunction with increased isolation measures, can act as stressors that may drive declines in students' mental health [1,9].

Rationale

In response to the COVID-19 pandemic, this study leveraged an mHealth platform in conjunction with saliva samples to monitor students at risk of COVID-19. Given the impact of the COVID-19 pandemic on college students, this study aimed to monitor student health and mental well-being. This study utilized the Roadmap 2.0 app, which is currently being evaluated among caregivers of patients undergoing hematopoietic stem cell transplantation [10-12]. The Roadmap 2.0 app was used to interface with a wearable sensor data from the Fitbit device and to deliver surveys to the subjects. This app also provided a set of positive psychology-based exercises that were available to participants to use as they desired. The study also utilized the Social Rhythms app to assess subjects' circadian rhythms and changes that occurred as a result of the COVID-19 pandemic.

In addition to a suite of mobile health apps, this study utilized a wearable sensor to gather physiological data continuously. Wearable devices are currently being used by millions of people worldwide and have the ability to measure physiological parameters, such as heart rate, skin temperature, and sleep in real time [13]. Given the known association between heart rate and infection, wearable sensors could be leveraged to help detect the disease and determine the health status of an individual [14,15]. Therefore, we hypothesized that continuous analysis of heart rate, sleep, and step data obtained from wearable sensors, in conjunction with COVID-19 diagnosis data and data from self-collected saliva samples, may help develop an early prediction or detection model for COVID-19 illness in students. In addition, we proposed that wearable sensor use combined with smartphone-based surveys of student health and wellness could provide a platform for students to self-monitor their well-being.

An additional challenge for monitoring students and other individuals for COVID-19 was the fact that the predominantly used specimen type for viral testing, the nasopharyngeal swab, requires sample collection by trained staff and the use of personal protective equipment because the collection process itself could make the virus airborne. Recent studies on other respiratory viruses, along with those on SARS-CoV-2, have indicated that a simple self-collected saliva sample could alternatively be used to test for infection accurately [16]. Self-collection of samples has had substantial benefits, including reducing the amount of required personal protective equipment and enabling collection at home, which could render widespread and repeated testing of students practical at the large scale. Thus, we posited that self-collected saliva samples would be feasible to collect in the college student population. This would help

determine the correlation between data obtained from wearable sensors and qualitative SARS-CoV-2 positivity in saliva biospecimens.

Study Purpose

Our aim for this nontherapeutic pilot trial was to improve efforts of monitoring students during the COVID-19 pandemic, for whom detecting infections in the asymptomatic and presymptomatic settings could be of critical importance for the protection of the community by limiting disease spread. By using a wearable device, a smartphone-based survey, and self-collected saliva specimens, our study can potentially (1) assist students in self-monitoring for COVID-19 illness as well as mental well-being and (2) provide key data toward our ultimate goal of creating a predictive model for COVID-19 in students as well as other individuals (eg, their friends and family) in the future.

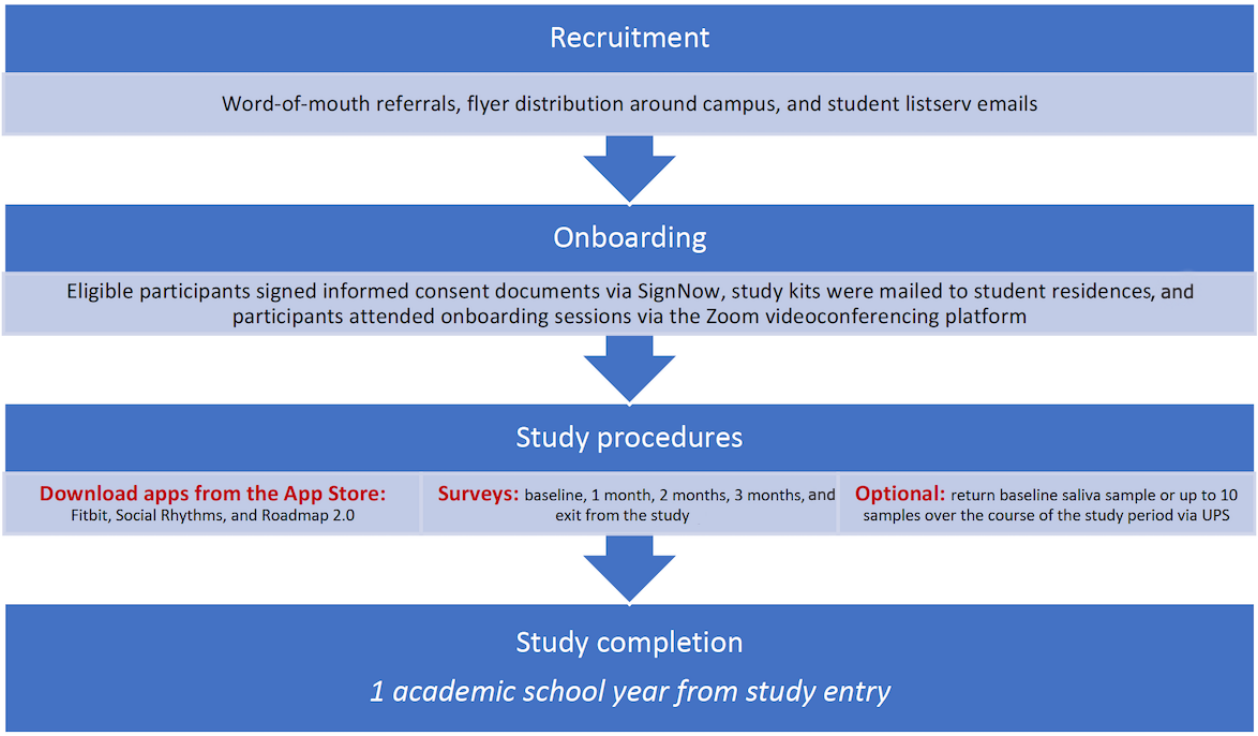
Methods

Study Design

Overview

This was a prospective study on students at the University of Michigan (Ann Arbor, Michigan). We aimed to enroll up to 5000 subjects in this study. Subjects self-collected a saliva sample at baseline and were asked to provide up to 10 samples throughout the academic year by using an easy-to-use at-home collection kit. In addition to samples, subjects were instructed to download the Fitbit, Social Rhythms, and Roadmap 2.0 apps on their smartphone devices (Android and iOS). Surveys were administered through the Roadmap 2.0 app at baseline, on a monthly basis for 3 months, and at study completion, and participants received push notifications as a reminder to complete the survey through the app. Subjects were unable to review or change any of their answers while taking their surveys. The study schema is shown in Figure 1.

Figure 1. Schematic representation of the study protocol. UPS: United Parcel Service.



Objectives

The primary objective of this study was to assess the feasibility of using wearable devices among college students. Feasibility was defined as wearing the Fitbit Charge 3 watch at least 8 hours per day up to at least 5 days of the week (~40 hours/week).

The secondary objective was to assess the survey completion rate, assuming that at least 50% of participants would complete the baseline, monthly, and exit surveys.

The exploratory objectives were to (1) analyze the time spent in performing the positive activities and data on circadian rhythms (by analyzing time stamps) and correlate mental health status to positive activity usage, (2) analyze continuous heart rate data from a wearable device alongside intermittent saliva samples for the development of an early prediction and detection model for COVID-19, and (3) identify individuals who may have already been exposed to COVID-19, once validated serologic tests for COVID-19 exposure are available for research purposes only.

Participant Enrollment

Eligibility Criteria

Subjects were required to be at least 18 years of age or older and attend the University of Michigan. Undergraduate or graduate students could either be on campus for the academic year or taking classes on the internet. Students completing school remotely were required to provide a mailing address within the United States where they could receive study material

(eg, Fitbit and saliva collection kits). In addition, subjects were required to possess a smartphone device (Android or iOS). Finally, subjects were required to understand and demonstrate a willingness to sign a written informed consent document remotely. Subjects were excluded from the study if they were unwilling or unable to comply with the study procedures.

Recruitment

The primary tools for recruitment were word-of-mouth referrals, flyer distribution around campus, and student listserv emails. We listed this study on the University of Michigan Health Research recruitment website, and we obtained permission from the School of Public Health to advertise on their job board and student flyers. Interested participants notified a study email address, or they used the QR code on the recruitment flyer to indicate their interest. In addition, the study team requested a targeted email to be sent out to all University of Michigan students, which captured other student populations on or off campus, and approval was obtained from the Registrar's Office.

Informed Consent

Following the social distancing guidelines issued by the Centers for Disease Control and Prevention, as well as the University of Michigan COVID-19 research guidelines, we conducted an entirely remote process for obtaining informed consent. Interested subjects who contacted the study team by phone or email received additional study information (ie, overview of study procedures, risks, benefits, etc). Following adequate discussion with the coordinator to answer any questions, the coordinator sent the informed consent documents via email through the SignNow platform, and the student signed the document electronically [17].

Enrollment

After signing the informed consent document through SignNow, the study coordinators assembled the study kit, which included the wearable Fitbit device and a saliva collection kit. Each study kit contained written directions for collecting the saliva sample and biohazard packaging to safely return the sample to the laboratory via the United Parcel Service. Once the subject received his/her study kit, the coordinators sent an email that included the dates and times of live onboarding sessions conducted via the Zoom videoconferencing, as well as a link to a prerecorded web-based onboarding video if they could not attend the live onboarding session. During web-based onboarding, a study coordinator instructed subjects on how to download the Fitbit, Roadmap 2.0, and Social Rhythms apps. The study coordinator then explained each app and explained how to use and sync their Fitbit watch. The baseline survey was also completed through the Roadmap 2.0 app. Finally, instructions on collecting and mailing the saliva sample were provided to subjects.

Biospecimens

Saliva Sample Collection

Subjects were asked to collect a saliva samples at baseline and were asked to collect up to 10 samples throughout the study. When signing the consent documents, subjects could choose to opt in or out of saliva sample collection. Subjects were provided the Zymo DNA/RNA Shield™ Saliva Collection Kit to self-collect their samples at home [18]. When providing a sample, subjects collected their saliva specimens prior to brushing their teeth, eating, or drinking, and collected approximately 1-2 mL of saliva in a tube that contained no preservative. They then added a preservative (DNA/RNA) shield reagent, which effectively preserved the nucleic acid content of the sample [19].

Specimen Handling, Processing, and Storage

Owing to the unknown COVID-19 status of subjects while they were enrolled and provided biospecimens for this study, our team developed a sample handling procedure to ensure the safety of all laboratory members. All activities in the laboratory were performed with disposable gloves while wearing safety glasses, a coat, and a face mask. All samples arriving at the laboratory were placed in the biosafety cabinet. Once in the biosafety cabinet, both the external packaging and primary sample container were sprayed with 70% ethanol and left to stand for 5 minutes before being stored at –80°C. When finished working in the biosafety cabinet, the cabinet was sprayed down with 70% ethanol, and the UV light in the biosafety cabinet was turned on for 15 minutes.

Wearable Devices

Fitbit Charge 3 is an advanced touch-screen fitness tracker that monitors variables such as heart rate, calories burned, pace, distance, and sleep cycles. The device can be worn either on the wrist and wirelessly connects with the patient's smartphone via Bluetooth to the Fitbit mobile app (available on Android and iOS systems). Subjects had access to their data and, if they wanted, could set fitness goals within the app.

The subject was instructed to wear the Fitbit device for at least 8 hours per day up to at least 5 days of the week. The smartwatch uploaded data to the subject's phone every 15 minutes via Bluetooth Low Energy [20]. The study team had access to the patient dashboard and data download for analysis through the Roadmap App. In addition to the study team, subjects also had access to view their health data in real time on their Fitbit app.

Apps Used in This Study

Roadmap 2.0 App

Each subject enrolled in the study was asked to download the Roadmap 2.0 app on their smartphone. The Roadmap 2.0 app was developed by University of Michigan investigator SWC and colleagues, and it served as an interface with the Fitbit app and provided activities designed to promote subjective well-being, based on the principles of positive psychology [21]. The activities were as follows: positive piggy bank, gratitude diary, savoring, pleasant activity, random acts of kindness, signature strengths, love letters, and engaging with beauty (Multimedia Appendix 1). On the app, participants were provided with graphs that showcase their daily mood, sleep, and steps data. The quality and quantity of the graphs data depended on whether the participants responded to the daily mood questionnaire—a scale with scores ranging between 1 and 10, corresponding to responses of "worst possible" and

"best possible," respectively—and wore and synced their Fitbit device.

Social Rhythms App

Each subject was instructed to download the Social Rhythms app. The Social Rhythms app was developed by University of Michigan investigator DBF and colleagues, and it provides information regarding one's circadian rhythm based on physiological data, which could inform how to organize daily schedules. Social rhythms are patterns of daily behaviors that could perhaps affect circadian timing directly or indirectly by modifying exposure to light [22]. The app collected data from either the Apple Health Kit on the app or Fitbit (health, sleep, and activity data). The app used these data to generate a report to the user about their circadian rhythm and supplied the report after a few days [23]. The report provided the user information on his/her activity pattern, regularity, internal clock, sleep time, light exposure, and documents on when the user should avoid light [23]. The user can submit his/her data and obtain a report at his/her preferred frequency.

Surveys

Baseline Surveys

During study onboarding, subjects were provided with a unique access code that allowed them to log in to the Roadmap 2.0 app. After entering the access code, the baseline survey was automatically pushed to their smartphones, and survey completion was required in order to gain access to the rest of the app. The baseline survey consisted of 192 survey items that gathered demographic data (Multimedia Appendix 2) and were distributed on 12 pages. The estimated time of completion was less than 25 minutes. This was a Qualtrics-based survey that was stored on HIPAA-compliant University of Michigan secure servers. Study subjects also completed a 9-item baseline survey in the Social Rhythms app, which gathered demographic data through their smartphone, which took less than 5 minutes to complete.

Monthly Survey

Study subjects completed a 127-item monthly survey at 1 month, 2 months, and 3 months after study entry, which were distributed on 12 pages. The survey gathered information about COVID-19 symptom tracking and mental well-being and resilience. Monthly surveys took approximately 15-20 minutes to complete. When subjects completed the study, there was also a final exit survey that had up to 60 items, which were distributed on 5 pages, regarding the number of COVID-19 tests received, COVID-19–related symptoms, vaccination status, and well-being (eg, COVID-19 compassion, fatigue, and hope), which was expected to take approximately 5 minutes to complete. Certain survey items were only conditionally displayed on the basis of responses to other items, including the number of COVID-19 tests conducted. Subjects were not able to review or change their survey responses. Subjects were compensated US $10 for completing the baseline survey and each additional monthly survey, with a total compensation of up to US $40. They were also allowed to keep the Fitbit device for personal use after study completion.

Data Collection and Analysis

Quality Assurance

The study team monitored device data regularly to assess data quality and subject compliance. When a subject consented to the device portion of the study, the coordinator discussed the subject's preferred methods of contact in the event of poor data quality, lack of data over an extended period of time, or other technical issues. The study team sent out weekly follow-up reminders via email to subjects to complete their surveys and return saliva samples.

Data Analysis Plan

Descriptive statistics will be used to analyze the subjects' characteristics including age, gender, race, ethnicity, education (years), and comorbidities. We aim to use computational techniques to assess the relationship among self-reported symptom data, continuous heart rate data, and the incidence of clinical respiratory illness, which may be diagnosed as COVID-19 or other types of infections. We will build on analytic approaches already developed in our study on oncology patients (ie, patients undergoing hematopoietic stem cell transplantation, who develop fevers leading to changes in heart rate, step, and sleep owing to infections, graft-versus-host disease, or other causes; patients receiving chimeric antigen receptor T cells, who develop cytokine release syndrome, display some similarity to the pathophysiology of severe COVID-19) [24,25].

In brief, we shall adopt a multitiered approach to data analysis. This will involve initial quality control analysis and nonspecific filtering of the data, data visualization, descriptive statistics, and multivariate analysis to calculate measures of correlation among the multiple streams of data themselves (eg, heart rate and steps) as well as with clinical outcomes (eg, COVID-19 status). We will consider examining such relationships, especially clinical outcomes, as exploratory and expect to obtain pilot data to power a subsequent study. We also aim to assess the relationship between student mental well-being and the use of the study apps, including Roadmap 2.0, Fitbit, and Social Rhythms.

Results

This study was approved by the institutional review board on August 20, 2020, at Michigan Medicine (Ann Arbor, Michigan) and was registered on ClinicalTrials.gov (NCT04766788). We enrolled a total of 2158 students in this study between September 24 and November 10, 2020. This sample included both undergraduates and graduate students. The entire study was conducted remotely owing to COVID-19 restrictions. Survey data collection remains active until the last subject completes the study procedures by June 2021. As of this writing, subjects will remain enrolled in this study for 1 academic year (August 2020 to May 2021: fall term 2020 and winter term 2021), during which they will continue wearing a noninvasive Fitbit device. Hence, data collection, processing, and analyses are ongoing.

Discussion

In this study, college students were instructed on the use of a smartwatch, downloaded several mobile apps, submitted saliva samples, and completed smartphone-based surveys with the aim of helping them self-monitor for COVID-19 infection and overall mental well-being. We enrolled 2158 students, of whom 1609 have completed the final exit survey to date. This study assessed the feasibility of wearable sensor use and survey completion among college students. This study also examined the effects of study app usage on mental well-being. Thus far, we have been encouraged by the high interest and engagement of college students who are willing to participate in the study, as well as the number of students who have followed through with each of the study procedures.

This long-lasting pandemic has affected college students worldwide in numerous ways. The pandemic has brought about major lifestyle changes and constraints on socialization for students. These stressors have highlighted the precarious mental health of this vulnerable population [26]. Recent studies have shown that longer periods of quarantine were linked to a decline in mental health [27]. Some other stressors have included fears of infection, frustration, boredom, and financial losses [28]. Given the critical importance of student mental well-being, beliefs, and resilience during this unprecedented time, this study aimed to provide them with tools that could enhance mental well-being.

With the growing use of smartphones and mobile apps, these tools are increasingly being used to target healthy behaviors and manage health conditions [26,29]. Previous studies have elucidated the important role of mobile apps in the maintenance of mental health [30,31]. Considering this, we designed this study to leverage an mHealth platform (Roadmap 2.0 app + Fitbit devices + symptom reporting) to monitor COVID-19 symptoms and student mental well-being. As the literature on mHealth interventions continues to grow, wearable sensors and mobile health technologies are likely to play an increasingly important role in the lives of college students. A recent study on college students tested a smartphone app, Nod, which was designed to deliver cognitive and behavioral skill-building exercises to reduce loneliness during the transition to college. The findings of their pilot randomized controlled trial suggest the unique potential of Nod to provide self-paced and confidential support in addressing mental health issues including depression and loneliness [32]. Indeed, by examining real-time data, mobile health apps and wearable sensors have the potential to inform real-time decision-making. Furthermore, these new tools and technologies may help improve access to care, care quality, patient-provider communication, and health outcomes [33]. Importantly, mHealth tools may serve as a cost-effective and scalable solution for deploying novel interventions that can impact the lives of people with physical and mental health conditions [34].

We acknowledge various limitations of this study. First, this study was limited to a single college campus setting. Making this study accessible to other campuses would help capture the diversity of other student bodies in the United States. Second, studies have shown that the usage of mHealth apps is often short-lived; one study found that among people who have downloaded an mHealth app, approximately half of that population deleted the app for various reasons including hidden costs, loss of interest, and high data entry burden [35]. Thus, future studies are required to address these barriers to mHealth app usage to increase engagement and sustainment of use. Finally, college students may experience fatigue and lose motivation when completing monthly surveys, which can take up to 30 minutes to complete. Thus, to keep subjects engaged, surveys could perhaps be shortened or be conducted less frequently. Despite the aforementioned limitations, this study will provide key pilot data toward developing novel tools, technologies, and methodologies for supporting student mental well-being, particularly during stressful life events, such as a global pandemic, examinations, presentations, or job interviews.

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Authors' Contributions

C Cislo, C Clingan, MT, and SWC drafted the manuscript. C Cislo, C Clingan, KG, MR, and JB coordinated the study, recruited participants, obtained informed consent, and managed study onboarding. C Cislo, C Clingan, KG, MR, JB, ES, MO, CF, JT, CM, MM, MT, and SWC curated the data. KG, MR, IG, CB, JB, ES, MO, CF, JT, CM, MM, JLC, DF, MT, and SWC reviewed and critically revised the manuscript. IG, CB, and JLC selected the survey measurements. IG, CB, CF, JT, CM, MM, JLC, DF, MT, and SWC designed the study methodology. ES and MO processed the samples. DF, MT, and SWC supervised the study. MT and SWC were responsible for data investigation, resources, supervision, and visualization.

Conflicts of Interest

DBF is the CSO of Arascope, a company that develops software for circadian rhythms. The University of Michigan is a part owner of Arascope. Arascope did not sponsor this study. The other authors have no conflicts of interest to declare.

Multimedia Appendix 1
Screenshots of Roadmap 2.0.
[DOCX File , 1305 KB - resprot_v10i6e29561_app1.docx]

Multimedia Appendix 2
Survey Measures.
[DOCX File , 37 KB - resprot_v10i6e29561_app2.docx]

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Protocol

Using Co-design to Explore How Midwives Can Support the Emerging Mother-Infant Relationship During the Early Postnatal Period: Protocol for a Mixed Methods Study

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Abstract

Background: The postnatal period can be a challenging time for women, with mothers experiencing a range of emotions. As a woman transitions to motherhood, she adjusts to a new sense of self and forms a new relationship with her infant. Becoming a mother is a complex cognitive and social process that is unique for each woman and is influenced and shaped by culture. The emerging mother-infant relationship is a significant factor in maternal well-being and infant development, with the bond between the mother and her baby being critical to the development of secure attachment. It has been recognized that the strength of this relationship is the main predictor of how well a child will do throughout life. There has been a global focus on the importance of the first 1000 days, with Australia identifying this as a national priority. Midwives are ideally placed to support mothers during the development of the mother-infant relationship, providing care through the early postnatal period, which has been identified as a *sensitive period* for the development of the mother-infant relationship.

Objective: The aim of this study is to explore how midwives can support the emerging mother-infant relationship in the context of cultural diversity and develop an appropriate co-designed intervention in the early postnatal period.

Methods: This study will use a mixed method approach, specifically the exploratory sequential design (intervention development variant). This study will be undertaken in 3 phases: 1 qualitative phase, which is followed by 2 quantitative phases. Phase 1 will include a scoping review to explore interventions that have influenced the development of the mother-infant relationship, and then, interviews will be undertaken with women exploring their early experiences of motherhood, followed by 3 co-design workshops. The workshops will engage with multilevel stakeholder representatives where, through partnership and participation, they will propose and develop an intervention to support the emerging mother-infant relationship. Phase 2 will develop and pilot 2 purpose-designed evaluation surveys to evaluate the co-designed intervention from the perspective of both mothers and midwives. Phase 3 will implement and evaluate the co-designed intervention using pre- and postmeasures and feedback from the purpose-designed surveys.

Results: Phase 1 has commenced and is expected to be completed by August 2021. Phase 2 is expected to be completed by September 2021, with phase 3 commencing in October 2021. The study will be completed by March 2023.

Conclusions: The results of this study will be shared with a variety of audiences and will contribute to the body of knowledge on the mother-infant relationship, potentially improving the understanding of this relationship for women and midwives. This may result in improved strategies for care, with mothers benefiting from enhanced experience and satisfaction during the early postnatal period.

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KEYWORDS

mother-infant relationship; mother-infant relations; mother-infant bonding; infant development; midwife; early postnatal; co-design; mixed methods

Introduction

Background

The mother-infant relationship is both complex and dynamic and benefits both the mother and infant. This relationship is developed through an interactional partnership, whereby the mother and her infant engage in a range of physical, cognitive, social, and affective behaviors [1]. Early interactions between the mother and her baby are essential for the formation of the mother-infant relationship, with the quality of the relationship being crucial to the psychological health and mental well-being development of the infant [2,3]. This relationship is commonly described in terms of bonding [3] and attachment [4,5].

Maternal-Infant Bonding and Attachment

Maternal-infant attachment involves the reciprocal connection between the mother and her baby, which is developed over time [5,6], whereas maternal-infant bonding involves a one-way connection between the mother and her infant [5,7]. This bond develops progressively, initially during pregnancy, then up to and including the infant's first year of life [5,7,8], with these first experiences forming the foundation for future relationships across a lifetime [8,9]. One of the critical periods influencing maternal-infant bonding is childbirth, where in the first few hours, maternal hormones play a positive role in enhancing sensitivity, reactivity, and receptiveness to their newborn [7]. The early bond developed between the mother and her baby is an important precursor for the development of secure attachment [6,10].

Attachment is the reciprocal relationship between the mother and her infant and can have an enormous impact on the infant's future mental, physical, social, and emotional health. Specifically, it has been asserted that the strength of this relationship is the main predictor of how well a child will do in school and throughout life [7,11]. Secure attachment is important, as it promotes the optimal development of the baby's nervous system, which is responsible for positive social and emotional development. It also establishes a safe base from which the child can explore and interact with the world [11,12]. Insecure attachment fails to meet the child's need for security and understanding, disrupting the infant's developing brain. This insecurity can inhibit emotional, mental, and physical development across the life span, leading to long-term physical and mental health challenges [11,12]. Secure attachment grows out of the success of a nonverbal communication process between the mother and baby [12,13]. Specifically, maternal-infant synchrony is a crucial aspect of the development of secure maternal-infant attachment [14]. During pregnancy, a psychosocial transition begins and continues after birth, where the woman moves from her known, current reality to an unknown, new reality in getting to know her infant [15]. Notably, due to hormones, neurochemistry, and experiences, there are dynamic changes that occur after birth, which increase the plasticity of the maternal brain, which, in turn, promotes caregiving behavior from the mother to her infant [16].

Several characteristics can influence maternal-infant synchrony, including maternal sensitivity, responsiveness, and emotional state as well as the infant's well-being and temperament [14]. Maternal sensitivity is recognized as one of the most significant contributors to maternal-infant synchrony and is therefore essential to the development of secure attachment in the mother-infant relationship [7,17]. Maternal-infant synchrony, where there is appropriate maternal sensitivity and responsiveness, promotes infant comfort and reduces distress and disengagement. Importantly, this synchrony underpins the development of secure attachment between the mother and infant and the ongoing emotional and cognitive development of the infant [14,17]. Protecting and nurturing these aspects within the emerging mother-infant relationship is crucial.

Although many attachment theories have been based on Western populations, there is a consensus that attachment is universal and not specific to Western cultures [18]. All infants require a primary caregiver to provide warm, responsive, protective, and linguistically rich environments for appropriate growth and development, regardless of culture. These characteristics are crucial in caregiving behaviors, although the way in which this is provided may vary according to cultural norms [1]. A recognition that cultural nuances may influence parents' responsiveness to their infant must be considered in offering support to the emerging mother-infant relationship; therefore, this study will seek to consider cultural diversity. According to the Australian Institute of Health and Welfare [19], 298,630 women gave birth in Australia in 2018, with one-quarter (27%) of these mothers born in a non-English speaking country. It has been reported by Hennegan et al [20] that culturally and linguistically diverse (CALD) women are more likely to face barriers throughout their maternity care, including challenges of relocation, distance from family and support networks, a language barrier, and potentially discriminatory or culturally insensitive care from maternity service providers.

Role of the Midwife

The foundations of social-emotional development of the infant are based on the primary caregiving relationship. Midwives are uniquely placed to support the emerging mother-infant relationship during this childbirth continuum, as their scope of practice begins in early pregnancy and concludes at 6 weeks postnatal [21]. Midwifery care is centered around the woman and her family, where the midwife works in partnership with the woman, promoting a healthy pregnancy, physiological birth, and a positive transition to motherhood [22]. The childbirth experience can have significant implications for early bonding between the mother and infant [23].

In 1991, the World Health Organization and United Nations Children's Fund launched the Baby-Friendly Hospital Initiative (now known as the Baby-Friendly Health Initiative), which significantly changed practices in birthing suites by implementing skin to skin to protect, promote, and support breastfeeding. Although the focus of this initiative was primarily to support exclusive breastfeeding, it was later recognized that this practice also supported the emerging mother-infant relationship [4,24]. Within the Baby-Friendly Health Initiative, there are several examples of midwives being well placed during the early postnatal period to influence the emerging mother-infant relationship. This includes the practice of skin to skin and rooming-in [24].

Kennell and Klaus [25] conceptualized the early postnatal phase as the *sensitive period*, which they defined as the first few hours or days after birth, and concluded that purposefully supporting positive mother-infant contact during this time could enhance the emerging relationship. Although more recent research has redefined the sensitive period to include pregnancy, it has also extended this time beyond the immediate postpartum period, continuing over the first few weeks and months of life [5]. Midwives provide care during the significant time when the woman transitions from pregnancy to the postnatal period and the change from her *inside* baby to *outside baby* occurs [26].

Methods

Study Design

The mixed methods typology chosen for this study is the exploratory sequential design, specifically the intervention development variant. This design involves 3 distinct phases: 1 qualitative phase, which is followed by 2 quantitative phases [27]. The rationale for using this approach is that the initial qualitative phase provides important insight into the phenomenon, which is vital to the development of the intervention, whereas the final quantitative phase provides an opportunity for an evaluation of the intervention [27].

Aim and Objectives

The aim of this study is to explore how midwives can support the emerging mother-infant relationship in the context of cultural diversity and develop an appropriate co-design intervention in the early postnatal period.

The objectives of this study are as follows:

1. To undertake a scoping review to explore interventions in pregnancy and the early postnatal period to support the mother-infant relationship
2. To engage in co-design with multilevel stakeholder representatives to explore culturally diverse ways to support the emerging mother-infant relationship and to develop a co-design intervention
3. To develop and pilot 2 purpose-designed surveys to evaluate the co-designed intervention from the perspective of mothers and midwives
4. To implement and evaluate the co-designed intervention.

Phase 1

Overview

Phase 1 will draw on a co-design process to explore and develop a co-designed intervention to support the emerging mother-infant relationship. Before the co-design workshops, a scoping review will be undertaken to examine the existing literature on interventions during pregnancy and/or the early postnatal period that support the mother-infant relationship. Interviews with mothers during the early postnatal period will also be undertaken to explore their experience of getting to know their baby. The findings from the scoping review and interviews will contribute to the co-design workshops and will help to inform the development of an intervention.

Scoping Review

A scoping review is one method that is used to review the literature, which can provide valuable information to the investigator when undertaking research [28,29]. This scoping review will explore interventions in pregnancy and the early postnatal period to support the mother-infant relationship. The review of the literature will seek to answer the following questions:

- What types of interventions have been used to support the mother-infant relationship from pregnancy to 6 weeks?
- What format was used to deliver the interventions?
- What interventions conducted in Western and non-Western countries have considered cultural diversity?
- What interventions have been evaluated?

A protocol for the scoping review will be developed following the process outlined in the *JBI Manual for Evidence Synthesis* [30], which will be made publicly available.

Interviews With Mothers

Interviews with mothers will seek to understand their experiences in the early postnatal period and their perception of influences on the emerging mother-infant relationship. Gathering these data is important for strengthening the voice of mothers in the co-design process. Mothers in a postnatal ward who meet the inclusion criteria will be invited to participate and complete a short demographic survey. Mothers who give consent will then receive an activity pack, which has a series of prompts designed to encourage them to reflect on their early mother-infant experiences. These prompts will include a polaroid camera and a journal. The mothers will be asked to capture some of their early experiences by taking daily photos and describing what helped them to get to know and respond to their baby during the first 2 weeks after birth. Using photo-elicitation is a powerful tool in research for the purpose of data generation, capturing the lived experiences of participants [31]. Shohel [32] suggested using photographs as a basis for discussion during research activities instead of other methods because of the former being a less threatening and more interesting approach to promote participation and engagement. In addition, photographs can act as a *memory anchor*, assisting participants to reflect and better explain their perceptions and experiences [33].

A semistructured face-to-face or virtual interview will be conducted between 4 and 6 weeks postnatal, where the mothers can discuss their visual journey and reflections. The interview will be guided by a few open-ended questions. These questions will explore what mothers found helpful or unhelpful in getting to know their baby to gain an understanding of the emerging mother-infant relationship. Collecting and analyzing the interview data relating to the mother's experience will provide a generative tool in the ideation process and inform the co-design. Using generative tools is helpful to aid engagement in the co-design process, as this approach promotes collaboration and imagination and encourages personal and emotional reflection [34].

Co-design

Co-design involves a group of people *using* creativity and collaboration during the design development process [35]. A co-design approach draws on the knowledge and expertise of both consumers and service users and clinicians and explores the care practices. The aim of using a co-design process in the research is to bring a group of multilevel stakeholder representatives together (consumers, clinicians, and professionals), who share an interest in the *study* but may have different motivations and experiences to discuss the topic, learn together, and make decisions [35]. Co-design workshops *use* a variety of activities to explore the phenomenon of interest. These workshops are helpful when considering a new project or if you want to understand the consumer's experience and find a solution for an existing challenge [36]. The co-design workshops will provide a forum to engage in creative group activities with all participants. As the co-design process involves a diverse group of people with differences in knowledge, interests, roles, and experience, strategies will be *used* to address the power differential to ensure that equal participation occurs and all views can be expressed [37,38].

In this proposed study, the co-design workshops will bring together multilevel representatives, including mothers and professionals who contribute to supporting the early development of the mother-infant relationship. In this study, professionals will include midwives, perinatal infant mental health (PIMH) professionals, occupational therapists (OTs), and cross-cultural consultants. The rationale for including these professionals is provided below.

Midwives provide maternity care to women from early pregnancy to 6 weeks postnatal, with women highly valuing the professional support they receive from midwives [21,39]. The midwife is ideally placed during their transition to motherhood to support the mother-infant relationship, focusing on the psychological and physical changes that occur during this time [39,40].

The field of PIMH is focused on providing mental health and well-being support to women, infants, and their families during the perinatal period [41]. PIMH services support the development of early parent-infant relationships to improve mother-infant outcomes, whereby the promotion of a positive parent-infant relationship and the mother's and baby's mental health are key elements [42,43].

Although relatively new, OTs provide support to mothers as they transition into motherhood, recognizing the adjustment to their new occupational role as a primary caregiver. OTs provide a valuable perspective with a focus on occupational performance in early motherhood, with co-occupation significantly influencing maternal and infant health outcomes [44,45]. This can provide valuable insight into the changing life roles, routines, and coping strategies through the transition to motherhood [44,45].

In addition, cross-cultural consultants will be invited to participate to ensure culturally appropriate interactions. The role of a cross-cultural consultant involves facilitating and shaping cross-cultural and intercultural interactions, ensuring cultural influence on how problems, opportunities, and responses are viewed [46]. Cross-cultural consultants facilitate collaboration or mediation between people or groups of different cultures to produce change or resolve conflicts [47]. There are a wide variety of settings that have used cross-cultural consultants [46], with the concept largely applied to anthropology until the 1960s, where it has since emerged in health care practice [48]. The use of cross-cultural consultants in maternity care has been adopted as a strategy to support culturally appropriate care [49]. Cross-cultural consultants are vital when working with people from various cultural backgrounds, as they are familiar with the language, cultural norms, practices, and worldview. This can provide a platform for effective dialog, avoiding misunderstandings by connecting one group to another, by providing explanations and appropriate translations that enable communication and effective relationship building [46]. Cross-cultural consultants seek to build bridges between the parties to support interactions to promote respect for cultural differences [48]. Using cross-cultural consultants in health care has become a positive strategy among the immigrant population to promote equity in service provision [48].

Participants and Setting

Multilevel stakeholder representatives (mothers, midwives, PIMH professionals, OTs, and cross-cultural consultants) who meet the inclusion criteria (Table 1) will be invited to participate in the study using nonprobability purposive sampling at the study site hospital in South Australia.

Table 1. Phase 1 and 2 inclusion and exclusion criteria.

Participants	Inclusion	Exclusion
Mothers	• Primiparous woman • Aged ≥18 years • ANRQ[a]<23 and EPDS[b]<13 (completed at first antenatal visit) • Baby direct room in • Term labor and birth[c]	• Multiparous woman • Aged <18 years • Inability to give informed consent • ANRQ>23 and EPDS>13 • Preterm labor and/or birth • Complications that may influence bonding • Baby is an inpatient in a special care baby unit or neonatal intensive care unit • Any previous mental illness history
Midwife	• All midwives employed at the study site hospital in South Australia on the postnatal ward, home visiting, and midwifery group practice	• All midwives who are not employed at the study site hospital in South Australia
Other stakeholders	• PIMH[d] professionals, occupational therapist, and cross-cultural consultant who work with mothers and their babies within the study site hospital in South Australia	• Health professionals who do not work with mothers and their babies within the study site hospital in South Australia

[a]ANRQ: Antenatal Risk Questionnaire; Antenatal Risk Questionnaire is a self-report 12-item psychosocial assessment screening tool administered during the antenatal period, which aids in the prediction of women who may develop postnatal depression. A score of 23 or more may suggest the presence of significant psychosocial risk factors that require consideration in mental health care planning [50].

[b]EPDS: Edinburgh Postnatal Depression Scale; the Edinburgh Postnatal Depression Scale is a self-report 10-item measure designed to screen women for symptoms of emotional distress during pregnancy and the postnatal period, reflecting the woman's experience in the last 7 days. A score of 13 or more and/or a positive answer to question 10 also needs to be considered as potentially clinically significant; therefore, mental health care planning should be considered [50,51].

[c]The word *birth* is inclusive of normal vaginal birth, instrumental (ventouse or forceps), and cesarean section (emergency or elective).

[d]PIMH: perinatal infant mental health.

An estimated sample size of 10-15 mothers will be recruited to participate in an interview. This estimated number is generally acceptable for interview data, recognizing that data saturation, where no new themes are identified, is generally achieved at this point [52-54]. However, due to a focus on cultural diversity, the researcher may recruit mothers until diversity is represented. To ensure that adequate cultural representation occurs, this study will aim to recruit one-third of the sample from CALD backgrounds. Representation will be sorted from 3 migration regions: Africa, South Asia, and Middle East [55]. If the participant woman with English as a second language requests an interpreter, an officially accredited interpreter from the Translating and Interpreting Service will be used via the telephone to meet the language needs of the participant. Alternatively, if the participant has a bilingual support person with them and requests that they interpret for them, then this will be acceptable. The primary researcher will use either the officially accredited interpreter or the bilingual support person. In addition, mothers will be asked if they would like to participate in the co-design workshop group.

A total of 8 to 10 multilevel stakeholder representatives who work with mothers and their babies within the study site hospital in South Australia will be invited to participate in the co-design group. This includes midwives who work in the postnatal ward, midwifery group practice, and home visits; OTs; PIMH professionals; and cross-cultural consultants.

Data Collection and Analysis

Interviews With Mothers

A short demographic survey will describe the characteristics of the participant mothers, for example, age, ethnicity, occupation, and education level. The demographic characteristics collected from the survey will be reported using descriptive statistics.

The interviews will be conducted face-to-face or by Zoom using a semistructured approach to ensure that the research aim and objectives are met while also allowing for flexibility to elaborate on any answers or to seek further clarification [53]. The journal and photos will not be analyzed; however, these will act as prompts for reflection during the interview. The interviews will be audio-recorded and transcribed verbatim to preserve participants' experiences by using their own words without interpretation [53,56]. The data will be analyzed using thematic analysis, as described using the 6 steps by Braun et al [56]: reading—familiarization of the data, generating codes, searching for themes, reviewing themes, defining and naming themes—and writing—finalizing analysis. The data will be read and reread by the researcher to identify codes and themes; a selection of data will be reviewed by 2 supervisors. The themes will then be reviewed and checked by the researcher's principal supervisor to ensure that all respondents' experiences were represented in the data [56].

Co-design Group Workshop

Co-design workshops will be undertaken using a variety of techniques. During the first 2 workshops, which will incorporate the predesign and design development process, a variety of tools and techniques will be used, such as probes, generative toolkits, and prototypes. These techniques contribute to disarming the power imbalance and support empowerment and democratic participation [37,57]. Using probes during the predesign stage is useful, as it invites individuals to reflect on and express their feelings, responses, reactions, experiences, and attitudes. Probes are tangible artifacts that take a variety of forms, such as diaries,

workbooks, cameras with instructions, and games [37,57]. This may include some of the mothers' artifacts from the interviews (with permission).

Generative toolkits help groups communicate and collaborate to jointly create new ideas and concepts. The toolkit approach is used to facilitate collaborative activities that purposefully steer participation, reflection, bringing vision, ideas, and concepts [37,57]. Toolkits may contain a combination of 2D or 3D components, pictures, words, phrases, blocks, shapes, buttons, pipe cleaners, and wires. These activities will lead to the development of a prototype that can then be evaluated in practice [37,57]. Prototypes can take the form of physical manifestations of ideas or concepts, ranging from an idea to a finished product. Prototypes can also include a wide variety of materials, such as clay, foam, wood, plastic, and digital or electronic elements [37].

The co-design workshop analysis will occur concurrently through group feedback, collation of the discussion, and reporting findings back to the group at the end of each session until an intervention is agreed upon.

Phase 2

Overview

Phase 2 will develop and pilot 2 evaluation surveys that will be used in phase 3. Two distinct purpose-designed surveys will be developed by the researchers to evaluate satisfaction and experience with the co-designed intervention for midwives and mothers: (1) midwives will complete a purpose-designed survey providing feedback on their experience of implementing the co-designed intervention and (2) mothers will complete a different survey designed to collect feedback on their experience and acceptability of the intervention.

Participants and Setting

The participants for phase 2 will be recruited from the co-design workshop group and will be invited to review the survey for content validity and to determine reliability. The inclusion and exclusion criteria will remain the same as for phase 1 (Table 1).

Data Collection and Analysis

The purpose-design surveys will consist of closed, open-ended, and Likert scale questions. Content validity will be undertaken, whereby a panel of experts will be invited to review the questionnaire and suggest ways to improve the design. The quality of the design was measured by the level of agreement between experts [58]. The recommended number of experts ranges from 2 to 9, with the content validity index used for the analysis [59]. To assess reliability, a pilot survey will be provided to the participants from the co-design group to ensure that the survey can be understood and works effectively. The test-retest method will be used to measure internal consistency, whereby the survey will be administered at different time intervals to the same participants [58,60]. In a test for agreement between 2 raters using the κ statistical test, a sample size of 14 subjects achieves 82% power to detect a true κ value of 0.70 in a test of H0: $\kappa=\kappa 0$ versus H1: $\kappa\neq\kappa 0$ when there are 2 categories with frequencies equal to 0.50 and 0.50. This power calculation is based on a significance level of .05 [61]. Both midwives and mothers will be engaged in the pilot process (n=14). The data from the test-retest will be collated into the SPSS and analyzed, and the findings will be presented as descriptive statistics [58,62].

Phase 3

Phase 3 will implement and evaluate the co-designed intervention as a pilot study to assess feasibility using pre-and postmeasures and acceptably using evaluation survey feedback. Education and training, as needed, will be provided to the midwives who will be offering the co-designed intervention to the mothers.

Pre- and Postmeasures

Pre-and postmeasure data will be collected from participant mothers to determine the effect of the co-designed intervention. Two validated self-reported scales have been selected: the Postnatal Bonding Questionnaire (PBQ) [63,64] and the Maternal Infant Responsiveness Instrument (MIRI) [65]. These tools will provide different but complementary data, measuring maternal bonding and maternal responsiveness, and will seek to establish whether the co-designed intervention influences maternal-infant bonding and responsiveness.

Brockington et al [63,64] developed the PBQ to identify relationship disturbances with the mother and infant during the postnatal period. This data collection tool is a self-rated questionnaire and has been validated in at least six studies [9]. The scale has 25 statements, each followed by 6 alternative responses ranging from *always* to *never*. Positive responses, such as "my baby is the most beautiful baby in the world," are scored from zero (*always*) to 5 (*never*). Negative responses, such as "I am afraid of my baby," are scored from 5 (*always*) to zero (*never*). This scale has high convergent validity with other measures of similar constructs [9]. Most studies have been undertaken after 6 weeks postpartum, with a few studies undertaken in the early postnatal period [66,67]. Alterations to factor one, specifically the question concerning smiling and playing, will need to be removed or adjusted to accommodate the early postnatal timeframe [67].

Amankwaa and Pickler [65] developed the MIRI, which is a 22-item scale designed to measure mothers' feelings about the infant and an appraisal of the infant's responses. Specifically, this tool measures the mother's recognition of their responses, the mother's recognition of the infant's responses to them, and any difficulties they notice in responsiveness. Response options ranged from 1 (strongly agree) to 5 (strongly disagree). The internal consistency of the measure is high (α=.86) [65]. The MIRI has been used in studies of mothers of term [68] and preterm infants [69]. The 22-item self-reported MIRI is a useful tool to use in clinical research to measure parenting interventions, particularly pre-and postmeasures that assess new programs or interventions [68].

Participants and Setting

Using purposive sampling, mothers (n=75) in the postnatal ward at the study site hospital in South Australia will be invited to participate in the study. As this is a pilot trial, using a formal

power calculation is usually not required, although it is still necessary to justify choosing a particular sample size [70]. Sample size has been determined based on advice from a statistician and guidance from the study by Whitehead et al [70] on pilot projects. The sample size seeks to detect a medium effect size of 0.5 (Cohen *d*) with a significance level of .05. This phase will draw on the same recruitment approach from phase 1, with the aim of recruiting one-third of the sample from CALD backgrounds. Representation will be sorted from the 3 migration regions (Africa, South Asia, and Middle East) [55]. If a participant woman with English as a second language requires an interpreter service, then it will be offered.

All midwives working in the postnatal ward, home visits, or midwifery group practice at the study site hospital in South Australia will be invited to participate (Textbox 1), with the aim of recruiting a minimum of 10 midwives.

Textbox 1. Phase 3 inclusion and exclusion criteria.

Inclusion Criteria

- Mothers
  - Primiparous woman
  - Aged ≥18 years
  - Antenatal Risk Questionnaire (ANRQ)<23 and Edinburgh Postnatal Depression Scale (EPDS)<13 (completed at first antenatal visit)
  - Baby direct room in
  - Term labor and birth
- Midwife
  - All midwives employed at the study site hospital in South Australia on the postnatal ward, home visiting, and midwifery group practice

Exclusion Criteria

- Mothers
  - Multiparous woman
  - Aged <18 years
  - Inability to give informed consent
  - ANRQ>23 and EPDS>13
  - Preterm labor and/or birth
  - Complications that may influence bonding
  - Baby is an inpatient in special care baby unit or neonatal intensive care unit
  - Any previous mental illness history
- Midwife
  - All midwives who are not employed at the study site hospital in South Australia

Data Collection and Analysis

In phase 3, the participants will be invited to complete the PBQ and MIRI before implementing the co-designed intervention (pretest). The PBQ and MIRI will be repeated after the co-designed intervention (posttest) [71]. The PBQ and MIRI will be completed by each mother on the same day. The amount of time between the pre- and posttest will be determined depending on the type of intervention developed. All participants will be matched to their pre- and postresponses as well as to their survey by allocating each participant a confidential code at the commencement of the study. The data will be analyzed using SPSS V.27 and presented as simple descriptive statistics. Paired *t* test will be used to demonstrate a change in maternal-infant bonding and responsiveness, as this test is designed to assess differences at 2 separate time points between the one group [62].

In addition, mothers and midwives who engage in the co-designed intervention will be provided with the purpose-designed surveys to evaluate satisfaction and experience with the intervention. The data will be analyzed using SPSS V.27 and presented as simple descriptive statistics. Simple descriptive statistics will describe, organize, and summarize the raw data, providing meaning through numerical data [62]. Open-ended questions will be analyzed using thematic analysis [56].

Ethical Considerations

This study was approved by the University of South Australia Human Research Ethics Committee (application ID: 203776). In addition, the Human Research Ethics Application Women's and Children's Health Network approved the study on February 11, 2021 (application: 2020/HRE01717; HREC/20/WCHN/154).

Results

Phase 1 commenced in February 2021, initially undertaking a scoping review. The recruitment and data collection for the interviews will commence in June 2021 and expected completion of the analysis is by July 2021, with the results to inform the co-design workshops in August 2021. Phase 2 is expected to be completed by September 2021, with phase 3 commencing in October 2021 and data collection and analysis to be completed by January 2022. The study will be completed by March 2023.

Discussion

Study Rationale

Research into the mother-infant relationship has included both normative and at-risk situations, with much of the research aimed at addressing and promoting parent-infant bonding for at-risk groups [72]. More recently, research has identified and confirmed a range of factors, including low education or income, psychosocial or depressive risk, infants with colic, infants with or at risk of developing a sleeping problem, and parents with an insensitive parenting style [73]. The literature highlights that there is a need for more research, which considers that mothers who do not meet the established *high-risk* criteria yet may be at risk and could benefit from supportive strategies during the early postnatal period. For instance, the increased prevalence of maternal anxiety and postnatal depression (1 in 5 women in Australia) may impact the mother-infant relationship [74].

In response to the impact that a disrupted mother-infant relationship can have on the infant's well-being, a number of early parenting interventions have been developed [73]. In a meta-analysis on early parenting interventions, Mihelic et al [73] identified that many interventions had taken an educational approach, which involved teaching specific strategies and/or provision of information on infant development and behavior. These sessions were often conducted after 3 months of age and were conducted over numerous sessions and in a range of settings [73]. Given the implications for lifelong health outcomes, supporting the developing relationship during the postnatal period is vital, with midwives being ideally placed during this sensitive period to offer professional support. There is emerging research where midwives have provided support to the early relationship, for example, providing instructions during antenatal classes on singing lullabies to improve bonding [72].

Using a co-design approach whereby multilevel stakeholder representatives share their knowledge and expertise to explore care practices has become a popular technique to address consumer needs [35,36]. This study will use an inclusionary approach to engage women from CALD backgrounds to ensure adequate representation of the community when designing an inclusive intervention. This is essential considering that one-quarter (27%) of the mothers who gave birth in 2018 were born in a non–English-speaking country [19]. This study aims to scope the literature and devise a co-design intervention that can be applied during routine care for all women inclusive of culture.

Conclusions

Research into the mother-infant relationship has predominately focused on at-risk situations. The results from this proposed study will contribute to the body of knowledge of the mother-infant relationship, in particular, mothers who are not identified but may be at risk of developing a bonding disorder. Furthermore, this study will contribute to the growing body of evidence using co-design to enhance health care practices. This research may also provide a better understanding of the mother-infant relationship for women and midwives, which could result in improved strategies for care, where mothers may benefit from an enhanced postnatal experience. The findings and results of this study will be shared with a variety of audiences, which will include the scientific community, government or policy makers, service planners, industry stakeholders or service professionals and participants and communities, and the wider community using a variety of techniques.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review 1 from the University of South Australia.
[PDF File (Adobe PDF File), 149 KB - resprot_v10i6e29770_app1.pdf]

Multimedia Appendix 2
Peer review 2 from the University of South Australia.
[PDF File (Adobe PDF File), 241 KB - resprot_v10i6e29770_app2.pdf]

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Abbreviations

CALD: culturally and linguistically diverse
MIRI: Maternal Infant Responsiveness Instrument
OT: occupational therapist
PBQ: Postnatal Bonding Questionnaire
PIMH: perinatal infant mental health

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Protocol

Integrated Prevention at Work: Protocol for a Concept Analysis

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Abstract

Background: Integrated prevention at work promises to eliminate the boundaries between primary, secondary, and tertiary prevention actions taken by stakeholders in the world of work. It is receiving increasing attention from the scientific community because of its concerted and harmonized approach, which promotes employment access, return, and healthy long-term continuation. Although promising, integrated prevention is not yet well-defined, which makes it difficult to operationalize.

Objective: This manuscript exposes the protocol of a study aiming to conceptualize integrated prevention at work on the basis of scientific and experiential knowledge.

Methods: Using a concept analysis research design, data collection has been planned in 2 parts. A meta-narrative literature review will first be conducted to document how integrated prevention has been defined in the literature. Then, phone interviews will be conducted with key informers (ie, managers, workers, ergonomists, occupational therapists, psychologists, physiotherapists, union and insurance representatives) to document their viewpoints and understanding of integrated prevention at work. Qualitative data gathered during these 2 parts of research will be analyzed using template analysis, which allows data from literature and empirical collection to be analyzed simultaneously. The analysis will bring out the points of convergence, divergence, and complementarity between the information gleaned from literature and key informers' experiences to arrive at a conceptualization of integrated prevention at work by identifying its uses, attributes, antecedents, and consequences. As a final step, validation and interpretation with a TRIAGE (Technique for Research of Information by Animation of a Group of Experts) group will be carried out in collaboration with the key informers to identify the tools for the implementation of integrated prevention at work and promote workers' health and safety.

Results: This study is expected to offer a contemporary conceptualization of integrated prevention at work that clearly lays out the variables of this concept and elicits the viewpoints of the different stakeholders.

Conclusions: This study will contribute to the advancement of knowledge about the professional injury prevention continuum. The clear identification of the uses, attributes, antecedents, and consequences of integrated prevention at work will offer concrete tools to stakeholders to implement innovative and promising approaches to integrated prevention at work.

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KEYWORDS

integrated prevention at work; concept analysis; occupational injury; meta-narrative review; qualitative research; focus groups

Introduction

Work is an activity practiced by millions of people and valued across cultures and societies [1]. It is estimated that more than 50% of the global population participates in the labor market [2], and the number of people employed is on the increase in industrialized countries. In Canada, the number of workers rose from 15.8 to 20.2 million between 2000 and 2019, which represents a jump of nearly 28% [3]. Identified as a determinant of health [4,5], work can have positive effects on an individual's health, well-being, and quality of life. For example, in addition to providing financial security, work can be a source of social recognition, protection against the decline of certain faculties, and social contacts [6-8]. However, work is not without risk, and can also have negative effects on people. Occupational injuries, whether related to a workplace accident or physical or mental illness, may diminish an individual's work participation and quality of life. Not only do occupational injuries affect workers and their families, but they also have repercussions on work organizations, particularly by increasing absenteeism [9] or decreasing performance [10]. The social impacts of occupational injuries are also considerable, with an estimated cost of €680 billion (US $828 billion) in the European Union [11] or US $171 billion in the United States [12], only for the year 2019. The contemporary COVID-19 pandemic situation that has afflicted the planet since the end of 2019 adds to the daily risks that threaten workers. Stress of contracting the virus, accessing appropriate protective equipment, constantly changing policies and procedures, modifications in work tasks, obligation to telework, or uncertainties in the work schedule are examples of the new risks afflicting workers [13-15]. In doing so, constant and innovative efforts for the prevention of occupational injuries are required to promote healthy work participation.

Various primary (ie, to prevent their appearance), secondary (ie, to reduce their duration), and tertiary (ie, to prevent prolonged disability) prevention practices coexist to manage occupational injuries [2]. These practices respond to different needs and are implemented independently by many stakeholders at different levels, such as the work environment (eg, managers, unions or workers), health care and social services system (eg, ergonomists and rehabilitation professionals), or insurance systems (eg, rehabilitation advisors) [16]. This compartmentalized prevention model makes communication and consultation between stakeholders difficult [16,17]. In fact, it has been noted that few bridges exist in practice between the various levels of prevention, and there are few links between stakeholders where the management of prevention practices is concerned [17]. The benefits of eliminating the boundaries between actions in primary, secondary, and tertiary prevention by various stakeholders to adopt an approach of integrated prevention at work have been suggested [18]. Integrated prevention is garnering increasing interest from the scientific community because it would help support injured workers' employment access, return, and healthy long-term continuation [19]. Actions traditionally associated with each of the 3 levels of prevention would then not be mutually exclusive and would gain from being integrated to increase benefits across the prevention continuum [18]. In addition to generating significant economic advantages in terms of effectiveness and resource allocation [18], integrated prevention would allow stakeholders to work synergistically [20], promoting a less fragmented prevention approach [18]. Although considered a promising avenue, integrated prevention is still an emerging concept and is not well-defined [17]. This gap in current knowledge makes it difficult to operationalize the concept, thereby impeding its implementation by stakeholders. Moreover, the concept was first defined in ergonomics, and described mainly in terms of workplace prevention interventions [17]. It would be required to ensure that the concept is formed from a perspective that includes the whole prevention continuum (eg, including also the rehabilitation level) so that all stakeholders share a common understanding of the concept.

The aim of this study is to conceptualize integrated prevention at work on the basis of scientific and experiential knowledge. The study will be guided by 3 research questions: (1) How is integrated prevention defined in the literature? (2) What are stakeholders' viewpoints on integrated prevention at work? (3) What are the points of convergence, divergence, and complementarity between the information gleaned from literature and stakeholders' experiences?

Methods

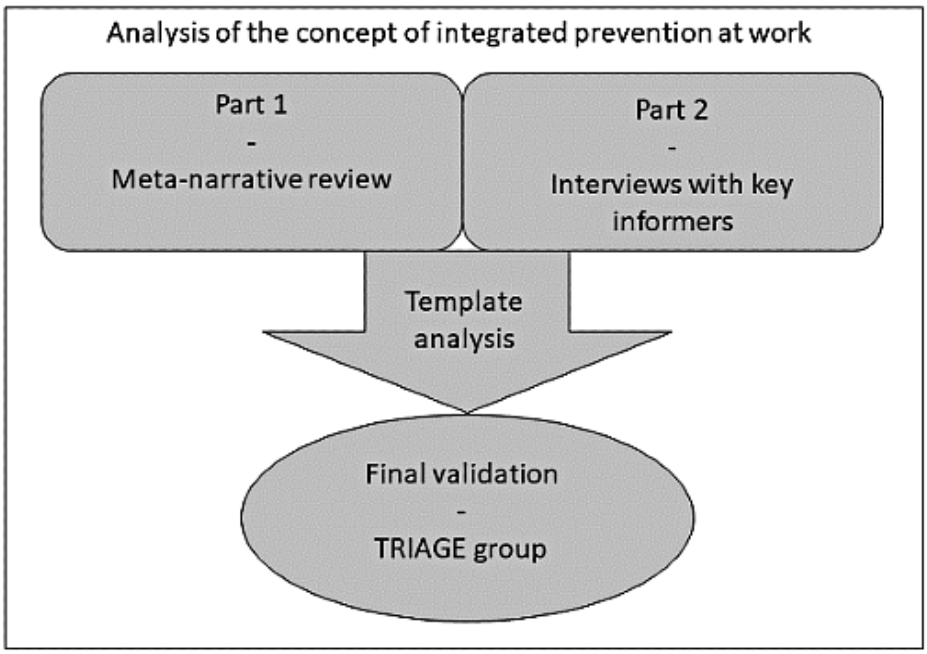
Design

A concept analysis research design [21] will be used to structure the study. This design goes beyond the linguistic analysis of a concept, leading to a theoretical construction [21]. It enables the integration of both scientific and experiential knowledge to define the variables to operationalize the concept, which are uses, attributes, antecedents, and consequences [21]. Concept analysis has been used in other occupational rehabilitation studies to better understand certain concepts such as mental workload [22] or preventive behavior at work [23].

Procedure and Participants

Data collection consists of 2 parts conducted in parallel, as shown in Figure 1.

Figure 1. Study design. TRIAGE: Technique for Research of Information by Animation of a Group of Experts.



Part 1

Meta-narrative Review

A *meta-narrative literature review* will first be carried out to collect information from literature [24]. This documentary research technique facilitates the interpretation of term meanings [25], which makes it compatible with the concept analysis research design. Furthermore, meta-narrative reviews propose a systematic method that offers the flexibility required to include diverse types of documents (eg, scientific articles and gray literature) [24]. To increase scientific rigor of the protocol, the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) recommendations [26] will be included, although they are not traditionally applied to meta-narrative literature reviews.

Documentary Search

To answer the question, "How is integrated prevention at work conceptualized?," a research strategy (ie, keywords and Boolean operators, eg, *integrated prevention AND work*, and databases, eg, *MEDLINE*) will be validated by a consultant librarian to ensure that all the fields of relevant literature are covered (eg, ergonomics, prevention, rehabilitation, management). The quality of the strategy will be evaluated according to Peer Review of Electronic Search Strategies (PRESS EBC) Elements criteria [27,28]. The reference lists of the selected documents will also be examined manually to ensure literature saturation. Moreover, the gray literature will be explored to include theses, professional papers, institutional documents, and textbooks. To do so, a search in Google with the same keywords as those used for the scientific databases will be performed. The results generated in the first 4 pages will be explored [29].

Selection of Manuscripts

Two members of the research team will conduct the documentary search according to the following inclusion criteria: (1) manuscripts concerning work and (2) manuscripts addressing the concept of integrated prevention (ie, documents proposing a definition of integrated prevention or a description of uses, attributes, antecedents, or consequences). For feasibility reasons, only documents written in French or English will be selected, and no limit regarding publication dates will be imposed.

Selection Study

The selected documents will be integrated into the Covidence reference management software. After the elimination of duplicates, 2 members of the research team will check for the relevance of all documents based on the title, abstract, and keywords. If ambiguity is present, the document will be read entirely to determine its inclusion in the study. Regular peer-debriefing meetings among the researchers will take place to rule on the inclusion or rejection of the documents [30]. This regular communication among researchers will heighten their reflexivity and guard against the undue influence of any one's perspective.

Data Extraction

Finally, the information will be extracted from the selected manuscripts by 2 members of the research team using an extraction grid constructed according to concept analysis–specific variables [22]. The extraction grid will include considerable descriptive information about the manuscripts (eg, authors and country), methodological information (eg, participants and study design), and results (eg, uses, attributes, antecedents, and consequences of integrated prevention at work). The use of the grid will be piloted during the data extraction of 3 manuscripts and the interrater reliability will be tested. To ensure the quality of the meta-narrative review, Realist And Meta-narrative Evidence Syntheses: Evolving Standards (RAMESES) [25] criteria will be respected.

Part 2

Interviews With Key Informers

Phone interviews will be conducted among key informers drawn from stakeholders in the occupational injury prevention continuum (ie, managers, workers, ergonomists, occupational therapists, psychologists, physiotherapists, union and insurance representatives). Key informers must have at least two years of work experience, be involved in 1 or more phases of the continuum of occupational injury prevention, and be fluent in French. They will be recruited through purposive sampling method and selected using a maximum variation strategy [31] to obtain diversity in terms of sex, age, workplaces, kind of implication toward prevention, and years of experience. The number of participants will be determined as the study progresses when saturation and redundancy are reached in the data gathered. Given the specificity of the subject of the study, the initial number of participants estimated is between 12 and 20 [32,33]. Indeed, some authors suggested that, for qualitative studies aiming to describe the experiences of people sharing a similar reality, interviews with a dozen participants are generally sufficient to achieve saturation of the results [32]. The final number of participants will be adjusted during the study and recruitment will stop when the interviews reveal a redundancy in the sense of the ideas reported by the participants [32]. Interviews of approximately 60 minutes in length will be conducted to elicit key informers' viewpoints and understanding of integrated prevention at work. Questions about definitions, uses, attributes, antecedents, and consequences of the concept will be asked according to a pretested interview guide. Interview recordings will be fully transcribed into verbatim. Sociodemographic data of participants will also be collected.

Analysis

Descriptive statistics will be done on sociodemographic data of the participants. Qualitative data extracted from articles (part 1) and interview transcription (part 2) will be analyzed using template analysis, a type of thematic analysis strategy [34,35]. This strategy is compatible with concept analysis and allows data from literature and empirical collection to be analyzed simultaneously.

A 5-step analysis will follow: (1) Several readings of the entire corpus will be done to obtain an overall sense. (2) The initial coding will start, and descriptive codes will be assigned to meaning units (single ideas) found in the data corpus. The aim of the study will be kept in focus to ensure the relevance of the proposed coding, as the codes are intended to help define the uses, attributes, antecedents, and consequences of the concept of integrated prevention at work. (3) The next step will consist of delineating categories and themes. The codes (micro level) will be classified into categories (meso level) and broader themes (macro level). Based on the concept analysis design, 4 a priori themes (ie, 1: uses, 2: attributes, 3: antecedents, and 4: consequences) will be used. (4) Thereafter, a general structure will be generated, and this step will enable the researchers to establish links between the selected codes, categories, and themes. (5) The raw data will be applied to the general structure multiple times to fine-tune the analytical process. This analytical process will be undertaken by 2 members of the research team, and interrater agreement will be monitored periodically. The QDA Miner [28] software program will be used to support this process. The analysis will triangulate results from the 2 parts of the study to answer the research questions, allowing to (1) highlight how literature defines integrated prevention at work; (2) present key informers' viewpoints; and (3) identify points of convergence, divergence, and complementarity between the data extracted from literature and the information collected from key informers. A conceptualization of integrated prevention at work with the identification of variables of interest (ie, uses, attributes, antecedents, and consequences) will emerge from the analysis. In addition to the identification of the variables that make up the concept, a graphic representation illustrating it and highlighting the links between these variables will be generated. Periodical meetings of research team members during the process of analysis will lead to the creation of successive versions of the understanding of the concept of integrated prevention at work until everyone agrees that the analysis performed represents the data as closely as possible.

Final Validation

A virtual discussion group between the research team and some of the key informers encountered during part B will be held to validate and interpret the results. A synthesis of results and the proposed conceptualization of integrated prevention at work will be sent to key informers a month before the meeting [36]. These documents will be discussed during a TRIAGE (Technique for Research of Information by Animation of a Group of Experts) [37,38] group meeting with participants (n=8) who took part in the study. The TRIAGE method allows discussions among participants to be structured so as to arrive at a consensus on specific ideas while facilitating the emergence of new ideas [37]. This method was shown to be economical and rigorous to reach a consensus on emerging subjects [37]. Various indicators (eg, applicability, relevance, clarity) will be documented.

The data will be interpreted in situ, which is consistent with the TRIAGE method [37,38]. This last consultation step will allow obtaining a common and shared conceptualization of integrated prevention. Intervention ideas to encourage the implementation of an integrated prevention approach by stakeholders will also emerge from this last step.

Results

From a research perspective, this study will contribute to the advancement of knowledge about the occupational injury prevention continuum. This study is expected to offer a contemporary conceptualization of integrated prevention at work that clearly lays out the variables of this concept and elicits the viewpoints of the different stakeholders. Such a definition could allow researchers interested in this subject to refer to a common definition, thus facilitating the comparison of research results. In a next step, a formal validation study to obtain a broader consensus from the scientific and practicing communities on the proposed conceptualization will be carried out. The research team will also be able to develop a concept measurement tool and an intervention model that can be used by stakeholders.

From a clinical and organizational perspective, the clear identification of variables of integrated prevention at work (ie, uses, attributes, antecedents, and consequences) will provide concrete tools to stakeholders for the implementation of innovative and promising approaches.

From a societal perspective, this study will offer avenues of intervention to innovate regarding prevention of occupational injuries. These avenues will be all the more useful because they will have been developed taking into account the emerging risks encountered by workers in connection with the COVID-19 pandemic. It is hoped that the future projects that will be carried out following this study will help reduce the societal costs linked to occupational injuries.

Discussion

This study uses a design involving data collection in 2 parts to be able to access a large pool of knowledge on integrated prevention at work from literature and data collection. In addition, the participation of different key informers from the world of work (eg, workers, employers, rehabilitation professionals, insurers) ensures that the results will be relevant to their reality, and optimizes the chances that the ideas for action that come out of the study are adopted in practice. The methodology of the study is described in detail to ensure scientific rigor and replicability. Nevertheless, as this study is conducted in Canada, the transferability of the results to other contexts cannot be guaranteed.

This article presents a research protocol to conceptualize integrated prevention at work on the basis of scientific and experiential knowledge. The results of this study will lay the ground for a contemporary conceptualization of occupational injury prevention in which the contribution of stakeholders is clearly explained. It is hoped that the results of this study will pave the way for further studies and interventions to ensure healthy work participation for all workers.

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Authors' Contributions

AL drafted this study protocol. M-EM, CV, VL, and M-EL carefully read the manuscript and made changes to improve it. The manuscript was submitted when all authors were satisfied.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by IRRST-REPAR (Quebec, Canada).
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Abbreviations

PRESS: Peer Review of Electronic Search Strategies
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-analysis Protocols
RAMESES: Realist And Meta-narrative Evidence Syntheses: Evolving Standards
TRIAGE: Technique for Research of Information by Animation of a Group of Experts

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Protocol

Building Social-Ecological System Resilience to Tackle Antimicrobial Resistance Across the One Health Spectrum: Protocol for a Mixed Methods Study

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Abstract

Background: Antimicrobial resistance (AMR) is an escalating global crisis with serious health, social, and economic consequences. Building social-ecological system resilience to reduce AMR and mitigate its impacts is critical.

Objective: The aim of this study is to compare and assess interventions that address AMR across the One Health spectrum and determine what actions will help to build social and ecological capacity and readiness to sustainably tackle AMR.

Methods: We will apply social-ecological resilience theory to AMR in an explicit One Health context using mixed methods and identify interventions that address AMR and its key pressure antimicrobial use (AMU) identified in the scientific literature and in the gray literature using a web-based survey. Intervention impacts and the factors that challenge or contribute to the success of interventions will be determined, triangulated against expert opinions in participatory workshops and complemented using quantitative time series analyses. We will then identify indicators using regression modeling, which can predict national and regional AMU or AMR dynamics across animal and human health. Together, these analyses will help to quantify the causal loop diagrams (CLDs) of AMR in the European and Southeast Asian food system contexts that are developed by diverse stakeholders in participatory workshops. Then, using these CLDs, the long-term impacts of selected interventions on AMR will be explored under alternate future scenarios via simulation modeling and participatory workshops. A publicly available learning platform housing information about interventions on AMR from a One Health perspective will be developed to help decision makers identify promising interventions for application in their jurisdictions.

Results: To date, 669 interventions have been identified in the scientific literature, 891 participants received a survey invitation, and 4 expert feedback and 4 model-building workshops have been conducted. Time series analysis, regression modeling of national and regional indicators of AMR dynamics, and scenario modeling activities are anticipated to be completed by spring

2022. Ethical approval has been obtained from the University of Waterloo's Office of Research Ethics (ethics numbers 40519 and 41781).

Conclusions: This paper provides an example of how to study complex problems such as AMR, which require the integration of knowledge across sectors and disciplines to find sustainable solutions. We anticipate that our study will contribute to a better understanding of what actions to take and in what contexts to ensure long-term success in mitigating AMR and its impact and provide useful tools (eg, CLDs, simulation models, and public databases of compiled interventions) to guide management and policy decisions.

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KEYWORDS

antimicrobial resistance; One Health; resilience; transdisciplinary; participatory; interventions; systems dynamics; social-ecological system

Introduction

Overview

Antimicrobial resistance (AMR) is a global health crisis that impacts the health and well-being of people and is projected to cause significant social and global economic losses [1-4].

AMR weakens the effectiveness of many antimicrobial agents (eg, antibiotics) used to treat infectious diseases in both humans and animals and is hard to contain because resistance spread between humans, animals, and the environment [5,6]. Through a Tripartite Collaboration, the World Health Organization (WHO), the Food and Agriculture Organization (FAO) of the United Nations (UN), and the World Organisation for Animal Health (OIE) have called for a globally coordinated multifaceted strategy, and a *One Health* approach, to sustainably address AMR and protect future generations from a post–antibiotic era [1,7,8].

A One Health Approach to AMR

One Health, a paradigm and an approach, recognizes how the health of people is connected to the health of the environment and animals. It emphasizes multisector and transdisciplinary collaborations to comprehensively understand issues and develop sustainable solutions to achieve the health and well-being of people, animals, and the environment [4,9-11].

AMR as a Complex Adaptive System

In addition to needing a One Health approach, AMR also benefits from being viewed through a complex adaptive system (CAS) lens [12]. CASs are open systems that continuously evolve and reorganize in response to environmental disturbances. These systems comprise multiple agents that act independently but are interconnected such that the actions initiated by one agent change the behavior of others in dynamic and often unpredictable ways [12,13]. AMR can be viewed as both the product and a component of an underlying CAS made up of social, ecological, economic, and other factors [14]. For example, bacteria develop resistance naturally through evolutionary processes and rapidly grow in population size, requiring people to live with resistance. Human behavior is the main driver of AMR, particularly through misuse and overuse of antimicrobials. This unnecessary antimicrobial use (AMU), together with increasing global connectivity of people and animals, growing and intensified human, terrestrial livestock and aquaculture populations, and weakened health because of social inequality, accelerates and exacerbates AMR and the emergence of superbugs [15-20]. Understanding how to build capacity within the underlying CAS to manage the complexities inherent in AMR is essential for finding effective solutions.

Building Social-Ecological System Resilience to Combat AMR

By viewing the factors that impact AMR as a CAS, we can then apply the lens of social-ecological system (SES) resilience, where resilience is the capacity of a system to cope, adapt, or transform itself into a new state, to manage disturbances in its environment [21,22]. Resilience occurs in 3 ways. Preventive resilience reflects the characteristics of a system that operates in a sustained, desired state (eg, a system in which low AMU or AMR exists). Control resilience is an attribute of a system that can revert to a desired state after a disturbance (eg, a methicillin-resistant *Staphylococcus aureus* hospital outbreak is resolved). Transformability is the capacity of a system to fundamentally change in the face of unsustainable conditions (eg, transforming from a diet high in animal protein to a primarily vegetarian diet to lower AMU and thus AMR). These concepts can be related to ideas of proactive and reactive resilience in supply chain studies [23] and adaptive and coping strategies in ecosystem management [24]. In the context of AMR, a resilient society is one that is able to cope, adapt, and transform in ways that can ensure effective treatment of infections while maintaining or improving economic, social, and environmental health and well-being.

Understanding How to Build System Resilience Through Interventions

Measuring system resilience to AMR is difficult, although some studies have identified factors associated with the magnitude of the problem [25]. In addition, we can explore and better characterize interventions, including (1) their *effectiveness* in preventing or controlling AMU or AMR, or transforming a system to ensure desired AMU or AMR levels, and (2) the factors that contribute to their success as a way to understand system resilience. As resilience is an emergent property of a system, interventions can be used to measure or test a system's resilience to AMR. If an intervention is successful, it means that the intervention within the system improved some

parameters related to mitigating AMR; in this case, understanding the details of the intervention can help uncover what parts of the underlying system contributed to that resilience. In contrast, if an intervention is not successful, it means that the intervention within the system did not improve parameters related to mitigating AMR; in this case, understanding the details of the intervention can help uncover gaps or deficiencies in the system, including aspects we need to build into the system to bolster resilience (Multimedia Appendix 1 [26-36]).

Understanding what interventions work in what contexts and the factors and conditions that underlie their success will help assess and ultimately improve resilience to AMR. However, limited knowledge exists in this area, particularly an understanding of how to build resilience in different contexts (eg, high-income countries vs low- or middle-income countries) [10].

Aims and Objectives

This paper describes a study that aims to examine the effects of interventions on AMU and AMR and identify the key factors that influence our ability to address AMR. Interventions will target regional, national, and subnational levels (ie, beyond a single setting such as a single hospital or farm), across the One Health spectrum in high-income (ie, Europe) and low- or middle-income (ie, Southeast Asia) regions of the world. We selected these regions because Europe has undertaken several efforts to address AMR [37], Asian countries, including Southeast Asia, are projected to become the largest users of antimicrobials [16,38,39], and these differences will enable a rich exploration of what interventions work, where, and under what conditions.

To address our study aims, we will complete the following objectives:

1. Identify interventions addressing AMU or AMR and determine the factors that challenge or contribute to the success of interventions.
2. Quantify and validate the ability of interventions to prevent or control rising AMU or AMR or transform the system from persistently high to lower levels of AMU or AMR.
3. Assess whether the types of national and regional indicators that are currently available can predict national AMU and AMR trends across animal and human health.
4. Create causal loop diagrams (CLDs) that depict the system of factors that influence AMR in a high-income region (ie, Europe) and a low- or middle-income region (Southeast Asia).
5. Describe the potential long-term impacts of select interventions that aim to reduce AMR under alternate future scenarios.

Theoretical Framework and Tools

Our study frames AMU and AMR as part of CAS. Within this framework, we will apply 3 different tools from the respective fields of our interdisciplinary research consortium (systems ecology and evolutionary biology, policy and governance, and epidemiology and public health), as follows.

SES Resilience Theory

Although ecological resilience stresses the capacity of a system to withstand shock and maintain function, SES resilience theory posits that a system can have varying capacities to cope, adapt, and transform when disturbances or shocks arise in its environment (eg, anthropogenic changes impacting AMR) [21,22,40]. This can positively or negatively impact the provision of services offered by the system (eg, safe food supply and water) to ensure human and ecological health and well-being. This theory has been predominantly used to understand how to enhance system capacity to withstand disturbances in a variety of fields relevant to the environment, and 7 principles have been theorized to influence system resilience [41].

The first 3 principles represent the key SES properties to be managed to enhance resilience: (1) diversity and redundancy, (2) connectivity, and (3) slow variables and feedback. The remaining 4 principles reflect the attributes of the governance system that manages the aforementioned SES properties: (4) understanding CAS (as described in the *Introduction* section); (5) learning and experimentation; (6) broadening participation; and (7) promoting polycentric governance [41] (Multimedia Appendix 2 [41-49]). Some principles of resilience have been previously described and theoretically applied to AMR [43,44,49]. Our study will allow us to determine whether and how these principles apply in the context of AMR and potentially identify additional factors to refine the SES resilience framework.

The Driver-Pressure-State-Impact-Response Framework

The Driver-Pressure-State-Impact-Response (DPSIR) framework is an analytical tool for analyzing environmental problems [50]. Adopted by the European Environment Agency, it is widely used to assess and manage environmental problems such as challenges to coastal regions and freshwater bodies [51], and it facilitates the selection of indicators to assess the implementation of different governance responses, such as environmental policies [52].

Within DPSIR, drivers are social activities that can increase or lessen a particular behavior (eg, why humans use antimicrobials to meet public demand for food animals). *Drivers* exert *pressures* (eg, through AMU) that change the *state* of the environment, which corresponds to the level of AMR measured in different pathogens, which leads to an *impact* (eg, an increase in morbidity and mortality among patients and farmed animals or an increase in economic cost), and results in a *response* by society to minimize the impacts by addressing any part of the DPSIR causal chain [53]. Building on this work, we will categorize information about the social (eg, forces that determine the use of antibiotics) and ecological (eg, microbes in aquaculture) factors related to AMR by the DPSIR components, which will allow us to identify the important cause-effect relationships and potential indicators of changing AMU, AMR, and the impact of responses across the One Health spectrum.

Causal Loop Diagrams

CLDs are models that help visualize how different factors in a system are related [54]. Systems dynamics, public health and

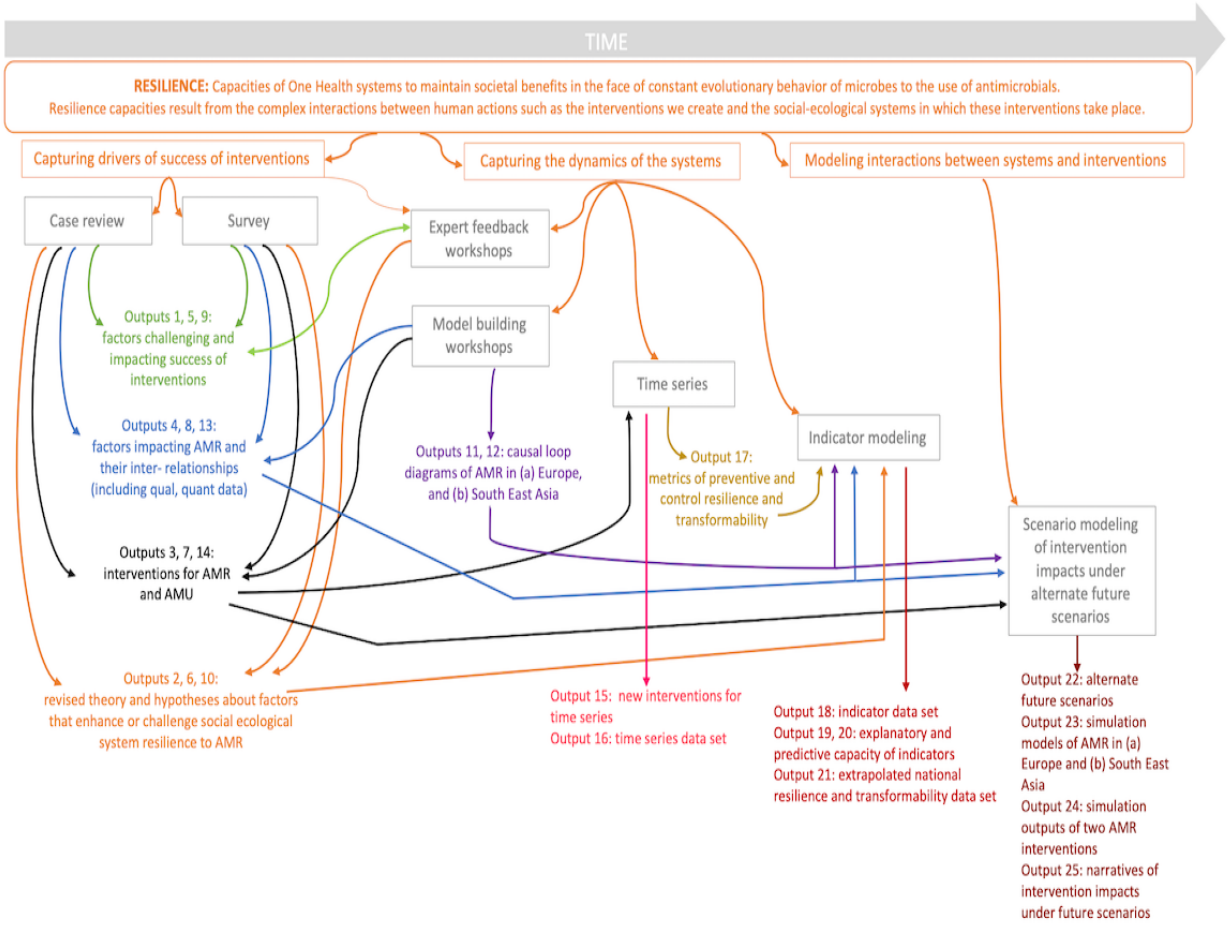
health care, and epidemiology use CLDs to illustrate relationships between explanatory factors and outcomes of interest [55-58]. We will use CLDs to create visual models of the underlying causal structure (factors, connections, and feedbacks) that generates AMR within One Health systems in a high-income region (ie, Europe) and a low-middle-income region (ie, Southeast Asia). These diagrams are useful because they provide a broad context in which decision makers can explore how particular responses and actions may influence the system [59].

Methods

Study Approach

We will conduct this study by applying the SES resilience theory for the first time in an explicit One Health and participatory context using mixed methods. Our approach includes 6 interrelated data collection and analysis activities: a review of interventions published in the scientific literature (herein termed *case review*), a web-based survey to collect information about interventions in the gray literature, participatory workshops, time series analysis, regression modeling of indicators, and scenario modeling of interventions. We will identify published and unpublished interventions addressing AMR or its key pressure AMU via a case review and web-based survey. Intervention impacts and the factors that challenge or contribute to the success of interventions will be determined, findings triangulated against expert opinion during participatory workshops, and complemented using time series analysis methods. Regression modeling to identify indicators that can predict national AMU and AMR dynamics across animal and human health will follow. We will then bring AMR experts (eg, physicians and veterinarians) and experts in other content areas (eg, economics and trade and consumer advocacy) who are not traditionally engaged in discussions about AMR together in participatory workshops to create CLDs of the factors influencing AMR in the European and Southeast Asian food systems. Using relevant data collected throughout our study, we will quantify and convert these CLDs into compartment models to simulate the long-term impacts of selected interventions on AMR under alternate future scenarios, re-engage the aforementioned workshop participants to validate simulation findings, and explore the actions and conditions that decision makers should consider to sustainably limit AMR under each future scenario. Figure 1 shows a visual illustration of our approach, including how theory, methods, and associated outputs interlink. We plan to consolidate our work into an evolving web-based learning platform that will house interventions related to AMR from a One Health perspective and be publicly available for decision makers to choose the interventions most likely to build long-term resilience to the challenge of AMR [60].

Figure 1. Interconnections between social-ecological system resilience theory, methods, and outputs. AMR: antimicrobial resistance; AMU: antimicrobial use.



Case Review

Identifying and Screening Interventions

We will search for interventions addressing AMU or AMR published at any time in the scientific literature using indexed search terms in PubMed and Scopus. The titles and abstracts of each publication will be screened for relevance, and for further screening, retained articles will be read in full. We will include articles that focus on interventions addressing AMU or AMR at subnational, national, or regional levels and exclude articles that are theoretical or policy comparisons or focused on recommendations (eg, AMU guidelines). Additional articles will be identified through reference lists of retained publications and articles recommended by the members of our research consortium. To manage the anticipated large volume of relevant interventions, we will focus on interventions that target important One Health organisms that are most likely to cross between human, animal, and environmental systems and can cause disease in humans and animals (ie, *Escherichia coli*).

Data Extraction

We will use a data extraction framework that is underpinned by the SES resilience theory to extract information about each intervention, including the (1) social system (actors, sectors, and any institutional settings involved with the intervention), (2) bioecological system (microorganisms, intervention targets, resistance of the microorganisms, host population or substrate, and the ecology of transmission), (3) triggers and goals of the intervention (what catalyzed the intervention, intervention aims, and strategies used), (4) implementation and governance of the intervention (the types of sectors or institutions responsible for the intervention and the techniques used to enhance intervention adoption, implementation, and sustainability), and (5) assessment (intervention outcomes and any reported factors challenging or contributing to the success of the intervention) [61]. Two researchers (AL and TG) will independently search, screen, and extract data from retained interventions and assess the study quality of interventions using the Grading of Recommendations, Assessment, Development, and Evaluation system [62]. A third researcher (DW) will review all extracted data and the assessment of study quality to ensure consistency in how data are coded. Discrepancies will be resolved through a consensus.

Analysis

Analysis will involve coding data from each intervention against the 7 principles of the SES resilience theory, highlighted earlier under the *Theoretical Framework and Tools* section, and the additional factors that emerge from the data and are not already captured by this theory, to identify the factors that challenge or contribute to the success of interventions. Where quantitative data exist, appropriate statistics will be applied (eg, nonparametric statistics to analyze trends in the reviewed interventions and conduct meta-analyses).

We will determine the factors that cross-cut interventions and then categorize interventions based on (1) an intervention's success in achieving intended outcomes with recognition that a publication bias toward *successful interventions* likely exists, (2) high-income versus low- or middle-income contexts (eg, Europe or Southeast Asia), and (3) settings (eg, aquaculture or community) to determine if any factors that challenge or contribute to the success of interventions differ by context. These factors will then be compiled and compared with the SES resilience theory, further characterizing the 7 resilience principles highlighted under the *Theoretical Framework and Tools* section, adding any additional factors that emerge from the data, and ultimately revising the theory about what factors enhance system resilience to AMR.

Case Review Outputs

The following lists the outputs for the case study for use in other data collection or analysis study activities: (1) factors that challenge or contribute to the success of interventions that address AMU or AMR found in published scientific literature; (2) revised theory and hypotheses about the factors that enhance or challenge SES resilience to AMR based on case review findings; (3) a list of interventions identified in the published scientific literature that have shown success or less or partial success in preventing or controlling rising AMU or AMR and in transforming a system to low AMU or AMR; and (4) if available, a list of factors that contribute to AMU or AMR and any qualitative or quantitative data that describe identified factors and any relationships between factors.

Web-Based Survey

A voluntary web-based survey will be used to collect interventions that address AMU or AMR in the gray literature to expand the understanding of factors that lead to the success of interventions beyond case review findings.

Sampling and Recruitment

As the survey is an environmental scan of existing interventions with no hypotheses to be tested, no sample size calculation is necessary. All survey activities will adhere to the approved procedures outlined by the University of Waterloo Research Ethics Committee. To identify potential survey participants, we will develop a matrix of regions based on the WHO's definition of regions (Africa, Americas, Southeast Asia, Europe, Eastern Mediterranean, and Western Pacific) [63] and populate it with individuals from human, animal, and environmental sectors per region who either work on AMR or do not work on AMR but work in industries that may impact it (eg, food-producing industry) as identified through (1) the WHO library of AMR National Action Plans [64]; (2) the research consortium's networks (eg, OIE or WHO); (3) web-based search engines (eg, Google); and (4) websites of professional, governmental, nongovernmental, and industry organizations. Contact information will be obtained only from public sources (eg, websites). Potential participants listed in the matrix will be invited to participate in the study via email, which will contain a nonanonymous survey link. Up to 3 reminder emails will be sent. We will announce the survey via a promotional message that will introduce the study and include an anonymous survey link through the mailing lists of national (eg, STRAMA [65]) and global (eg, ReACT [66]) AMR networks. The survey link will direct potential participants to the study information letter in the web-based survey. This letter identifies the study purpose, study investigators, the estimated time to complete reporting

one intervention, data storage, and data protection measures that involve replacing personal identifiers from survey responses with an identification code and storing this code and personal information separately on a secure password-protected platform. Potential participants will provide informed consent by clicking *yes* or *no* to participate before starting the survey. Data collection will cease when (1) no new interventions are reported across participants or (2) within 1 month of the survey implementation, whichever comes first.

Survey Development, Pretesting, and Implementation

This survey will collect the same information as the data extraction framework described under *Case Review*, including the following: (1) social system, (2) bioecological system, (3) triggers and goals of the intervention, (4) implementation and governance of the intervention, and (5) assessment. One question will be presented per screen, and the *not applicable* response option will be offered. On the basis of input from the type of people that will complete the survey, we will ask survey respondents to coordinate reporting with their collaborators to ensure that a given intervention is reported once, share documents relevant to each reported intervention, and provide permission to include their reported intervention(s) and contact information in the web-based learning platform [60].

Up to 5 individuals, identified by the research consortium as highly knowledgeable about AMU and AMR interventions, will be invited through email to pretest the web-based survey and complete a 30-minute follow-up telephone interview to determine if they interpret and answer questions as intended and obtain their impressions about the web-based survey and its contents. Research team members will test the functionality of the survey. Feedback will inform survey revisions.

Analysis

The analysis will involve coding reported intervention data against the 7 principles of SES resilience theory and any additional factors that emerge from the data to determine the factors that challenge or contribute to the success of interventions. Where quantitative data exist, appropriate statistics will be applied (eg, nonparametric statistics to analyze trends in the reviewed interventions and conduct meta-analyses). We will determine the factors that cross-cut interventions and then categorize interventions based on (1) an intervention's success in achieving intended outcomes with recognition that a publication bias toward *successful interventions* likely exists, (2) high-income versus low- or middle-income contexts (eg, Europe or Southeast Asia), and (3) settings (eg, aquaculture or community) to determine factors unique to these contexts that challenge or foster the success of interventions. These factors will be compiled and compared with the SES resilience theory, providing information that further characterizes the 7 principles highlighted under the *Theoretical Framework and Tools* section, adding any additional factors that emerge from the data, and developing hypotheses about what factors enhance system resilience to AMR. We will use the Checklist for Reporting Results of Internet E-Surveys as a guide to inform the reporting of methods and analysis in future publications of the web-based survey [67].

Survey Outputs

The following lists the outputs from the web-based survey for use in other data collection and analysis study activities: (5) list of factors that challenge or contribute to the success of interventions in gray literature; (6) revised theory and hypotheses about the factors that enhance or challenge SES resilience to AMR based on survey findings; (7) a list of interventions that have shown success or less or partial success in preventing or controlling rising levels of AMU or AMR and transforming a system to lowered levels of AMU or AMR from the gray literature; and (8) if available, a list of factors that contribute to AMU or AMR and any qualitative or quantitative data that describe identified factors and any relationships between factors.

Participatory Workshops

Overview

Workshops are a type of research methodology that brings groups of people together to learn from one another, problem-solve, or innovate and, through the process, generate integrated knowledge about a domain of interest to fulfill a research purpose [68]. We will bring together diverse perspectives in 2 types of in-person participatory workshops: (1) expert feedback workshops to triangulate the results of the case review (output 1) and a survey (output 5) against expert opinions to determine factors that challenge or contribute to the success of interventions in a high-income region (Europe) and low- or middle-income region (Southeast Asia) and (2) model-building workshops to develop CLDs of the factors influencing AMR in the food system of a high-income region (Europe) and low- or middle-income region (Southeast Asia). Workshops will last for 8 days (4 days in Europe and 4 days in Southeast Asia). As our expert invitees may be relevant for both types of workshops, we plan to carry out the workshops together to maximize attendance.

Procedures Common to Both Expert Feedback and Model-Building Workshops

For both workshop types, we will select participants from across Europe and Southeast Asia who represent diverse perspectives. For the expert feedback workshops, we plan to recruit 12 to 28 participants in total (n=6-14 in Europe and n=6-14 in Southeast Asia) representing the human, animal, and environmental sectors. These participants will have a broad understanding of interventions addressing AMU or AMR in animals, humans, or the environment and will include stakeholders who work directly with end users (eg, farmers). For the model-building workshops, we plan to recruit new participants for each workshop session and aim for 24 to 56 different participants in total (n=12-28 in Europe and n=12-28 in Southeast Asia) that ideally represent an equal distribution of experts in AMR (eg, physicians, epidemiologists, or veterinarians) and experts in other areas of content (eg, farmers, food retailers, consumer advocates, pharmacists, trade and economics, food security, or conservationists), who may not usually be considered in discussions about AMR, but may directly or indirectly impact AMR. AMR experts will provide a deeper understanding of the AMR context in Europe's and Southeast Asia's food systems

whereas nontraditional experts will help to advance the current understanding of a broader range of factors that may generate AMR, beyond what AMR experts already know. Participants will be identified from (1) the research consortium's networks and (2) web-based search engines (eg, Google), professional networking sites (eg, LinkedIn), social media sites (eg, Twitter or LinkedIn), and websites of professional, governmental, nongovernmental, and industry organizations that address AMR in human, animal, and environmental sectors.

Both workshop types will be led by a facilitator, guided by a semistructured interview guide, audio recorded, and involving note takers to record discussion points. We anticipate that recruited participants will speak English, and we will provide translation if needed.

Key informant interviews may be conducted after both workshop types to capture additional perspectives identified during workshop discussions as important to fill knowledge gaps. Interviews will follow the same semistructured interview guide used in the workshop and be conducted over the phone, 60 minutes in duration, and audio recorded. All participants will receive via email an anonymous and voluntary web-based survey to evaluate the extent to which the workshop or interview approach fosters open dialogue and learning and participants' intentions to apply what they will learn in their work. Data will be descriptively analyzed, and findings will inform improvements to future workshops (eg, scenario modeling workshops described later).

Expert Feedback Workshop Procedures and Analysis

Workshop sessions will begin by welcoming participants and describing the workshop objectives and agenda. After presenting the findings from the case review (output 1) and web-based survey (output 5), experts will discuss whether they agree or disagree with the findings and identify any missing factors that may challenge or contribute to intervention success based on their expert opinion. Discussions will continue until no new information emerges.

Transcripts from workshops and any interviews will be coded and compared across coders (TG, IAL, and MC) for consistency and thematically analyzed to identify the factors that challenge or contribute to the success of interventions. We will compare these findings to outputs 1 and 2 from the case review and outputs 5 and 6 from the survey to further refine the theoretical framework of factors influencing the success of interventions and draw hypotheses about what factors enhance system resilience to AMR.

Expert Feedback Workshop Outputs

The following lists the outputs from the expert feedback workshops for use in other data collection and analysis study activities: (9) factors that challenge or contribute to the success of interventions based on expert opinion and (10) revised theory and hypotheses about factors that enhance or challenge SES resilience to AMR.

Model-Building Workshop Procedures and Analysis

Workshops will begin by welcoming participants, describing the workshop objectives and agenda, and providing background information on AMR as participants will have varying levels of understanding about the topic. The facilitator will introduce a previously developed CLD of factors influencing AMR in Canada's food system [14], and participants will brainstorm what factors and relationships to add, remove, or change in the model to reflect AMR in the European or Southeast Asian food system contexts. They will also identify leverage points and actions that may shift these food systems toward more sustainable management of AMR. Changes to the model will continue until the participants have no new information to share. Although no system model is 100% correct because the external landscape is ever changing, the CLDs will reflect the best estimation of the dynamics that influence AMR in Europe and Southeast Asia based on the perspectives of the participants at the time of data collection [55].

To build these CLDs, 1 researcher (MC) will extract every factor from the workshop and any interview transcripts—any descriptions about the direction and nature of relationships between factors (ie, positive and negative associations) and potential interventions to address AMU or AMR mentioned by participants. Missing information will be added to the model produced during the workshops using appropriate software. Each relationship between factors will be depicted by an arrow (→) to denote its direction, and a positive (+) or negative (−) sign will be added to the arrow to illustrate the nature of the relationship. A positive relationship indicates that 2 factors are moving in the same direction (eg, an increase in X leads to an increase in Y, or a decrease in X leads to a decrease in Y). A negative relationship indicates that 2 factors move in opposite directions (an increase in X leads to a decrease in Y, or a decrease in X leads to an increase in Y). Researchers (IAL, SEM, JP, CC, and MC) will review the transcripts and model and discuss areas requiring clarification regarding the placement of factors and relationships. Disagreements will be resolved through consensus. Each factor in each CLD will be measurable (eg, AMU increases or decreases) and written as a short textual phrase. Transcripts will be thematically analyzed (IAL) to describe key findings from the workshops. The CLDs and a workshop summary of key themes will be sent to participants for validation via feedback.

Model-Building Workshop Outputs

The following lists the outputs from the model-building workshops for use in other data collection and analysis study activities: (11) CLD of factors influencing AMR in the European food system; (12) CLD of factors influencing AMR in the Southeast Asian food system; (13) qualitative or quantitative data that describe each factor and relationship in the CLDs; and (14) a list of potentially promising interventions to address AMR.

Time Series

Overview

The aim of the time series analysis is to complement findings from case reviews, surveys, and expert feedback workshops by quantifying resilience and transformations using time series analysis methods. We will quantify (1) preventive resilience, approximated by the stability of resistance levels over time; (2)

control resilience, approximated by the ability to lower resistance levels following a relatively large increase; and (3) transformability, approximated by the size and duration of reduction in the specific metric.

We will identify different types of interventions (prevention, control, and transformability) with quantitative data to run time series analyses. By creating and applying metrics of resilience and transformability to standardized data formats, a more objective comparison will be developed and can be applied in the future to standard time series. The widespread quantification of resilience in high-frequency time series is challenged by the limited availability of data, different formats, and separating, for example, internal seasonal dynamics from external shocks. We will overcome these challenges by devising metrics designed to standardize reporting formats and annual time series of at least 10 years of length. The methods involve (1) specification of the metrics, (2) data collection and analysis, (3) sensitivity analysis, and (4) cross-validation.

Data

We will use human data from national and regional authorities such as ResistanceMap [69] and the European Center for Disease Control [70]. We will analyze metrics annually for the rates of AMU and AMR (data parameters) in humans and animals from high-income regions (eg, Europe) and low- or middle-income regions (eg, Southeast Asia). For the animal side, standardized and reliable data are limited but will test methods such as the Centers for Disease Control's National AMR Monitoring System for Enteric Bacteria [71]. We will limit our analyses of AMU to drug classes of relevance to *E coli*, an important One Health organism that can live in different places (eg, animals, people, or soil) and can cause diseases in humans and animals.

Analysis

Metrics

Our method quantifies stylized metrics as proxies for the 3 types of resilience and metrics that can be varied in terms of 2 or more threshold values. For example, the adapted control resilience method quantifies the years to achieve an x% reduction in AMU and AMR after a y% increase over a 1- to 5-year period. By varying y and x over the observed variation, a bivariate density distribution is produced, which can be analyzed in terms of quantiles and compared using standard nonparametric or parametric statistics, depending on skew and sample size. Preventive resilience measures the x-year increase in AMU and AMR and can, in contrast to control resilience and transformative success, be applied as a rolling metric to the time series. Transformations will be quantified in terms of duration and proportional decrease following 3 to 5 years of stable high values. For both resilience and transformation metrics, we will apply the metrics to (1) a general set of time series and (2) a subset of time series where we know of specific interventions from the case review and web-based survey (outputs 3 and 7).

Sensitivity Analyses

We will explore the sensitivity of measuring preventive resilience in absolute versus relative terms, the latter by accounting for the mean level of AMR. Similarly, control resilience can be corrected for mean levels of resistance, assuming either a first-order linear or a polynomial relationship between reduction in AMU and reduction in resistance. To overcome the challenge that many countries only have either AMU or AMR data available, but not both, the resilience metrics will be quantified for both AMR and AMU data; the latter serving as a surrogate, for example, by analyzing the ratios of second- to first-line AMU.

Validation

We will cross validate the time series analyses against a subset of the particularly well-documented interventions identified through the case review (output 3) and survey (output 7). For interventions at the national or regional level, this can be done through direct comparison with the broader time series analysis. For local-level interventions, we will acquire the relevant local time series data for cross-validation.

Time Series Outputs

The following lists the outputs from the time series for use in other data collection or analysis study activities: (15) any new interventions identified for the specific purpose of time series analysis; (16) time series data set; and (17) metrics of preventive and control resilience and transformability.

Regression Modeling of National and Regional Indicators of AMU, AMR, and Impacts

Overview

To assess whether currently available indicators predict national AMR dynamics, we will identify, test, and extrapolate indicators of preventive and control resilience and transformability. This will involve (1) specifying, collecting, and analyzing national and regional indicators of resilience and transformability; (2) quantifying the explanatory and predictive capacity of indicators through regression and simulations; and (3) producing an extrapolated data set of resilience and transformability based on these indicators.

Collecting and Specifying Indicators

We will use metrics of preventive and control resilience and transformability from time series analyses (output 17) as a basis for identifying indicators that explain variation in resilience and transformability metrics. National and regional statistics will provide the basis for selecting indicators, and these statistics will be collected from existing databases, such as those hosted by the UN and by contacting regional and national statistics offices. We will select indicators using specific hypotheses about their contribution to resilience and transformability based on findings from the case review (output 2), survey (output 6), expert feedback workshops (output 10), and previous work of coauthors (PSJ and DW) in applying resilience theory and principles in the context of AMR [43,44,49].

We will then code the indicators according to the DPSIR framework.

Driver Indicators

Context-specific driver indicators will be added to a previously developed DPSIR framework [53] using the list of factors contributing to AMU and AMR from the case review (output 4), survey (output 8), and participatory workshops (outputs 11

and 12). For instance, key distal driver variables are sanitation, hygiene, vaccine coverage, animal (farm) densities, husbandry type, and social norms regarding common pool resources. Key proximate driver variables are disease prevalence and incidence and access to antibiotics. We will collect these indicators from international statistics compiled by the UN, WHO, FAO, OIE, and European Union and where national agencies are needed. A preliminary assessment during ongoing work on the DPSIR framework indicates that data availability is sufficient to cover the countries in the time series.

Pressure and State Indicators

We will use data on the key pressure variable (AMU) and the key state variable (AMR) used in the time series.

Response Indicators

Response variables will be scored from a review of national or regional policies led by coauthor DW and grouped into categories of preventive responses (addressing drivers), mitigative (addressing AMU), restorative (addressing AMR), and adaptive responses (addressing impacts). For national indicators, we will in part rely on the WHO-FAO-OIE survey of national actions to limit AMR [72].

Analysis

The explanatory capacity of indicators will be tested on a training subset of the time series and their predictive capacity tested on the full subset of the time series. On the basis of this analysis, we will use a broader data set of national (and possibly regional) statistics and run regression modeling or simulation modeling to perform an extrapolative analysis predicting the resilience and transformability of countries and regions without the necessary time series data available.

Regression Modeling of Indicator Outputs

The following lists the outputs of the regression modeling of national and regional indicators of AMU, AMR, and impacts: (18) data set of social-ecological indicators; (19) explanatory capacity of indicators; (20) predictive capacity of indicators; and (21) extrapolated data set of national resilience and transformability.

Scenario Modeling

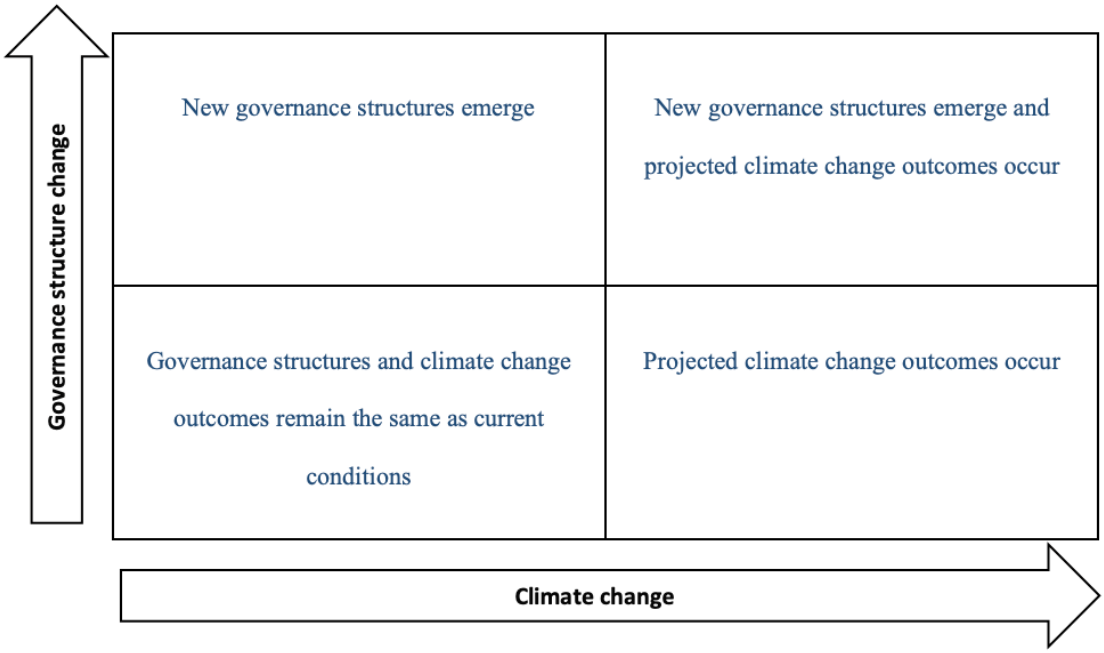
We will conduct 2 types of scenario modeling: (1) mixed methods simulation modeling using fuzzy logic and (2) group-based scenario modeling using a participatory approach [73,74] to explore the range of possible outcomes of selected interventions on AMR in the food system of Europe and Southeast Asia under future alternate scenarios.

Mixed Methods Simulation Modeling Procedures

We will use the CLDs of AMR in the European and Southeast Asian food systems (outputs 11 and 12) and fuzzy set theory [75-77] to build 2-compartment models. We will populate these models using quantitative and qualitative data from the case review (output 4), web-based survey (output 8), modeling workshops (output 13), and from published studies and surveillance data and then convert the data to categorical variables (eg, *high*, *medium*, and *low* categories) to create differential equations [75-77] to simulate the development and movement of AMR in the European and Southeast Asian systems using appropriate software. In the absence of data, we will make reasonable assumptions and document them for transparency.

We will then use these models to explore the impact of selected interventions on AMR over a 50-year timeframe under alternate future scenarios. To select these interventions, our multidisciplinary research consortium will independently rank the list of interventions from the case review (output 3), survey (output 7), and modeling workshops (output 14) from most to least promising and come to an agreement about the top 2 interventions that may impact AMR. To develop our scenarios, we will construct a two-by-two matrix with climate change on one axis and governance structure change on the other axis, two key factors likely to impact the food system over time, to produce the 4 future scenarios illustrated in Figure 2.

Figure 2. Two-by-two matrix of alternate future scenarios circa 2070 based on governance change and climate change.



As a limited amount of data at the European or Southeast Asian food system scale make it difficult to validate the simulation model against a data set, we will take the simulation outputs to the group-based scenario workshops for participant validation [78,79]. If there are insufficient data to construct a mixed methods simulation model, we will only conduct group-based modeling workshops.

Group-Based Scenario Modeling Workshop Recruitment and Procedures

A total of 4 virtual workshops (2 in Europe and 2 in Southeast Asia) lasting 4 days will be conducted. These workshops will bring together diverse perspectives to (1) validate the model and intervention outcomes from the simulation and (2) brainstorm what factors and conditions (eg, polycentric governance systems or multisector participation) are necessary to strengthen the potential for selected interventions to combat AMR over 10-, 30-, and 50-year timeframes under the alternate future scenarios in Figure 2 [80]. These timeframes are common with foresight methods (eg, [81,82]).

To increase stakeholder commitment and their potential to apply what they learn about AMR into action, we will invite via email selected individuals who participated in our model-building workshops described earlier for a total of 12 to 30 participants (n=6-15 in Europe and n=6-15 in Southeast Asia). These participants will represent an equal distribution of experts in AMR (eg, epidemiologists, veterinarians, or physicians) and other areas that may directly or indirectly impact AMR (eg, corporate food industry, trade and economics, or consumer advocacy). If a participant is unavailable, we will identify and approach a new individual representing a similar perspective using the sampling procedures described for the model-building participatory workshops.

Workshops will be led by a facilitator, guided by a semistructured interview guide, and audio recorded. Members of our research consortium will take notes to record the discussion points. After the welcome, introduction, and overview sessions of workshop objectives, the facilitator will present the simulation model and how the 2 interventions impact AMR over a 50-year horizon under various scenarios. Participants will then discuss whether the model and intervention outcomes align with their expert opinions about how the system should behave to validate the model. Through facilitated discussions, participants will also discuss (1) why they believe each intervention will impact AMR under future scenarios, (2) what barriers and challenges may impact intervention success, and (3) what actions and supports (eg, resources, communication systems, or actors) are necessary to ensure intervention success and circumvent barriers and negative consequences over time. Participants will be encouraged to bring forth all ideas until no new information emerges.

Analysis

A researcher (MC) will extract data from transcribed workshop audio recordings to determine whether participants agree with findings from the simulation modeling and any adjustments made to the model about each intervention's probable impact(s) under each scenario of the future in the European and Southeast Asian context. A researcher (IAL) will conduct a thematic analysis and develop narratives that describe how each intervention will behave under each alternate future scenario, and the factors and conditions that should be implemented to sustainably mitigate AMR while maintaining social, economic, and environmental health over time, based on participant feedback.

Scenario Modeling Outputs

The following lists the outputs from the scenario modeling activities: (22) scenarios of alternate futures; (23) simulation model of AMR in the European and Southeast Asian food system; (24) simulation outputs of the impacts of 2 interventions on AMR; and (25) narratives that describe intervention impacts under alternate future scenarios.

Results

Ethics Approval

Ethics approval for activities involving participants has been granted by the University of Waterloo's Office of Research Ethics (ethics clearance numbers 40519 and 41781).

Case Review

A total of 669 interventions have been identified. In addition, 42 interventions specifically targeting *E coli* were analyzed in full based on the SES resilience theory (reporting is underway).

Web-Based Survey

The survey has been sent to 891 individuals who work on AMR or carry out work that may impact AMR from 6 regions of the world (Africa, n=27; Americas, n=443; Southeast Asia, n=117; Europe, n=249; Eastern Mediterranean, n=12; Western Pacific, n=43). Survey analysis is pending.

Participatory Workshops

A total of 4 in-person expert feedback workshops that engaged stakeholders (n=8 from Europe; n=6 from Southeast Asia) representing human (n=5), animal (n=4), human and animal (n=3), and environment (n=2) sectors have been completed.

A total of 4 in-person model-building workshops that engaged 32 stakeholders (n=17 from Europe; n=15 from Southeast Asia) representing advocacy (n=2), nutrition, food security, and food safety (n=5), economics and trade (n=2), human medicine (n=5), pharmaceutical (n=3), agricultural food and animal health (n=10), sustainable food innovations (n=2), environment (n=1), peace and leadership (n=1), and law (n=1) perspectives have been conducted. Analysis is underway.

Time Series

Time series analysis activities are anticipated to be completed by spring 2022.

Regression Modeling of National and Regional Indicators of AMR Dynamics

Activities are anticipated to be completed by spring 2022.

Scenario Modeling

Mixed methods simulation modeling activities and 4 virtual group-based scenario modeling workshops and analysis are anticipated to be completed by spring 2022.

Discussion

Anticipated Findings and Contributions

To our knowledge, this is the first study to apply SES resilience theory, systems thinking, and a One Health approach to better understand how to sustainably combat AMR. Our study is in progress and is not yet complete. However, we anticipate that our study will help make sense of the diversity of actions to tackle AMR and add to our limited understanding of which actions work under what conditions. We intend to consolidate our findings into a web-based platform that will allow stakeholders to add interventions and use the tool to determine what actions to take in their respective contexts. We also anticipate that through a series of participatory workshops that engage AMR experts and stakeholders who may not usually be engaged in discussions about AMR, our study will produce useful tools (ie, CLDs of AMR in Europe and Southeast Asia, and alternate future scenarios) to help build stakeholder capacity to recognize AMR as a CAS and plan interventions under uncertain future conditions. The time series and regression of indicators analyses will help to gain a better understanding of the relationships among drivers, pressures, states, and responses regarding AMR. In addition, as we quantify and carry out simulation modeling using data from our study and the literature, our study will help to identify data gaps for future research.

Conclusions

One Health and systems thinking have gained prominence in public health but can be challenging to conduct because they necessitate collaboration and the integration of knowledge from science and practice across different sectors and disciplines. Our protocol provides other researchers with an example of how to apply these approaches to study a complex public health problem such as AMR with an interdisciplinary research team and involving AMR experts and nontraditional stakeholders. In fact, we developed this paper to help our research consortium bridge our disciplinary-specific knowledge, skills methods, and tools and make our processes transparent so that others can learn from our experiences as we implement this mixed methods study.

Acknowledgments

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Authors' Contributions

PSJ (study coordinator), DW, SH, SEM, and EJP conceptualized the study, and all authors have contributed to the study methods and analyses described in this manuscript. IAL developed the research ethics applications and wrote and revised the manuscript, except for the sections written by PSJ relating to the time series analyses and regression modeling of AMR indicators. MC provided content relevant to her PhD dissertation related to simulation modeling. All authors read, provided revisions in the form of important intellectual content to the manuscript, edited, and approved the final manuscript.

Conflicts of Interest

SH declares Sandoz SAB fees. The remaining authors declare no competing interests.

Multimedia Appendix 1
Examples of how interventions can inform the building of social-ecological system resilience.
[PDF File (Adobe PDF File), 109 KB - resprot_v10i6e24378_app1.pdf]

Multimedia Appendix 2
Social-ecological system resilience principles.
[PDF File (Adobe PDF File), 108 KB - resprot_v10i6e24378_app2.pdf]

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Abbreviations

AMR: antimicrobial resistance
AMU: antimicrobial use
CAS: complex adaptive system
CLD: causal loop diagram
DPSIR: Driver-Pressure-State-Impact-Response
FAO: Food and Agriculture Organization
OIE: World Organisation for Animal Health
PI: principal investigator
SES: social-ecological system
UN: United Nations
WHO: World Health Organization

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Protocol

Understanding the Lived Experience of North American Dental Patients With a Single-Tooth Implant in the Upper Front Region of the Mouth: Protocol for a Qualitative Study

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Abstract

Background: Assessment of the subjective experiences of individuals with maxillary anterior (ie, the upper front region of the mouth) single-tooth implants is limited mainly to quantitative measurements of satisfaction with appearance. Interestingly, there is unexplained variability in the relationship between satisfaction and appearance.

Objective: This qualitative study protocol aims to explore and better understand the satisfaction with appearance and function in a Canadian population with maxillary anterior single-tooth implants treated at a postgraduate university clinic. Thus, we aim to obtain diversity among participants relating to the identification of esthetically pleasing and displeasing cases from a clinician perspective.

Methods: A qualitative research design using interpretative phenomenology analysis (IPA) will provide an adaptable inductive research approach. The participants will be recruited, and consent documents, photographs, digital intraoral scans, and self-administered questionnaire responses will be obtained from them. The transcribed verbatim data from audio-recorded, in-depth, semistructured, one-to-one interviews of the participants will be managed, coded, and analyzed thematically with computer-assisted qualitative data analysis software. The IPA will consider the COnsolidated criteria for REporting Qualitative (COREQ) guidelines when applicable.

Results: For the qualitative interview, we plan to include at least eight patients to conduct up to 1.5 hours of open-ended interviews with each participant aided by an interview guide. Ethical approval was granted by the University of British Columbia Behavioral Research Ethics Board (H19-00107) in May 2019. Two American dental foundations funded this study.

Conclusions: The analysis in this study will elucidate the aspects (including their value) that influence participant satisfaction at different dental implant treatment stages. This will be the first qualitative study on this group of the population to explore and obtain a better understanding of their satisfaction with appearance and function, as well as any other patient-reported outcome measures that could be identified.

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KEYWORDS

esthetic dentistry; esthetics; implant dentistry; patient perception; patient-reported outcome measures; personal satisfaction; phenomenology; single-tooth dental implants; single-unit implant-supported restoration

Introduction

Background

A single missing maxillary tooth in the esthetic zone (ie, tooth sites that are visible in the smile) is increasingly managed with a dental implant, especially when the adjacent teeth are relatively free from disease or damage. At the moment, the problem is that there is an incomplete understanding of the experiences and perceptions patients have with the treatment outcomes of anterior single-tooth implants. Although the prevalence of tooth loss has been decreasing in recent decades [1], up to one-quarter of adults in Western countries are missing at least one anterior tooth [2,3].

It has been indicated that early reports on patient-reported outcome measures (PROMs) in implant dentistry focused on general patient satisfaction, which may not serve to adequately assess the range of impacts of implants on treatment outcomes as perceived by patients. Thus, researchers recommended adding more detailed questions to provide insight into a broader range of aspects that might affect patient satisfaction with implant prostheses [4-12]. Naturally, patient satisfaction with maxillary anterior single-tooth implants is likely influenced by appearance in addition to a range of outcomes broadly related to function, including maintenance and complication issues, and other factors like body image, patient expectations, and financial restrictions, as well as successfully re-establishing comfortable oral function and stable dental occlusion [13-16]. Understanding patient functional experiences, perhaps most notably involving chewing and speech, will be useful for discussing realistic functional outcomes with patients relative to their expectations [17,18]. Having a more thorough explanation of this from a patient perspective would be useful in further understanding patient satisfaction with maxillary anterior single-tooth implants.

It is noteworthy that qualitative studies concerning patient accounts of their experiences with dental implants are limited [19]. The only qualitative study of patients with single-implant crowns focused on the posterior zone [20]. To our knowledge, no study has explored experiences and perceptions among patients with single implants in the anterior zone. Therefore, the ultimate purpose of this research study is to provide a deeper understanding of the lived experience of Canadian patients who have received a single implant in the anterior zone in a university setting. The results from this study will constitute the first dedicated evidence to address this question qualitatively. The analysis of the findings may provide tools to clinicians for improved understanding and communication with this group of the dental population.

Objectives of the Study

This study aims to (1) provide a deeper understanding of patient experiences and perceptions with a single-tooth implant in the anterior zone and (2) explore their satisfaction with their perceived outcomes.

Research Question

The research question is as follows: “What are the experiences and perceptions of patients relating to their satisfaction with a single-tooth implant in the maxillary esthetic region?”

Methods

Design

The study’s aim requires a holistic assessment of the phenomenon in question, which suggests using an inductive qualitative method that allows for broad exploration, including matters that may have been overlooked with existing quantitative approaches. The qualitative research design used to address the research question will be adapted from an interpretative phenomenological analysis (IPA) [21-23].

To optimize the opportunity for participants to tell their stories, the researchers need to acknowledge and try to mitigate the effects of the unequal power relationship that regularly exists between researchers and their participants [24]. Semistructured open-ended interviews play an important role here, since they offer the possibility of contradicting researchers’ preconceived categories of understanding [25-30].

van Manen [31] emphasized that the highest value of phenomenological research in the health sciences may not lie so much in its potential for understanding treatment outcomes and stated, “The ultimate aim of a phenomenology of practice is modest: to nurture a measure of thoughtfulness and tact in the practice of our professions and in everyday life.”

Contrary to following a defined set of methods, IPA involves adjusting an approach to thinking; thus, it can easily become challenging [31]. Thus, the researchers will subscribe to van Manen’s recommendation for a dynamic interaction between six research steps that allow flexibility in working intermittently or simultaneously, back and forth between steps, as a form of an “interpretative circle,” depending on the evolving research needs [31,32].

Planning and Developing the Method Based on van Manen’s Framework

Step 1: Turning to the Nature of Lived Experience

This step involves framing a research question. The deep questioning of a research subject will encourage researchers to reflect on their thoughts more profoundly, which initiates the interpretation process. For instance, the research question associated with the phenomenon will constantly be on the researchers’ mind, which will allow for its intentional refinement in the context of this study.

Step 2: Investigating Experience as We Live It

An important point to “as we live it” is that the researchers shall abandon preconceived notions on a topic since our experience is full of assumed prejudices. Interpreting a lived experience is both the aim and the source of IPA. Thus, every part of a

participant's life world (ie, the world as immediately experienced, not only the natural world, but also the world of values and human practices) needs to be scrutinized for lived experience material to generate ideas about its essence. Probing questions will facilitate the assessment. For example, "How important is this to you?" and "Does this aspect have any other meaning for you?" are two of several probing questions used to support the interview guide.

Step 3: Reflecting on the Essential Themes That Characterize the Phenomenon

In this step, content analysis and the determination of essential themes are accomplished. The analysis is subjected to scrutiny by reflecting on the recognized themes. Additionally, it aims to extract the essential meaning of a phenomenon by asking what constitutes the nature of this lived experience. Thus, this study will try to explore what constitutes the nature of perceptions associated with having a single-tooth implant in the esthetic zone and how these perceptions are shaped by beliefs, values, and needs. A lived experience in an interview context is really the spoken perception of lived experience and even the participant's interpretation of these perceptions.

Step 4: Describing the Phenomenon in the Art of Writing and Rewriting

This is particularly critical in the analytic phase, where writing is integral to the interpretive process rather than simply its final step. Concerning the integral nature of writing, van Manen [32] stated, "To write is to measure our thoughtfulness. Writing separates us from what we know and yet it unites us more clearly with what we know. Writing teaches us what we know, and in what way we know what we know."

Moreover, writing demands the researchers display the interpretive views on paper and thereby externalize what is inside. In other words, the thoughts and feelings of the participants become perceptible through writing.

Step 5: Maintaining a Strong and Oriented Relation to the Phenomenon

In this step, producing appropriate depth and richness in the written text helps researchers remain attuned to the central research question. Not doing so may yield written interpretations with overly superficial speculations or presumptions. Thus, the researchers will try to persist with an intentional focus on reflecting participant experiences related to the research question.

Step 6: Balancing the Research Context by Considering the Parts and the Whole

IPA aims to construct text as a comprehensive representation of the phenomenon. In the process, van Manen suggests it is essential that researchers pay attention to each evolving part concerning the whole of one's study. As such, the results of this study will be interpreted and presented by arranging them as themes and subthemes, relating these to the "whole" relative to the research question.

Setting

This is a single-center study involving a postgraduate teaching clinic at the University of British Columbia (UBC) Faculty of Dentistry in Vancouver, Canada. The dental specialties of Periodontology/ Periodontics and Prosthodontology/ Prosthodontics are involved in the implant surgery and the implant planning and restoration, respectively.

Patient and Public Involvement

There is no patient or public participation in the design or discussion of this qualitative study protocol.

Qualitative Data Collection

To conduct this study, in-depth, semistructured, open-ended interviews using an interview guide will be conducted to collect data. The interviews might be pilot tested.

Participant Recruitment and Informed Consent

Participants will be recruited from among existing Faculty of Dentistry patients. Postgraduate dental students from the Prosthodontics and Periodontics specialty programs will be contacted and exposed to a standardized study advertisement to identify potential participants among their assigned patients, after which the students will provide the advertisement to potential participants. The students will not share the patients' names or contact information with the researchers without first obtaining the patients' permission. Once potential participants identify themselves to the researchers by stating interest in participating in the study, a letter of initial contact will be sent via email, followed by a tentative invitation to participate in the study if their interest is confirmed. Next, an informed consent form will be sent to the participant candidates more than 48 hours in advance of arranging a time to meet for data collection. When each potential participant arrives at the clinic, the informed consent will be reviewed with the aim of having their questions answered and the informed consent signed if agreeable. The ranges of participant demographic characteristics will also be obtained and presented as a group and individually.

Participant Interviews

The primary data collected for this project will be qualitative participant perceptions gathered through a semistructured, one-to-one, in-depth interview with each participant, using an interview guide based on open-ended questions (Textbox 1 and Multimedia Appendix 1), guided by literature on the subject and the research question [33]. An advantage of face-to-face interviews is that they can often be conducted in a relaxed atmosphere to offer better communication than telephone interviews to develop rapport potentially; however, the cost is higher [34].

Textbox 1. Interview topic guide.

Part 1: Introductory background questions (icebreaker)
Part 2: Is about your overall satisfaction with the implanted tooth
Part 3: Is about your satisfaction with the appearance (or look) of your implanted tooth
Part 4: Is about satisfaction with your functioning and social experiences relating to your implanted tooth
Part 5: Any other important experiences that affect satisfaction with your implanted tooth, such as complications, maintenance, and financial aspects
Part 6: Surgical aspects of the implant-tooth treatment

The interview guide to be used in this study will contain several central questions in an open format to stimulate the interviewee to dialogue, as well as probing questions to evoke past experiences and to stimulate more reflective thinking. Phenomenological questions seek to reveal perceived meaning in the experiences related to the phenomenon. Therefore, phenomenological description refers to understanding the meaning of a phenomenon. This resulting description and interpretation are not associated primarily with outer knowledge based on generalizing observations and measurable data [31,32]. Moreover, phenomenological questions should not necessarily be seen as complete, in an a priori fashion more typical of deductive investigations, and are more usually ambiguous and unfinished, especially at the outset. However, in the context of health science research, these questions might be more profoundly understood to enable health professionals (eg, dental clinicians) to become more openly sympathetic and sensitive to the difficult situations that patients could face [31].

Additionally, the participants' identities would remain anonymous and their answers would be independent of their continued opportunity for clinical care. It will be clearly explained to the participants that these interviews would not have any consequence for their future relationship with their dental specialty students or staff.

After establishing contact with each participant and collecting their basic clinical data (as noted), they will be invited individually to a small quiet seminar room near the dental clinic to have a conversation in privacy. Additionally, active listening techniques will be used to encourage participants to elaborate on their experiences but without unnecessarily interrupting them [35]. The researchers will audio record the interview using two small digital recorders only with the participant's consent. The reason for double recording is in case one recorder malfunctions. The participants will be informed when recording is started and stopped. When the interview concludes, participants will be asked if they could be contacted again if there is a need for clarification. The informed consent states the authorization for audio recording the participants' interviews. If some participants decide that they do not approve the audio recording of the interview at any stage, they will be excluded from the study.

Reflective Methods for Data Analysis

As an analytical process, phenomenological reflection aims to understand the central meaning of an experience and of conglomerations of experiences as reflecting the phenomena of interest, which can become a strenuous and challenging assignment [31]. As mentioned earlier, the philosophical basis for phenomenology intentionally avoids following a prescriptive scheme for analysis; thus, "data explication" may be a more accurate term in this context than "data analysis." Data explication is fundamentally a multilayered progression of defining emerging themes [31,36]. Nonetheless, it is necessary to use the idiographic and hermeneutic philosophical basis of phenomenology in the data explication process [35,37].

Thematic Statement Isolation

The analyzed interview transcriptions will be tabulated initially as anonymized analytical themes with the assistance of NVivo version 12 qualitative software (QSR International Pty Ltd) [38,39]. Consistent with an emerging IPA approach, the qualitative themes will be developed from analysis of the transcript data derived from the first three interviews to develop additional avenues for the emerging investigation, which will be adopted through an ongoing iterative modification of the interview guide for subsequent interviews. A word frequency query will be used to verify possible themes at the early stages in the project. The major and minor themes related to the research question will be narratively presented.

Isolation of thematic statements will commence after the interviews are transcribed. van Manen has proposed the following three approaches for isolating themes [32]:

1. The detailed or line-by-line approach: The researchers question the meaning of each sentence related to the phenomenon only after paying close attention to the sentence.
2. The highlighting or selective approach: The researchers question the sentences that appear crucially related to the experience of interest, which are then highlighted after iteratively reviewing the related paragraphs.
3. The holistic reading approach: In reviewing the whole text (or at least a whole section of text), researchers' questioning of an individual sentence reveals the meaning of the text as a whole, in the context of the phenomenon of interest. In other words, these sentences contain the meaning of the phenomenon of interest.

Therefore, a balance of research perspectives will be attempted considering both the individual elements and the whole [31] in the context of keeping the enriching notion of the "interpretive circle" active in the analysis [40]. When writing in IPA, the way that ideas are expressed is as important as the ideas themselves because that is what will transmit the meaning of the experiences to the reader who is then inducing their reflection and understanding [32,41]. Themes will be supported in writing the results by displaying participants' quotes along with a subjective interpretation of their experiences

Field Notes

Field notes will also be considered throughout the data collection and analysis process. These are mainly to assist in building a description of the context of the interview and analysis processes, which prompt researchers to pay attention to the physical environment and encourage them to reflect and identify any potential bias [42].

Rigor

In qualitative studies, rigor indicates being precise, meticulous, and firm with accuracy to decrease possible subjectivity [43]. If rigor were lacking, qualitative research would be seen as fictitious and meaningless for enlightening the phenomenon of interest [44].

IPA also aims to safeguard fidelity and integrity despite there being no consensus on specific techniques for establishing rigor in interpretative research [45]. Nonetheless, the idea is that an independent audit of the research methods should still be feasible when defined coherently and where trustworthiness is elegantly attained [45,46].

This study will take into consideration the COnsolidated criteria for REporting Qualitative research (COREQ) guidelines [47]. Among the strategies for ensuring the validity of a study, the concepts of "rich, thick description," "member checking," "clarifying research bias," and "peer debriefing" will be used [24].

Reflexivity

It is understood that researchers' behaviors, interests, and knowledge might impact the study atmosphere and data; consequently, critical reflective discerning, or reflexivity, is required during the whole study development [48].

In using van Manen's framework, controversy arises from the fact that each academic may not comprehend a phenomenon in the same manner [45,49]. This is not difficult to understand since each investigator or academician carries personal preunderstandings, perspectives, and experiences into IPA [49,50]. Thus, the appraisal of researchers' personal preunderstandings and experiences forms part of reflexivity [49]. The researchers will practice reflexivity during the study.

Member Checking

Member checking has been defined as criticism attained from interviewees to correct, comment, or approve the investigators' findings, interpretations, or results [51]. There are many strategies for member checking, such as having a participant review a synthesis of their case report, a copy of the research report, a copy of emerging findings, a complete copy of the transcript, or some combination of these strategies [51]. Automated transcription services will be generated from the audio recordings, and these will be verified and corrected by the authors.

Many scholars doubt that member checking can improve the attributes of qualitative research [47,52]. Nevertheless, the authors will apply member checking because it would be another opportunity to confirm the participants' interpretations of their perspectives and experiences.

Triangulation

In IPA, triangulation refers to assessing the value of data through the convergence of discoveries from diverse sources. Triangulation can also refer to analyst triangulation, which is the development of a broader understanding of the phenomenon in question along with improved analysis [53,54].

In this study, such analyst triangulation will be attempted by various methodological perspectives available for observing the data and developing the interview topics followed by the analysis [21,55]. The processes of isolating themes and interpretive analysis, as well as the writing, will be monitored and examined by the authors and research collaborators, hence further fulfilling the praxis of analyst triangulation. More specifically, an experienced qualitative senior researcher (SRB) will revise the work in full at every stage.

Results

Participant Sampling

"Purposive sampling" will secure participants with a variety of characteristics in this study [46,55]. To satisfy one of the secondary aims, "criterion sampling" is the type of purposive sampling used [56] to look for at least two participants meeting the criterion of having the experience of living with a maxillary anterior single-implant tooth that clinicians objectively consider esthetically unsatisfactory, but the participants consider satisfactory. Thus, this study attempts to include a minimum of eight patients whether or not saturation had been achieved earlier. Moreover, understanding the satisfaction of an inadvertently homogenous sample of participants, who would have either pleasing or displeasing outcomes based on objective parameters, would unnecessarily limit a diverse interpretation of the study as a whole.

To facilitate identification of diversity among participants relating to the identification of esthetically pleasing and displeasing cases from a clinician perspective, standardized photographs from a digital camera (Canon EOS Rebel T7i; Canon Inc) with a macro lens (EF 24-105 mm f/4L IS II USM; Canon Inc) and maxillary virtual cast models (ie, Standard Tessellation Language [STL] files in Preview app version 11.0; Apple Inc) generated from an intraoral scan (TRIOS intraoral scanner; 3Shape A/S) will be obtained for each participant, based on the materials required for using a validated objective esthetic index (the pink esthetic score [PES]/white esthetic score [WES]) [57-59]. Two experienced clinician researchers (KIA and KI), calibrated for esthetic analyses, will independently evaluate these materials, and the resulting objective scores will be used to categorize the participants descriptively. A score of 6 (out of a maximum of 10) for either PES or WES, and 12 (out of a maximum of 20) for PES and WES combined will generally be considered satisfactory.

The study inclusion criteria and the patients' characteristics are provided in Table 1. The exclusion criteria are as follows: (1) two or more adjacent maxillary premolar or anterior teeth restored with implants; (2) any missing maxillary premolar or anterior teeth not yet restored with a fixed dental prosthesis; (3) lack of attendance at follow-up appointments regularly

scheduled in the Faculty of Dentistry clinics; and (4) inability to converse in English.

Ideally, our sample would also have an heterogenous distribution of age and sex. In other words, at least four men and four older participants would be included. As is the nature of phenomenological research, the sampling strategy is adaptable, depending on the research needs. The in-depth and rich nature of individual cases is another important factor in defining sample size in phenomenological research [35].

Table 1. Purposive sampling for the study: participant characteristics.

Variable	Inclusion criteria	Rationale
Sex	Female or male	To include experiences from both sexes
Age	People older than 18 years	At age 19 years, people are considered adults in British Columbia. A person rarely receives an implant prior to 19 years of age
Dental condition	Partially edentulous patients who had a maxillary anterior tooth or premolar replaced by an implant-supported crown, where natural teeth have adjacent and contralateral teeth	To explore the experiences and perspectives of this sample exposed to the homogenous intervention
Esthetic objective score	Acceptable or unacceptable pink esthetic score and white esthetic score	To report a range of thoughts and to explore whether patients' implant crown experiences are influenced by the objective esthetic outcomes
Treatment stage	After the patient had the final implant crown for at least 12 months	To include all ranges of experiences at different follow-up periods
Capacity to consent	Stable mental health	The participant should be able to give details of the experience during the interview and be able to provide or reject consent
Language	Conversant in English	Because translation will not be considered, the interviews will have to be carried out in English
Location	Regular patient of the University of British Columbia Dental Clinics	This is the location where the treatment has been fully delivered (surgery and prosthesis) and where the study will be conducted

Data Saturation

The concept of saturation posits that new information does not improve a previous understanding of the studied phenomenon; hence, in IPA, it signifies there is no need to conduct more interviews. Saturation has been criticized for the inherent degree of vagueness and discrepancies in determining how to accomplish, measure, and judge it appropriately. Moreover, it has been stated that when considering the sample size of a qualitative study, six to 10 interviews may suffice to reach data saturation, but only when the research question is considered to be well focused and the participants' characteristics are not overly diverse [60]. As a reasonable comparison, previous qualitative studies on patients with dental implants included between five and 16 participants [17,61,62]. As noted, this study estimates achieving saturation in the process of including a minimum of eight participants.

Additional Data Collection

Each participant will be scheduled for a maximum of 2.5 hours for the background data collection and interview session. At the beginning of the session, the consent form will be read and signed. The participants will have two digital photographs taken of the maxillary teeth (a social smile expression [dynamic position] with and without standard dental cheek retractors to display the teeth). A digital impression or intraoral scan of the upper jaw will be performed, and a semistructured interview will be conducted (see the Methods section). A subjective self-administered questionnaire will be applied with the purpose of having repository data in case this may be needed for a quantitative objective that has not been considered in the present protocol. At the end of the session, a payment receipt form will be signed by the participants.

Ethics

Ethical principles for medical research involving human subjects specified in the Declaration of Helsinki were considered when applying for ethical approval [63]. A Minimal Risk Certificate of Approval has been obtained from the UBC Behavioral Research Ethics (BREB) Board. This warrants due consideration of the participants' safety, dignity, and well-being, in addition to respecting their rights. Ethical approval was granted by the UBC BREB Board (H19-00107) in May 2019.

Peer Review

This study has been funded by two American dental foundations. This study protocol has undergone an independent, high-quality, and impartial peer review by its funders and four external reviewers of *JMIR Research Protocols*.

Dissemination of the Findings

The authors will prepare manuscripts and disseminate the findings through appropriate peer-reviewed journals.

Availability of Data and Materials

This protocol does not contain data sets. All data generated or analyzed during this study will be included in a data repository in the published article.

Discussion

Study Significance

This paper describes how to use quantitative data for further categorizing the recruited participants purposively and how the qualitative data will be synthesized in an interpretive phenomenological approach. This is valuable since a previous study about mandibular implant overdentures suggested that patient satisfaction may be influenced by several factors that may not be considered in previous quantitative studies [6]. To the authors' knowledge, this is the first study specifying qualitative methods in the field of oral health and dental medicine to explore patient perceptions of experiences with single-tooth implant restoration in the maxillary anterior region of the mouth. This information is expected to deepen dental clinicians' understanding of the unexplained results previously reported in quantitative studies about this particular group of the dental population. The findings can also inform further development of PROMs to provide clinicians with tools to improve their communication with these patients [64]. This may also direct future developments in dental intervention satisfaction research and the creation of patient information and education resources [65], concentrated on strategic areas to be highlighted after data analysis.

Limitations

There is an exceptional opportunity to understand holistically (eg, behaviors, perceptions, beliefs, and emotions) the phenomenon in question for the first time by analyzing the rich detailed data to be collected from the in-depth interviews. Quantitative approaches have failed to do so since their settings might not reproduce genuine comportment, and the interpretation of unusual or conflicting outcomes is nearly impossible [21]. However, the authors acknowledge that qualitative research is not a limitation-free approach. The main drawbacks of qualitative methods are the complexities to collect and analyze the data, which consume resources (ie, time and money), and the imperfect ability to envisage and generalize (ie, external validity) the results [21]. Nevertheless, the proposed qualitative study is required to complement what is evidenced by the vast amount of quantitative studies available [4,59,65-67].

Conclusions

This is the first IPA study protocol to propose exploring dental patients' lived experience after having a missing maxillary anterior tooth replaced by a single-tooth implant. The study will use a rigorous design and methodology to capture the lived experience of this group of the population. The findings may provide tools to clinicians for improved understanding and communication with dental patients. This qualitative study will recruit participants from only one university clinic and may not be considered entirely representative of all Canadian dental patients with a single-tooth implant in the esthetic zone.

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Authors' Contributions

KIA and SRB conceptualized this study protocol and approved the final version of the protocol. KIA wrote the initial draft of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide about the experiences and perceptions of patients with a single-tooth implant crown in the esthetic zone.
[PDF File (Adobe PDF File), 132 KB - resprot_v10i6e25767_app1.pdf]

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Abbreviations

BREB: Behavioral Research Ethics Board
IPA: interpretative phenomenological analysis
PES: pink esthetic score
PROM: patient-reported outcome measure
UBC: University of British Columbia
WES: white esthetic score

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Protocol

COVID-19 Infection, Reinfection, and Vaccine Effectiveness in Arizona Frontline and Essential Workers: Protocol for a Longitudinal Cohort Study

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Abstract

Background: COVID-19 has spread worldwide since late 2019, with an unprecedented case count and death toll globally. Health care personnel (HCP), first responders, and other essential and frontline workers (OEWs) are at increased risk of SARS-CoV-2 infection because of frequent close contact with others.

Objective: The Arizona Healthcare, Emergency Response, and Other Essential Workers Study (AZ HEROES) aims to examine the epidemiology of SARS-CoV-2 infection and COVID-19 illness among adults with high occupational exposure risk. Study objectives include estimating the incidence of SARS-CoV-2 infection in essential workers by symptom presentation and demographic factors, determining independent effects of occupational and community exposures on incidence of SARS-CoV-2 infection, establishing molecular and immunologic characteristics of SARS-CoV-2 infection in essential workers, describing the duration and patterns of real-time reverse transcription–polymerase chain reaction (rRT-PCR) positivity, and examining postvaccine immunologic response.

Methods: Eligible participants include Arizona residents aged 18 to 85 years who work at least 20 hours per week in an occupation involving regular direct contact (ie, within 3 feet) with others. Recruitment goals are stratified by demographic

characteristics (50% aged 40 years or older, 50% women, and 50% Hispanic or American Indian), by occupation (40% HCP, 30% first responders, and 30% OEWs), and by prior SARS-CoV-2 infection (with up to 50% seropositive at baseline). Information on sociodemographics, health and medical history, vaccination status, exposures to individuals with suspected or confirmed SARS-CoV-2 infection, use of personal protective equipment, and perceived risks are collected at enrollment and updated through quarterly surveys. Every week, participants complete active surveillance for COVID-like illness (CLI) and self-collect nasal swabs. Additional self-collected nasal swab and saliva specimens are collected in the event of CLI onset. Respiratory specimens are sent to Marshfield Laboratories and tested for SARS-CoV-2 by rRT-PCR assay. CLI symptoms and impact on work and productivity are followed through illness resolution. Serum specimens are collected every 3 months and additional sera are collected following incident rRT-PCR positivity and after each COVID-19 vaccine dose. Incidence of SARS-CoV-2 infections will be calculated by person-weeks at risk and compared by occupation and demographic characteristics as well as by seropositivity status and infection and vaccination history.

Results: The AZ HEROES study was funded by the US Centers for Disease Control and Prevention. Enrollment began on July 27, 2020; as of May 1, 2021, a total of 3165 participants have been enrolled in the study. Enrollment is expected to continue through December 1, 2021, with data collection continuing through at least April 2022, contingent upon funding.

Conclusions: AZ HEROES is unique in aiming to recruit a diverse sample of essential workers and to prospectively follow strata of SARS-CoV-2 seronegative and seropositive adults. Survey results combined with active surveillance data on exposure, CLI, weekly molecular diagnostic testing, and periodic serology will be used to estimate the incidence of symptomatic and asymptomatic SARS-CoV-2 infection, assess the intensity and durability of immune responses to natural infection and COVID-19 vaccination, and contribute to the evaluation of COVID-19 vaccine effectiveness.

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KEYWORDS

SARS-CoV-2; COVID-19; health care personnel; first responders; essential workers

Introduction

COVID-19, caused by the betacoronavirus SARS-CoV-2, has spread worldwide since late 2019, with at least 80 million confirmed cases and 1.8 million deaths reported globally in the year since discovery of the virus [1].

COVID-like illness (CLI) includes symptoms of fever or chills, cough, shortness of breath, sore throat, diarrhea, muscle aches, and loss of smell or taste [2]. Outbreak reports and mass testing initiatives suggest that a substantial proportion of individuals who test positive have no symptoms [3-6]. However, the proportion of confirmed cases with true asymptomatic infection is likely overestimated due to incomplete symptom assessment, inadequate follow-up to accurately classify presymptomatic individuals, and potential misclassification of those with previously unrecognized infection as asymptomatic [7]. Immigrant, racial and ethnic minority, and low-income communities have experienced a disproportionate burden of SARS-CoV-2 infections [8]. Severity of illness also differs by sociodemographic characteristics, with older adults and those with underlying health conditions at the highest risk of severe outcomes and death [9]. Optimizing public health responses requires further scientific study to estimate the incidence of infection, severity of illness, and variable immune response in sociodemographically diverse communities at high risk for infection [10].

Individuals in certain occupations are at increased risk of SARS-CoV-2 infection because of frequent close contact with others, including health care personnel (HCP), first responders, and other essential and frontline workers (OEWs). Recent studies highlight the elevated risk of exposure and infection among HCP [11-13], with more severe outcomes experienced by racial and ethnic minority HCP [14,15]. Less evidence exists, however, on transmission risks and severity of illness among OEWs [16,17]. First responders face a variety of exposures, including entering the homes of people with unknown disease status and performing aerosol-generating procedures, such as resuscitation [18]. Other essential and/or frontline occupational sectors with potentially high SARS-CoV-2 exposure include schools and childcare, agriculture and food production, energy, water and wastewater, retail (eg, grocery stores and warehouses), trades (eg, construction and plumbing), and nonprofits and social service organizations [19-21].

Prospective monitoring of symptomatic and asymptomatic infection is necessary to assess the combined epidemiological, immunological, and clinical impact of COVID-19 among essential workers [22]. Recent studies suggest that SARS-CoV-2 immunoglobulins M, G, and A (IgM, IgG, and IgA) are detected in various combinations in variable numbers of individuals in the first 2 weeks of infection, with IgG detected in most subjects after 14 days [23-25]. Although antibody response peaks at 16 to 42 days postinfection [23-26], and IgM and IgA levels decline, levels of IgG against the spike protein remain stable; protective immunity of at least 6 months has been measured, and much longer immunity is anticipated based on previous studies of coronaviruses—up to 17 years for SARS-CoV-1—and other acute viral infections [27-29]. Factors associated with variable immune response, including neutralizing (no infection), protective (mild to asymptomatic infection), or enhanced (severe symptoms) [30,31], are not yet fully understood for SARS-CoV-2.

The US Food and Drug Administration (FDA) has authorized the distribution of the first COVID-19 vaccines under Emergency Use Authorization (EUA), and the US Centers for Disease Control and Prevention (CDC) has recommended prioritization of vaccination for HCP, first responders, and OEW populations [32,33]. However, there is limited knowledge of vaccine intent and hesitancy among essential workers and of vaccine efficacy among those who were seropositive for SARS-CoV-2 prior to vaccination.

The Arizona Healthcare, Emergency Response, and Other Essential Workers Study (AZ HEROES) will follow a cohort of 4000 essential workers who are demographically representative of Arizona and stratified by prior exposure to SARS-CoV-2, such that about half are seronegative and half seropositive. The study affords researchers the opportunity to assess multiple knowledge gaps regarding the epidemiology and immunology of SARS-CoV-2 infections among a diverse statewide sample of essential workers with high exposure potential. AZ HEROES has also been expanded to evaluate immune parameters and incidence of SARS-CoV-2 infection following COVID-19 vaccination in previously seronegative and seropositive individuals (Table 1).

Table 1. Primary and secondary objectives for the AZ HEROES[a] study of SARS-CoV-2 infection and immunity in a statewide cohort of essential workers stratified by seronegative and seropositive cohorts.

Type of objective	Objectives per cohort	
	Seronegative cohort[b]	Seropositive cohort[c]
Primary	• Estimate incidence of SARS-CoV-2 infection in essential workers by symptom presentation and demographic factors • Estimate the relative risk of infection with SARS-CoV-2 versus influenza during influenza season • Determine independent effects of occupational and community exposures on incidence of SARS-CoV-2 infection	• Establish molecular and immunologic characteristics of SARS-CoV-2 infection in essential workers • Describe the duration and patterns of rRT-PCR[d] positivity • Describe levels of total antibodies, neutralizing antibodies, and other immune parameters over time • Examine postvaccine immunologic response in those previously infected
Secondary	• Examine the role of knowledge, attitudes, and practices related to SARS-CoV-2 in exposures and incident infection • Identify predictors of vaccine hesitancy and uptake by occupation • Compare incidence of infection in vaccinated vs unvaccinated essential workers	• Describe severity and impact of illness on essential workers • Examine predictors of severe disease among those naturally infected with SARS-CoV-2 • Estimate incidence of SARS-CoV-2 reinfection • Assess predictors of vaccine hesitancy and uptake among those with history of natural infection

[a]AZ HEROES: Arizona Healthcare, Emergency Response, and Other Essential Workers Study.

[b]Includes person-time contributed by individuals enrolled as seronegative who do not become naturally infected during the study *and* person-time contributed by individuals enrolled as seronegative *before* becoming infected during the study.

[c]Includes person-time contributed by individuals enrolled with prior evidence—viral or serologic—of SARS-CoV-2 infection *and* person-time contributed by individuals enrolled as seronegative *after* becoming naturally infected during the course of the study.

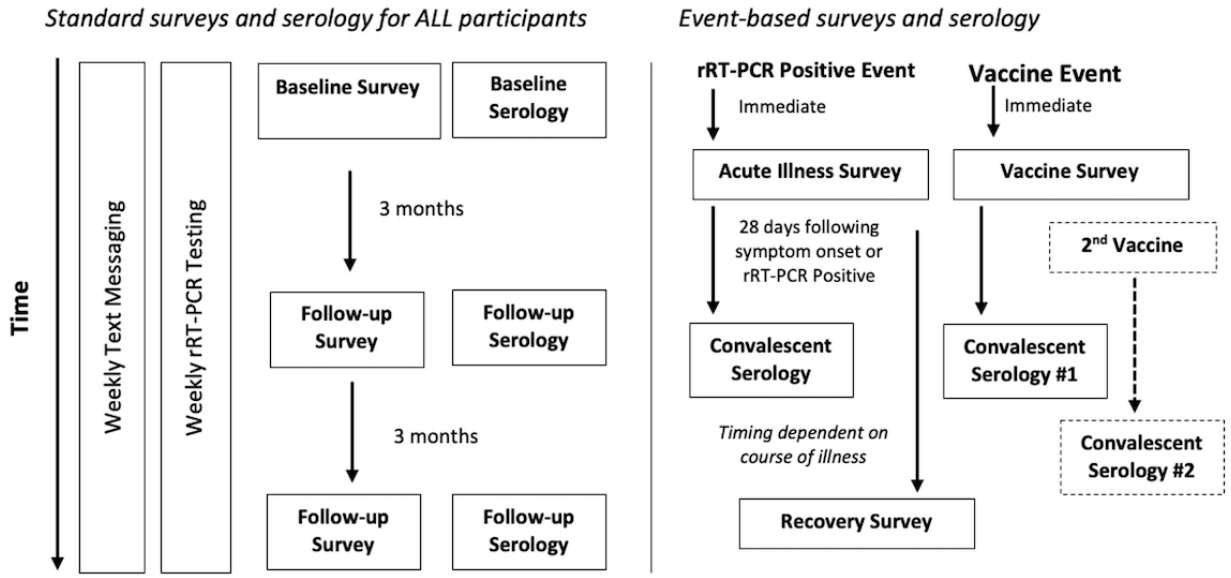
[d]rRT-PCR: real-time reverse transcription–polymerase chain reaction.

Methods

Study Design

AZ HEROES is a prospective cohort study with the goal of following 4000 essential workers, including 2000 seronegative and 2000 seropositive—defined as evidence of SARS-CoV-2 infection by serologic testing—individuals throughout the state of Arizona (Figure 1). The study duration is planned for July 2020 through April 2022.

Figure 1. AZ HEROES flow of activities for baseline, follow-up, and event-based surveys and serology occurring in the context of weekly rRT-PCR testing and text-based symptom surveillance. AZ HEROES: Arizona Healthcare, Emergency Response, and Other Essential Workers Study; rRT-PCR: real-time reverse transcription–polymerase chain reaction.



Setting

The state of Arizona has 7.2 million people residing in 15 counties and 22 sovereign American Indian communities. Nine of Arizona's counties are designated as rural [34], although the majority of the population resides in the greater Phoenix and Tucson metropolitan areas. Arizona has large minority populations, with 32% Hispanic and 5% American Indian populations [35].

Participants

Eligibility Criteria

Eligible participants include Arizona residents aged 18 to 85 years who currently work at least 20 hours per week in an occupation involving regular direct contact (ie, within 3 feet) with others, assessed at the participant level. We have intentionally chosen a broad occupational category for frontline and essential workers in order to capture the full breadth of occupations that cannot socially distance when conducting their work [36], as well as an inclusive age range because 13.9% of the Arizona workforce is over the age of 65 years [37]. The occupations are categorized as HCP, first responders, or OEWs. HCP include clinical providers and support staff in inpatient, outpatient, or residential settings. First responders include firefighters, emergency medical services, law enforcement, border patrol, and correctional officers. OEWs include workers in the following sectors: education, agriculture and food processing, public and other transportation services, solid waste collection, warehouse and delivery, utilities, government and community-based services, childcare, information technology, environmental services, and hospitality. All participants must have access to a smartphone or internet-connected computer, a mailing address, and the ability to speak or write English or Spanish. Exclusion criteria include receipt of a COVID-19 vaccine prior to enrollment, although we continue to follow participants who are vaccinated during the study. The majority of the cohort of the HCP and first responders were recruited prior to vaccine availability.

Recruitment Strategy

In order to enroll 4000 participants as quickly as possible, we have employed a multipronged recruitment strategy. First, we are recruiting from ongoing Arizona-based COVID-19 testing activities, such as university-driven antibody and saliva testing initiatives and serology surveillance conducted by the state health department in selected occupations (eg, nursing homes and correctional facilities). Second, we have partnered with community-based COVID-19 cohorts to recruit participants. The selected cohorts are low-touch and send periodic surveys to participants with little to no overlap in scope. For the testing and existing cohort populations, we directly contact individuals that indicate they would be willing to be contacted for future research. Third, the study accepts self-referrals, so we have developed a marketing strategy to increase general study awareness through press releases, targeted recruitment to occupations, and social media.

All recruitment and enrollment activities are conducted remotely utilizing a virtual call-center platform and REDCap (Research Electronic Data Capture) [38] to ensure staff and participant safety. Direct recruitment is conducted via phone and email. Participants are given the option to complete a self-screening questionnaire survey that is emailed to them or to complete a screening interview over the phone. Once deemed eligible and the participant is interested in the study, an electronic consent form is emailed to participants to review and sign electronically through REDCap.

Sampling targets are based on the employment demographics of Arizona, and we seek to enroll essential workers in the following proportions: 50% from 18 to 40 years old and 50% between 41 and 85 years old, 50% women, and 50% Hispanic or American Indian. By occupation, we seek to enroll 40% HCP, 30% first responders, and 30% OEWs. These sampling

breakdowns are presented in Table 2. Our goal is to enroll these proportions in both seronegative and seropositive specimens (Table 2). As specified targets are met, recruitment and enrollment priorities will shift to underenrolled groups and to replace individuals that become COVID-19 positive throughout the study (Figure 2).

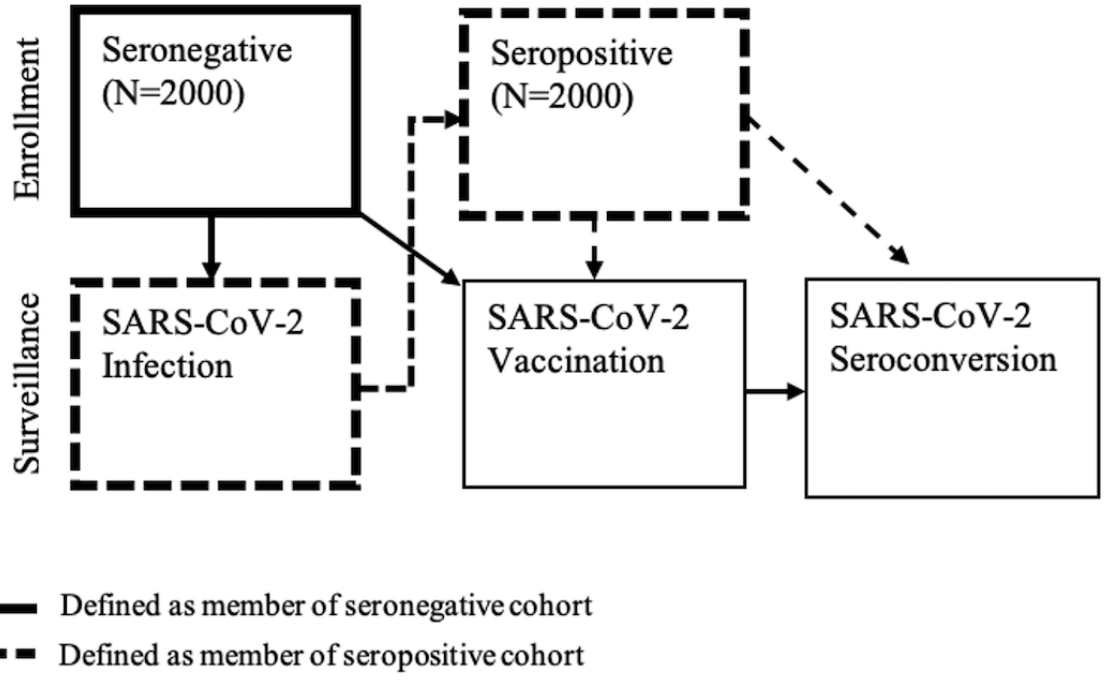
Table 2. Enrollment strata for age, race, ethnicity, and occupation with minimum enrollment targets for participants in the AZ HEROES[a] study.

Age group and race or ethnicity (target %)	Sex (target %)	Health care personnel (n=1600), n	First responders (n=1200), n	Other frontline and essential workers[b] (n=1200), n
18 to 39 years (50%)				
White and Non-Hispanic (50%)	Female (50%)	200	152	152
	Male (50%)	200	152	152
Hispanic or Native American (50%)	Female (50%)	200	152	152
	Male (50%)	200	152	152
40 to 85 years (50%)				
White and Non-Hispanic (50%)	Female (50%)	200	152	152
	Male (50%)	200	152	152
Hispanic or Native American (50%)	Female (50%)	200	152	152
	Male (50%)	200	152	152

[a]AZ HEROES: Arizona Healthcare, Emergency Response, and Other Essential Workers Study.

[b]Includes frontline personnel who interact with the public as well as personnel who work in close proximity to each other (eg, call centers, warehouses, agriculture, and food processing).

Figure 2. Participants who enroll as seronegative will switch to the seropositive cohort during the course of the study if they become infected as confirmed by rRT-PCR or serology prior to vaccination. rRT-PCR: real-time reverse transcription–polymerase chain reaction.



Enrollment

Upon enrollment, participants are asked to complete a baseline questionnaire that collects information about sociodemographic characteristics; health status and behaviors; occupational exposure, tailored to the occupational category; history with and attitudes toward COVID-19; and influenza vaccination history during 2020-2021 and the previous five seasons (Table 3). Participants are asked to schedule a blood draw (40 mL) within 5 days of enrollment at a laboratory facility in their area in order to complete their baseline serology; a box of self-collection respiratory supplies are shipped to them so they can begin their active surveillance.

Table 3. Information sources and timing of collection for key variables through surveys, the bidirectional text platform, and specimen collection.

Collected information	Surveys				Active surveillance texts			Specimen submission		
	Screen	Baseline	Follow-up	Event based[a]	Weekly	Monthly (rotating)	Off schedule	Weekly	Quarterly	Event based[a]
Demographics										
Age and gender	✓[b]									
Race or ethnicity	✓									
Date of birth	✓									
Education and income		✓								
Household composition		✓	✓							
Occupation information	✓	✓	✓							
Health and medical history										
Overall health		✓	✓		✓					
Sleep quality		✓			✓					
Tobacco history		✓								
Comorbidities and medications		✓								
Height and weight		✓								
Pregnancy		✓	✓							
Influenza infection								✓		
Vaccine knowledge and attitudes		✓	✓			✓				
SARS-CoV-2 infection										
rRT-PCR[c] pre-enrollment	✓									
rRT-PCR postenrollment								✓		✓
Serology pre-enrollment	✓									
Serology postenrollment									✓	✓
Occupational exposure		✓	✓			✓				
Community exposure		✓	✓			✓				
Symptoms	✓			✓	✓		✓	✓		✓
Illness duration and recovery			✓	✓						
Illness severity and impact			✓	✓						
Vaccination										
Influenza, history		✓								
Influenza, current			✓							
SARS-CoV-2, intent			✓				✓			
SARS-CoV-2, 2020-2021				✓			✓			

[a]Events include acute illness, recovery, and vaccination, which prompt additional study follow-up.

[b]Checkmarks indicate the information was collected at the indicated time and by the indicated method.

[c]rRT-PCR: real-time reverse transcription–polymerase chain reaction.

Active Surveillance

As part of active surveillance for incident SARS-CoV-2 infection, all participants provide weekly self-collected mid-turbinate nasal swabs appropriate to test for SARS-CoV-2 and influenza, during the influenza season. Upon enrollment, study participants are provided with information that the study duration could be up to 2 years, but initial expectations are for at least 36 weeks of weekly self-collected respiratory specimens. If an individual experiences CLI, they are asked to collect an additional respiratory specimen on the date of onset of the first CLI symptom. Weekly and illness kits are differentiated by color so participants know which to take and so study staff can track supplies. Respiratory specimens are analyzed utilizing the CDC-designated reference laboratory for real-time reverse transcription–polymerase chain reaction (rRT-PCR) assay

testing. Specimens are tested and results obtained 2 to 5 days from collection. If participants receive a positive test result, trained study staff contact participants to provide CDC guidance on quarantine practices and warning signs requiring medical care as well as to answer any questions they may have.

AZ HEROES staff prepare and distribute self-collection kits to the study participants, including detailed paper and video instructions. The laboratory provides feedback on specimens that were unable to be tested because of participant error in collection or shipping of the sample (eg, leaking or missing required components). This feedback is utilized to re-educate participants.

Enrolled participants participate in active surveillance via weekly surveys, explained in detail in the Data Collection section.

Data Collection

Overview

Active surveillance for acute illness is conducted throughout the study period. Participants are prompted to begin surveillance in the week following study enrollment and completion of the baseline survey. Each week, all participants are contacted via text message on their predesignated surveillance day (described in detail below). At the end of each text message exchange, the participant is reminded to collect a weekly specimen on their assigned day for collection.

Active Surveillance Surveys

As a part of active surveillance, participants are contacted weekly via secure SMS text messages, via Twilio, asking them two standardized questions about their general health status and presence of CLI symptoms. Twilio is a text messaging service that can read and write into the study REDCap database and customize questions based on participant responses. In addition to the two standardized questions, each week they receive one of four sets of rotating questions about changes in their occupational SARS-CoV-2 exposure, community and household exposure, and attitudes and beliefs surrounding COVID-19 risk. Any individual who indicates CLI in a weekly survey, or by contacting AZ HEROES staff directly, completes additional information via a mobile-friendly webform, including the participant's symptoms, self-reported severity, duration, self-reported medical treatment, function during and after illness, and details about the resolution of their illness.

Self-reported Data

Participants who indicate they have experienced CLI in the last 7 days are moved to an acute illness monitoring flow, where they are instructed to collect and ship an acute illness kit and complete additional questions about their illness episode. Individuals can also be placed into the acute illness monitoring flow by notifying study staff that they are ill. Participants remain in the acute illness arm until they self-report that their illness has resolved. Before returning to the weekly active surveillance flow, participants complete a recovery survey in which they confirm duration of illness and answer questions about atypical symptoms, productivity loss, and use of health services. Participants continue to take weekly respiratory specimens throughout their acute illness monitoring.

Vaccine Information

Participants are asked a series of questions to assess their knowledge, attitudes, and practices (KAPs) related to SARS-CoV-2 vaccination in the enrollment and/or follow-up survey to capture the information prior to vaccination. Similar to previous KAP studies of influenza vaccines [39,40], participants are asked how much they know about the COVID-19 vaccines, if they received the vaccine, their intention to receive one if they have not, how safe and effective they think the vaccines are, and how likely they are to get sick if they do not receive a vaccine.

Through partnerships with state and county health departments, we track the timing and distribution of COVID-19 vaccines to know when they will be available to individuals within the study.

To capture vaccination information, participants are periodically asked if they have been vaccinated. If they have not, they indicate if they plan to be vaccinated in the upcoming 8 weeks, indicating how many weeks. The form is re-sent in 8 weeks if the participant indicates that they do not know when they will be vaccinated. Once vaccinated, participants complete a brief webform including date of vaccination, vaccine manufacturer, and order in sequence (eg, first or second) for vaccines requiring multiple doses. State Immunization Information System registries will be used as a backup to capture vaccine information about individuals who do not share the information with the study via text message, and for confirmation and completeness on individuals who do receive the vaccine. Participants consent to having their vaccination verified upon enrollment.

Laboratory Methods

Respiratory Specimens

Participants are asked to self-collect a respiratory specimen each week of the study period. Sampling kits are provided to all study participants, which include collection and shipping supplies for 8 weeks of collections, along with illustrated instructions on how to properly collect and ship their respiratory specimens. Study staff track the use of specimen kits and ship replenishments to participants as needed. Each week, regardless of symptoms, participants collect an anterior mid-turbinate nasal swab on both nares, using a flocked swab or equivalent, and place it into a tube containing viral transport media (VTM). If participants experience CLI, they use an *acute illness kit*, which consists of materials to collect a nasal swab in VTM and a saliva specimen in a saliva collection tube. All specimens are shipped with a cold pack, using priority overnight express shipping to a CDC-designated laboratory following International Air Transport Association guidelines [41]. Upon receipt by the laboratory, specimens are aliquoted and analyzed for SARS-CoV-2 using an rRT-PCR method [42] under FDA EUA. Remaining aliquots are maintained for additional analysis, banking, or long-term storage.

Blood Specimens

All participants contribute 40 mL of whole blood at enrollment, at 11- to 13-week intervals, and following positive rRT-PCR or vaccination events. Participants can submit specimens at participating laboratories closest to the participant's residence or work. If a participant does not develop symptoms, but SARS-CoV-2 is detected in a weekly specimen, participants are instructed to submit a blood sample approximately 4 weeks following the date of first rRT-PCR detection; if the participant experiences CLI within 2 weeks of virus detection, they are instructed to submit a blood sample 4 weeks after initial symptom onset. If the participant has a convalescent blood specimen drawn prior to another planned repeat blood collection, the scheduling of the following blood collections will be 11 to 13 weeks following the convalescent draw. Participants who receive the COVID-19 vaccine during the study period are asked to provide a blood specimen 14 to 21 days after each dose of the vaccine—with the first postvaccination blood draw collected prior to the second vaccination dose, if relevant—and then every 11 to 13 weeks as described above. Information on adverse events and symptoms related to vaccination will be collected retrospectively after participants receive both doses of the vaccine.

Whole blood is collected and processed using CDC guidelines for serum collection [43]. The serum specimens are divided into aliquots labeled with the same study ID and specimen ID on all tubes, and an aliquot ID unique to each tube. All specimens are stored at −70 °C or colder prior to SARS-CoV-2 antibody analysis or long-term storage. At the University of Arizona, the serum is tested for antibodies against the receptor binding domain of the spike protein and verified with the S2 domain of S protein antibodies, as previously described [24], using the FDA EUA test (ID 201116). This testing at study entry is used to ensure correct placement of AZ HEROES participants into seronegative or seropositive groups.

Data Collection and Security

Most research activities occur through electronic communications (ie, email, text, and internet-based surveys), telephone contacts, or via postal or express mail, minimizing direct contact between study staff and participants. All surveys are self-administered by participants on a computer or smartphone. Surveys can also be administered by telephone or mail should participants be unable or become unwilling to access them online. Participant information given to study staff via phone or email conversation is entered and stored in the REDCap database by study staff. Alternatively, data are imported into the REDCap database from Twilio for participant responses to text surveillance or by direct participant response into the REDCap database.

Data Management

REDCap

A study database is maintained in REDCap. Tracking databases with patient identifiers and contact information are securely kept according to the University of Arizona standard operating procedures with respect to cybersecurity, privacy, patient confidentiality, and compliance with applicable patient privacy regulations. Any study-related documents with personal identifiers are stored in a locked cabinet in lockable offices on campus. All study-related documents and specimens contain a unique identifier for each participant. Data entry forms provide some quality assurance using logic and range checks as well as automated skip patterns. The research team performs additional data quality checks on a weekly basis, including assessments of missing data. Laboratory results are entered directly into the REDCap study database from the study reference laboratory, including results from rRT-PCR assays and serologic assays. If a reference laboratory is not able to enter data directly, the laboratory is provided with a laboratory results reporting template that is then merged with study data using the specimen ID.

Twilio

Twilio is a cloud-based communications platform that allows for automated text messaging chains to be sent to study participants. It is used to send weekly and illness monitoring questions to participants. Participant responses are stored in Twilio until sent as a batch to the REDCap database once per day.

Statistical Considerations

Power Analysis

Our goal is to recruit 4000 participants, split evenly between seronegative and seropositive individuals. Among the seronegative cohort, we estimated that a sample of more than 852 participants is required to achieve 80% power (α=.05) to detect a true incidence of SARS-CoV-2 infection of 4%; the enrolled cohort exceeds this sample estimate at the drafting of this report. Thus, we expect to be sufficiently powered to make overall estimates and estimates by two-level strata, such as age, sex, or HCP versus others. Power estimation for COVID-19 vaccine effectiveness (VE) was performed using Monte Carlo simulation to generate survival time over 12 months based on varying vaccine coverage—with quarterly increases in two-dose vaccine coverage from 0% to 80% among HCP, 70% for first responders, and 30% for OEWs—and varying SARS-CoV-2 incidence rate, from 0.67% to 1.42% monthly attack rate, using the equations proposed by Austin and a Cox marginal model [44]. Based on 1000 simulations, with 2000 participants in the seronegative stratum, the study is estimated to have over 80% power to detect a true VE of 75%. If the data are pooled with similar studies using common methodologies to a total of 5000 subjects, the combined analysis is estimated to have 99% power to detect a true VE of 75% using the same assumptions.

Data Analysis

To estimate the incidence of SARS-CoV-2 infection and the corresponding 95% confidence intervals in essential workers, we will fit negative binomial regression models with person-time at risk as an offset. We will examine incidence of rRT-PCR–confirmed infections by occupation, symptom presentation, close contact exposure, and demographic variables. Logistic regression and negative binomial models will be used to estimate the risk of infection in different occupational groups. In the logistic regression model, we will include the log-transformed person-weeks as the offset. The model will

then be adjusted by symptom presentation, demographic factors, study site, and health care utilization. The VE (1 − confirmed cases of COVID-19 illness per 1000 person-weeks among vaccinated essential workers ÷ confirmed cases of COVID-19 illness per 1000 person-weeks among unvaccinated essential workers × 100%) with 95% confidence interval will be estimated by a negative binomial regression model. The potential confounders, such as study site and previously seropositive status, will be included in the model. We will apply nonlinear mixed models to describe individual and group mean trajectories in neutralizing antibody titers over time. We will classify and identify subgroups of cases by self-reported clinical severity, health care utilization, occupational and community exposures, and duration of symptoms. These models will help elucidate the patterns of serologic immunity.

Ethical Considerations

This study was reviewed and approved by the Arizona Department of Health and the University of Arizona Institutional Review Boards (IRBs) (see Code of Federal Regulations, Title 45, Part 46.114 [45]). The CDC and the Arizona Department of Health Services (ADHS) IRBs have reviewed the project. The ADHS IRB has approved the project and the CDC IRB deferred to the University of Arizona IRB. The College of Public Health at the University of Arizona houses all IRB and required study documentation. All participants complete informed consent electronically through the REDCap study database system. Research staff verify that participants understand key study activities, are aware of risks, and agree to participate prior to countersigning to confirm consent. Participants receive the results of their weekly and illness COVID-19 tests as well as the results of their antibody testing.

Results

The AZ HEROES study was funded by the CDC. Enrollment began on July 27, 2020; as of May 1, 2021, a total of 3165 participants have been enrolled in the study. Enrollment is expected to continue through December 1, 2021, with data collection continuing through at least April 2022, contingent upon funding.

Discussion

Overview

Submission of weekly and CLI-onset swabs for SARS-CoV-2 rRT-PCR testing by AZ HEROES study participants is a high priority, as it allows researchers to estimate incidence of symptomatic and asymptomatic COVID-19. Currently, interest in receiving weekly nasal swab testing is high, with participants considering regular testing to be a substantial benefit, given high SARS-CoV-2 transmission rates in the community. When transmission rates in the community drop, or seropositivity increases due to natural infection or vaccination, this testing may be perceived by the study participants as more of a burden than a benefit. To maintain submission at acceptable rates at later time points in the study, monetary incentives have been included in the protocol. Methods for participant engagement through newsletters and reminders from study staff continue to evolve as the pandemic unfolds.

Strengths

One strength of the study is the inclusion of 4000 individuals with substantial occupational exposure to SARS-CoV-2 owing to their work as HCP, first responders, and OEWs. Additionally, the enrolled population will be generally representative of the racial and ethnic demographics of Arizona, which ensures inclusion of high-risk groups, such as Hispanic and American Indian communities, previously found to be at increased risk for COVID-19 [8]. The longitudinal cohort study design allows for ongoing consistent and comprehensive symptom assessment, exposure assessment, and examination of KAPs related to SARS-CoV-2 infection and vaccination. Further, the serial blood sampling component of the study enables us to fully examine variations in immune response to infection and vaccination.

Limitations

This study has several limitations. First, the ability to generalize trends related to infection incidence, disease severity, and immunologic response in our population of essential workers will likely be biased by the healthy worker effect. Second, the information retrieved from participants is principally self-reported or self-collected, which might introduce recall bias, particularly if participants do not complete rRT-PCR specimen collection and surveys consistently. Third, there may be a sampling bias related to the requirement that participants utilize computers and phones to complete surveys. Finally, not meeting enrollment targets and/or the length of the study period (1 year) may hamper the ability to assess reinfection rates, for example, because immunity for SARS-CoV-2 might last for more than 1 year.

Conclusions

In conclusion, the design, recruitment, enrollment, and research activities of the AZ HEROES study provide a unique opportunity to improve our understanding of the incidence of SARS-CoV-2 infection, disease course, antibody and vaccine response, and KAPs among essential workers in the state of Arizona.

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Authors' Contributions

JB, KL, KE, JG, XS, BL, SB, PR, BC, SC, MT, JML, and PK were responsible for the study concept and design. KL, KE, PR, SB, ZB, and XS wrote the manuscript. JG, KK, EK, BL, LG, YY, AK, JML, BC, SC, NT, JM, PK, JNZ, MT, and JB were responsible for drafting and critical revision of the manuscript. All authors read and approved of the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ADHS: Arizona Department of Health Services
AZ HEROES: Arizona Healthcare, Emergency Response, and Other Essential Workers Study
CDC: Centers for Disease Control and Prevention
CLI: COVID-like illness
EUA: Emergency Use Authorization
FDA: Food and Drug Administration
HCP: health care personnel
IgA: immunoglobulin A
IgG: immunoglobulin G
IgM: immunoglobulin M
IRB: Institutional Review Board
KAP: knowledge, attitude, and practice
OEW: other essential and frontline worker
REDCap: Research Electronic Data Capture
rRT-PCR: real-time reverse transcription–polymerase chain reaction
VE: vaccine effectiveness
VTM: viral transport media

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Protocol

The Impact of COVID-19 Vaccine Communication, Acceptance, and Practices (CO-VIN-CAP) on Vaccine Hesitancy in an Indian Setting: Protocol for a Cross-sectional Study

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Abstract

Background: COVID-19 vaccines are considered to be a key to limiting and eliminating the infectious disease. However, the success of the vaccination program will rely on the rates of vaccine acceptance among the population.

Objective: This study aims to examine the factors that influence vaccine hesitancy and vaccine acceptance, and to explore the unintended consequences of COVID-19 infections. The study will further explore the association between sociodemographic characteristics; health status; COVID-19–related knowledge, attitude, and practices; and its influence on vaccine hesitancy and acceptance among individuals living in urban and rural settings of Chennai, Tamil Nadu in the southern state of India.

Methods: A cross-sectional study will be conducted between January 2021 and January 2023. A sample of approximately 25,000 individuals will be recruited and enrolled using a nonprobability complete enumeration sampling method from 11 selected urban and rural settings of Chennai. The data will be collected at one time point by administering the questionnaire to the eligible study participants. The collected data will be used to assess the rates of vaccine acceptance; hesitancy; and knowledge, attitudes, practices, and beliefs regarding COVID-19 and COVID-19 vaccines. Lastly, the study questionnaire will be used to assess the unintended consequences of COVID-19 infection.

Results: A pilot of 2500 individuals has been conducted to pretest the survey questionnaire. The data collection was initiated on March 1, 2021, and the initial results are planned for publication by June 2021. Descriptive analysis of the gathered data will be performed using SAS v9.1, and reporting of the results will be done at 95% CIs and P=.049. The study will help explore the burden of vaccine acceptance and hesitancy among individuals living in urban and rural settings of Chennai. Further, it will help to examine the variables that influence vaccine acceptance and hesitancy. Lastly, the findings will help to design and develop a user-centered informatics platform that can deliver multimedia-driven health education modules tailored to facilitate vaccine uptake in varied settings.

Conclusions: The proposed study will help in understanding the rate and determinants of COVID-19 vaccine acceptance and hesitancy among the population of Chennai. The findings of the study would further facilitate the development of a multifaceted intervention to enhance vaccine acceptance among the population.

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KEYWORDS

COVID-19 vaccine; vaccine hesitancy; vaccine acceptance; unintended consequences; vaccination; COVID-19; pandemic; coronavirus; infectious disease; protocol; vaccine

Introduction

Background and Rationale

The COVID-19 pandemic continues to impose burdens of morbidity and mortality while disrupting societies and economies worldwide since 2020. These negative impacts motivated pharmaceutical companies to develop a vaccine immediately. Vaccination of people against COVID-19 has now started in many countries [1]. Governments prepare themselves to ensure large-scale equitable access and distribution of safe and effective COVID-19 vaccines. This will require sufficient health system capacity and effective strategies to increase trust in vaccines and those who deliver them [2]. For decades, vaccines have been a successful measure to eliminate and prevent numerous infections. However, concern about vaccine hesitancy is growing worldwide, prompting the World Health Organization (WHO) to declare it among the top 10 health threats in 2019 [3]. In 2015, the WHO Strategic Advisory Group of Experts on Immunization defined vaccine hesitancy as a "delay in acceptance or refusal of vaccination despite the availability of vaccination services" [4]. In many countries, vaccine hesitancy and misinformation present substantial obstacles to achieving a high coverage rate necessary to attain herd immunity to flatten the epidemic curve [5,6]. Several determinants influence whether an individual refuses, delays, or accepts some vaccines. These include historical, socioeconomic, cultural, ecological, health system/institutional, and political factors [7].

Governments, public health officials, and advocacy groups must be prepared to address the issue of vaccine hesitancy and lower vaccine acceptance rates [2]. Misinformation regarding the benefits, medicinal composition, and adverse effects of vaccination spread through multiple channels could have a considerable effect on the acceptance and increased COVID-19 vaccine hesitancy [8]. Effective interventions should directly address community-specific concerns or misconceptions and be sensitive to religious or cultural beliefs [9]. Trust in government is strongly associated with vaccine acceptance and can contribute to public compliance with recommended actions [10]. Clear and consistent communication by government officials is central in building confidence in vaccine programs among individuals. This includes explaining the development of vaccines, how it works, and its safety and efficacy. Campaigns should also aim to explain a vaccine's level of effectiveness, the time needed for attaining protection, and the importance of population-wide inoculation with the COVID-19 vaccine to achieve herd immunity. Health communication must reach all communities to enhance vaccine literacy to prevent future infections and mortality [11,12]. Effective and strategic health messages are one of the key approaches in assisting higher authorities to deal with increased vaccine hesitancy and to slow the spread of the infection. Improving vaccine uptake among those most hesitant will be of utmost importance in reaching the immunization rates needed for community immunity [13,14].

Further, some unintended consequences have emerged since the inception of the COVID-19 pandemic, such as lifestyle and behavior changes, impacts on mental health, and economic consequences. These consequences are likely to increase over time as the multiple waves of the COVID-19 pandemic continue to develop [15].

India, being one of the most populated countries in the world, has been struggling to attain the goal of 90% vaccine coverage under the national immunization schedule due to several reasons including vaccine hesitancy [16,17]. According to the National Family Health Survey (NFHS) 1 (1992-1993), there was 65% vaccine coverage, which increased to 82% in NFHS 2 (1998-1999). This was followed by 81% as per NFHS 3 (2005-2006) to a substantial decline to 69.7% as per the NFHS 4 (2015-16) in Tamil Nadu [18]. In the region of Chennai, Tamil Nadu, a southern state in India, a considerable decline in the vaccine coverage rate has been observed over the past 20 years [19,20].

The government of India has now opened up COVID-19 vaccinations for everyone 18 years and older. Until May 8, 2021, 169,439,663 total doses were administered, out of which 133,980,544 received the first dose and 35,459,119 were administered the second dose. Meanwhile, in Tamil Nadu to date, 6,480,287 have been vaccinated, of which 4,835,514 received the first dose and 1,644,773 received the second dose. As of May 8, 2021, Tamil Nadu stands 10th in India in administering total vaccine doses. Tamil Nadu recorded a decline in the vaccination rate between April 1 to 10, 2021, compared to March 22 to 29, 2021. The vaccination coverage once again recorded a dip on April 18, 2021. On April 18, 41,120 were newly vaccinated as compared to 138,298 the previous day. Even though the new cases in Tamil Nadu are rising and the vaccinations are open for individuals 18 years and older, the new vaccinated rate is low and inconsistent [21]. This reduction and inconsistency in the vaccine coverage rates could be due to vaccine hesitancy among individuals. There also seems to be a paucity of data on the rate of COVID-19 vaccine acceptance, vaccine hesitancy, and factors contributing to them. To control vaccine preventable diseases, it is imperative to identify the key challenges and opportunities to reduce vaccine hesitancy and recoup vaccine confidence among individuals. Hence, this study aims to examine the factors that influence vaccine hesitancy and vaccine acceptance, and to explore the unintended consequences of COVID-19 infections. The study will further explore the association between sociodemographic characteristics; health status; COVID-19–related knowledge, attitude, and practices; and its influence on vaccine hesitancy and acceptance among individuals living in urban and rural settings of Chennai District of Tamil Nadu, a southern state in India.

Study Objectives

This study aims to assess the rates of vaccine acceptance and vaccine hesitancy among the adult population of Chennai, Tamil Nadu; to investigate the determinants of vaccine acceptance and vaccine hesitancy; to explore the unintended consequences of COVID-19 infection; and to formulate an evidence-driven intervention model to facilitate uptake of the COVID-19 vaccine in Chennai and other states of India.

Methods

Study Design and Population

A cross-sectional study will be conducted between the period of January 2021 and January 2023. The study participants will be recruited from 11 selected urban and rural settings of Chennai District of Tamil Nadu, a southern state in India. A total of 11 primary health centers (PHCs) of Chennai District were selected for the study, namely, Thiruninrarvur, Thirumazhisai, Kathavur and Pallavedu, Veppampattu, Mittinamallee, Vilinjiyambakkam, Periyar Nagar, Parithipattu, Papparambakkam, Ulundai, and Poonamallee. It was made sure that all the selected PHCs are comparable with regard to available resources and living conditions. This ensured that these PHCs are not systematically different from each other and are representative of all the PHCs in Chennai.

The study plans to recruit a total of 25,000 individuals using a nonprobability complete enumeration sampling method. The selected sampling method would allow the researchers to study more than one aspect of all items of the population and obtain data from each and every unit of population. Each item will be observed personally by the researchers. The collected data will be reliable, accurate, and truly representative of the whole population. In addition, the data obtained using the complete enumeration method can be used as a basis for future studies [22]. The eligible study participants will comprise the following: individuals 18 years and older, individuals residing in the selected urban and rural settings, and individuals consenting to participate in the study. Individuals having any mental or physical challenges that might affect their ability to participate in the study will be excluded from the study.

Informed Consent

The institutional review board–approved informed consent form will be administered by the research team to the eligible individuals for the study. The research team will describe the study, time required, and benefits of the study results to the participants, and those willing to participate and give their consent will be enrolled in the study. The participants should be able to read and understand the questionnaire. In case any participant is illiterate, ethical consent will be obtained with the help of a legally acceptable representative or an impartial witness [23]. In addition, the illiterate participants will be explained the questionnaire in the local Indian dialects to aid in the usefulness and generalizability of the study. Data gathered will be stored in a secure manner ensuring data privacy and confidentiality. Written informed consent will be obtained in both English and local Indian dialects. Study participants will be allowed to withdraw from the study at any time mentioning the reasons for withdrawal. All data including those from study withdrawals will be reported in the final analysis. No monetary compensation will be given, and those agreeing to participate will be offered snack meals. Every individual's time will be respected, and their voluntary participation will be appreciated. Nonmonetary forms of compensation would help to avoid coercion and undue inducement that might impact the results of the study [24].

Data Collection, Data Entry, and Quality Assurance

Data collection and data entry will be performed by a team of data collectors and data management personnel. The data will be collected at a one-time point by administering the study questionnaire to the eligible study participants (Multimedia Appendix 1). For designing and standardizing the questionnaire, the researchers performed a pilot study involving a sample of 2500 individuals. Initial data will be gathered on paper and then entered into the computer using Microsoft Excel (Microsoft Corporation). For the main survey, the data will be recorded electronically using computer-based software. To ensure efficiency and high-quality data collection and processing, the following data management protocol is in place: a clearly defined study manual, a well-trained team of data collectors, weekly meetings with the research team, weekly data checks, maintenance of study participant contact, and maintenance of study participant data instrument logs.

Variable Assessment

Sociodemographic Profile

This data will be gathered on study participants' age, gender, income level, education level, employment status, occupation, region of residence, marital status, parenthood, and religion.

Health Status Profile

This will include data on comorbidities, health insurance, COVID-19 diagnostic tests, and anthropometry measurements such as height and weight using a standard technique. The two measurements will aid in calculating the BMI of study participants.

Prior Immunization

This would include questions related to experiences with previous seasonal, influenza, and COVID-19 immunizations.

History of COVID-19

This comprises questions related to individuals and their family members' history of COVID-19.

Knowledge, Attitude, and Practices Related to COVID-19

This data gathers participant's COVID-19 knowledge levels and their attitude and practices toward preventive practices to minimize the spread of COVID-19. The information recorded will help to design targeted public health messaging to address knowledge, attitude, and practices related to COVID-19.

Knowledge, Attitude, and Barriers Related to COVID-19 Vaccination

This data would gather participant's knowledge, attitudes, and barriers related to COVID-19 vaccination so that appropriate

public health messaging can be established to enhance uptake of COVID-19 vaccination and follow through on safe, preventive COVID-19–related practices.

COVID-19 Vaccine Acceptance and Hesitancy

Data on individuals' preferences related to the COVID-19 vaccine will be gathered.

Communication and Misinformation About the COVID-19 Pandemic and Vaccination

This data records the sources of COVID-19 information. Additionally, data on the use of protective measures against the infection will be gathered.

Unintended Consequences of COVID-19

This records data related to the lifestyle and behavioral changes including impact on mental health. Information related to mobile and internet use as sources of COVID-19 information will also be gathered. Generalized anxiety disorder will be assessed using the Generalized Anxiety Disorder 7 self-administered patient questionnaire [25], while anxiety as a result of COVID-19 will be assessed using a 7-item COVID-19 anxiety scale [26].

Data Security and Privacy

Data security will be ensured through regular backups, password-protected computers, and data files stored in a locked file cabinet in an office. The information will be accessible to members of the research team only. Data will be stored in a password-protected computer in a locked office of the principal investigator for 3 years from the point of study completion at which time they will be destroyed.

Outcomes

The study outcomes include factors associated with COVID-19 vaccine acceptance and hesitancy, and knowledge, attitude, and practices related to COVID-19 and vaccination. The authors of the study will also explore the factors affecting unintended consequences of COVID-19 infection across urban and rural settings in an Indian setting.

Data Analysis Plan

The gathered data will be presented in tables comprising the recorded characteristics of all variables. These tables will serve the purpose of data quality control to find out inconsistencies in the data patterns and outliers or any missing data. Descriptive analysis will be conducted to report the means and SDs of the continuous variables and frequency analysis of the categorical variables. *T* tests will be performed to compare the means between the continuous variables and a categorical dependent variable, while chi-square analysis will be performed for the categorical variables. Multivariate regression analysis will be performed to determine the predictors of the outcome variables of vaccine acceptance and hesitancy. All analysis will be performed using SAS v9.1 and reporting of the results will be done at 95% CIs and P=.049.

Project Timeline and Milestones

A detailed research plan and scheduled timeline of the tasks involved in the study are presented in Table 1.

Table 1. Scheduled timeline of the tasks in the CO-VIN-CAP study.

Task	Month											
	1	2	3	4	5	6	7	8	9	10	11	12-24
Review of the literature, initial designing, and planning of the study	✓[a]	—[b]	—	—	—	—	—	—	—	—	—	—
Development of study proposal and ethical approval	✓	—	—	—	—	—	—	—	—	—	—	—
Approval of the study proposal	✓	—	—	—	—	—	—	—	—	—	—	—
Development of survey items and the questionnaire	✓	—	—	—	—	—	—	—	—	—	—	—
Review and revision of the questionnaire by the research team	—	✓	—	—	—	—	—	—	—	—	—	—
Recruitment and training of the data collector team	—	✓	—	—	—	—	—	—	—	—	—	—
Pilot testing of the representative sample of the target population	—	—	✓	✓	—	—	—	—	—	—	—	—
Initial data analysis, results write up, and dissemination of the pilot survey	—	—	—	—	—	✓	✓	—	—	—	—	—
Revision of the questionnaire based on the pilot testing	—	—	—	✓	—	—	—	—	—	—	—	—
Development of electronic survey	—	—	—	✓	—	—	—	—	—	—	—	—
Recruitment of the target sample	—	—	—	—	✓	✓	✓	✓	✓	✓	✓	—
Reviewing collected data by the research team	—	—	—	—	✓	✓	✓	✓	✓	✓	✓	✓
Data analysis	—	—	—	—	—	—	✓	✓	✓	✓	✓	✓
Results write up and preparation of the manuscript	—	—	—	—	—	—	—	✓	✓	✓	✓	✓
Dissemination	—	—	—	—	—	—	—	✓	✓	✓	✓	✓

[a]Indicates it will be done in this month.

[b]Indicates it will not be done in this month.

Ethics and Dissemination

The study bearing protocol number PMCHRI-IHEC-029 gained approval from the Panimalar Medical College Hospital and Research Institute Institutional Human Ethics Committee (Central Drugs Standard Control Organization Registration No. ECR/1399/Inst/TN/2020) in January 2021 with approval No. PMCH&RI/IHEC/2021/037 dated January 13, 2021. The study will be conducted according to the Declaration of Helsinki, as it involves human participants [27].

Findings of the study will be disseminated through peer-reviewed publications and national and international conference presentations. Findings will also be disseminated to the local community health leaders and other state officials and policy makers for data-driven, evidence-based informed decision making.

Results

The proposed research study will help explore the burden of vaccine acceptance and hesitancy among individuals living in urban and rural settings of Chennai, Tamil Nadu. Further, it will help to examine the variables that influence vaccine acceptance and hesitancy. The data collection was initiated on March 1, 2021, and the initial results are planned for publication by June 2021. The result findings of the study will help to design and develop a user-centered informatics platform that can deliver multimedia-driven health educational modules tailored to facilitate vaccine uptake in varied settings.

Discussion

The study will provide insights toward the barriers and challenges leading to lower vaccine acceptance rates. The research would help in identifying the key areas that need to be addressed through intervention to enhance the compliance of COVID-19 vaccine acceptance. There is a need for strategies to increase vaccine literacy and to directly address community-specific misconceptions regarding vaccines and at the same time be sensitive to religious or philosophical beliefs. The survey would help in assessing the rates of vaccine acceptance and hesitancy and its determinants among the population of Chennai, Tamil Nadu. The findings from this research project would help in identifying, developing, and implementing data-driven, evidence-based, and human-centered behavior modification interventions to address COVID-19 vaccine hesitancy among populations living in diverse settings.

The study would provide an in-depth understanding of various factors related to COVID-19 vaccine acceptance, intention, and hesitancy among individuals living in urban and rural Indian settings. The results of the study may be used to conduct a statistical comparison with similar studies to test and evaluate similarities or differences in the outcomes across diverse settings nationally and internationally. It would help the researchers of the study to formulate appropriate interventions. However,

further research involving long follow-up is needed to explore the impact of such interventions on long-term outcomes.

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Authors' Contributions

All authors have contributed to the design of the study, development of the questionnaire, preparation of the manuscript, and have approved the manuscript for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Full text of the survey questionnaire.
[DOCX File , 54 KB - resprot_v10i6e29733_app1.docx]

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Abbreviations

NFHS: National Family Health Survey
PHC: primary health center
WHO: World Health Organization

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Protocol

Psychological Impacts of the COVID-19 Pandemic Among Portuguese and Swiss Higher-Education Students: Protocol for a Mixed Methods Study

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Abstract

Background: Higher-education students are particularly vulnerable to both everyday stressors and mental health problems. Public health emergencies may generate a range of unforeseen potential stressors for vulnerable individuals and communities. The current pandemic has apparently led to an increase in psychiatric symptoms among these students.

Objective: The goal of this study is to characterize the psychological impact of the COVID-19 pandemic among Portuguese and Swiss higher-education students.

Methods: This project will use a mixed methods sequential explanatory design in Portugal and Switzerland, with two consecutive phases. During Phase I, a quantitative study will assess the psychological responses of higher-education students during the COVID-19 pandemic. A convenience sampling method will be used for collecting information from students. The association between variables will be determined with univariable and multivariable analyses. During Phase II, qualitative data will be collected in order to understand the determinants of psychological stress and the strategies adopted by students as a result of the COVID-19 pandemic, as well as to identify their opinions and feelings about the teaching-learning process during quarantine. In this phase, participants will be selected using a maximum-variation sampling method. Data from focus group discussions will be coded and inductively analyzed using a thematic analysis approach. Finally, quantitative and qualitative results will be merged during interpretation to provide complementary perspectives.

Results: This paper describes and discusses the protocol for this mixed methods study, which will be completed in December 2021. This study was formally approved by the local ethics committee (CE/IPLEIRIA/22/2020) in Portugal and authorized by the Swiss Association of Research Ethics Committees, swissethics (CER-VD-2020-02889).

Conclusions: This research can contribute to the development of teaching tools and methods that reinforce positive mental health strategies, hope, and adaptive coping among students, and to the development of a class on mental health interventions in the context of catastrophic and traumatic events. This project will also help government stakeholders as well as health and education professionals safeguard the psychological well-being of students facing an expanding COVID-19 pandemic.

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KEYWORDS

study protocol; pandemic; students; mental health; COVID-19

Introduction

Background

Disasters may have an adverse impact on the mental health of affected populations [1]. Statistics show that 20% to 40% of affected people suffer from mild changes, and 30% to 50% suffer from moderate to severe psychological distress [2,3]. Those who already had a mental disorder need more help than before, because timely mental health support reduces the chances of becoming mentally and psychologically ill [2,3]. Catastrophes are traumatic events with health implications that can affect a large number of people [4].

Events that are neither predictable nor preventable, over which people have no control, tend to have the worst consequences for people. The more serious the consequences (eg, loss of life, irreparable physical damage, and irretrievable loss of resources), the greater the need for psychosocial support [4]. People suffer from various mental health problems during and after disaster situations, so it is crucial to promote a feeling of security, tranquility, and hope and to provide access to social, physical, and emotional support [3]. Trauma-enhancing situations are opportunities to improve mental health services and develop support strategies [3].

For an adaptive response to a stressful situation, a person must develop coping strategies [5]. This biopsychosocial reaction is part of daily life. A positive reaction (ie, eustress) allows for learning and development of functional strategies, while a negative reaction (ie, distress) disrupts a person's stability and becomes harmful [6]. Different coping strategies have been modeled in mental health research, by isolating and analyzing the behavioral, cognitive, and affective processes that subjects use during threatening events in order to control, diminish, tolerate, and/or minimize their impact on physical and psychological well-being [7]. These strategies are known as *coping strategies* and typically include coping or avoidance behaviors, management of human and material resources, social support, positive revaluation, and engagement in activities [8].

The severity a person attributes to an event will influence the development of this response [9]. When a person is unable to resolve a situation, there is a maladaptive response, which increases vulnerability to both physical and psychological diseases [5]. Some pre-existing mental illnesses can get worse after a disaster, such as depression, alcoholism, or schizophrenia. Other conditions can be induced by situations such as bereavement: alcohol or drug abuse, anxiety, and posttraumatic stress disorders. However, not all people who experience such situations will need support; most will recover favorably over time, finding a way to resume their routines [3]. Statistics indicate that in the coming decades, the number of disasters could increase and affect human development indicators, such as life span, health, education, and standard of living [10]. It is, therefore, necessary to provide and improve access to long-term mental health services. Professionals should be trained on how to intervene in disaster situations and acquire strategies to deal with difficulties and to prevent disease [2]. Nursing interventions integrated into daily routines are relevant to rebuilding-life projects, promoting feelings of hope, and addressing more complex situations. Greater awareness of the mental health issues caused by disasters is increasingly relevant [11].

The ongoing COVID-19 pandemic, caused by SARS-CoV-2, is promoting physical and physiological health problems, including fear, anxiety, and high stress levels. The development of appropriate mental health assessments and treatments is urgently needed [12]. Previous research revealed a profound and wide range of psychosocial impacts during infectious disease outbreaks at the individual, community, and international levels. On an individual level, people are likely to experience fear of becoming sick or dying themselves, feelings of helplessness, as well as stigma [13].

At the time of writing (May 2, 2021), more than 150 million people around the world had been infected and more than 3.1 million had died from COVID-19 [14]. In Switzerland, from January 3, 2020, to May 2, 2021, there were 667,557 confirmed cases of COVID-19 and 10,057 deaths. A total of 2.8 million vaccine doses were administered. In Portugal during the same period, there were 838,475 confirmed cases of COVID-19 and 16,988 deaths. A total of 3.4 million vaccine doses were administered [15]. The differences between both countries spring from a combination of factors, such as personal values, social and cultural background, gender roles, and education levels [16]. Moreover, the degree of impact was also affected by the level of national fiscal health before the COVID-19 crisis. While Switzerland has experienced strong fiscal health and possessed a well-equipped health care system to face the crisis, Portugal and its National Health Service have experienced, since 2010, economic austerity and health care budget cuts, whose effects were exacerbated during this pandemic [17].

Portugal and Switzerland faced the pandemic differently, and distinct societal and economic characteristics between the two countries can have impacts on the mental health of each population. Currently, there is very little available information on the psychological impact and mental health of the general public during the peak of the COVID-19 pandemic. Based on our preliminary analysis of the literature, much of the research related to this pandemic focuses on the epidemiology and the clinical characteristics of infected patients [18], the genomic characterization of the virus, the challenges for global health governance [19], and economic impacts [20]. In contrast, there seems to be a scarcity of research articles examining the psychosocial impact of COVID-19 on the general population or specific groups (elderly, children, students, etc).

Psychological Impact of the COVID-19 Pandemic Among Higher-Education Students

The *student* stage constitutes an important transition in an individual's life. Certain recurring elements concerning mental health and well-being can be observed during this period, such as an increase in anxiety and stress, the appearance of depressive states, or a high risk of exhaustion. In some recent studies, such problems have been found in up to 50% of higher-education students [21-23]. Numerous studies have used coping strategies as an explanatory model regarding mental health problems among students (eg, stress, anxiety, and psychological distress) [24-26].

While these epidemiological data are important, most were collected prior to the COVID-19 pandemic. During 2020, most national governments implemented sanitary health measures to stop or slow down the transmission of the virus responsible for the COVID-19 pandemic. Numerous measures were imposed on the population, such as closing schools and public places, instituting widespread quarantine, requiring social distancing, and almost completely ceasing recreational and cultural activities.

The response to the COVID-19 health emergency also disrupted academic and social life in many universities, increasing anxiety and distress among students [23]. Many universities cancelled their activities and closed campuses, shifting to online classes or ending their semesters early, leading many students to return home. Given the travel restrictions, many international students were not able to return to their home countries. Students from underprivileged families, with marginal housing or other financial or physical challenges, faced disproportionate amounts of difficulty finding last-minute transportation and housing. Furthermore, at home, some students lacked the technological infrastructure to follow classes online and engage with their, now virtual, social community. Students in quarantine risked losing opportunities critical to their scholarly or professional advancement [27,28]. These circumstances could understandably further social isolation and perpetuate stress, anxiety, and low mood. Even students not under quarantine and from well-resourced families faced stress due to the sudden changes and uncertain climate of relocations, changes in the academic schedule, and the shift to online teaching [28,29]. The combination of regular academic stress, compounded by the academic changes in response to the pandemic, and the general experience of a potentially traumatic public health crisis may lead to clinically significant psychiatric symptoms and illness among higher-education students [30].

Moreover, this population, mostly between the ages of 18 and 25 years, is a particularly at-risk population [31], open to very significant consequences, both psychological (ie, mental health) and social (ie, educational attainment). However, not all students suffer from psychological difficulties. Some seem to have resources and coping strategies that enable them to diminish or even counter the current situation's adverse effects. Therefore, it is necessary to identify these strategies and evaluate them, in order to propose possible solutions and improvements when caring for students, and to provide them with assistance and high-level education.

One meta-analysis of 27 studies from 15 countries, analyzing the psychological impact of COVID-19 among college students, showed a disproportionate burden of mental health problems among participants, with females having higher anxiety and depression levels than males. Increased stress, anxiety, and depressive symptoms were seen as a result of changes and uncertainty in university education, technological concerns about online courses, being far from home, social isolation, decreased family income, and future employment [32]. These impacts were also observed in universities across the world [33-36].

A similar scenario was found in Portugal. One study observed high levels of anxiety, depression, and stress among a population of 460 university students [37]. In Switzerland, a study by Elmer et al [38] revealed that students' levels of stress, anxiety, loneliness, and depressive symptoms got worse with the pandemic, compared to previous levels. Stressors shifted from fears of missing out on social life to worries about health, family, friends, and their future. The results suggest that concerns regarding COVID-19, lack of interaction and emotional support, and physical isolation were associated with negative mental health trajectories.

We currently have little data on student reactions to the COVID-19 pandemic, from both national studies and international comparisons. The latter could be important to compare the solutions instituted in different countries and to suggest possible solutions. All these elements support the implementation of a policy for assessing student mental health with a standardized methodology and, if possible, an international scope, since policy choices are more or less similar.

Project Description

This study will investigate the psychological impact of the COVID-19 pandemic among higher-education students in Portugal and Switzerland. In this research, we are interested in the following: (1) assessing the prevalence of psychological symptoms, (2) correlating risk and protective factors related to psychological stress with student characteristics, (3) comparing the levels of psychological symptoms between both countries, (4) identifying strategies adopted by students to promote better psychological adjustment during the pandemic crisis, and (5) characterizing the perception and experience of the teaching-learning process during quarantine.

Our research questions are as follows: (1) How has the COVID-19 pandemic affected student mental health? (2) What individual strategies were adopted to deal with the consequences of the COVID-19 pandemic? and (3) What challenges did students face when adapting to the teaching-learning process during the pandemic?

A quantitative approach can reveal how risk factors (ie, depression, stress, and anxiety) and protective factors (ie, hope, resilience, and coping) are correlated with student characteristics, such as level of education, social support (ie, living alone or in a family context), knowledge and perception of the illness, and perception of the effectiveness of protective measures against COVID-19.

In addition, levels of stress and anxiety are expected to be correlated with coping strategies, hope levels, and the perception of the impact of events on oneself and one's surroundings.

A qualitative approach can help us understand the adjustment patterns and the impact of the COVID-19 pandemic on student work and potential psychological consequences. Furthermore, we also intend to clarify student perceptions about new teaching-learning processes compared to in-person teaching.

Methods

Type of Study

In order to carry out our research, we chose a cross-sectional study with a mixed methods sequential explanatory design (Multimedia Appendix 1). This approach consists of two distinct phases: a quantitative phase followed by a qualitative phase [39]. In this design, a researcher first collects and analyses the quantitative (ie, numeric) data, and then collects and analyses the qualitative (ie, text) data. The latter can help explain or elaborate on the quantitative results obtained in the first phase. In this approach, the quantitative data and their subsequent analysis provide a general understanding of the research problem [40], while the qualitative data and their analysis refine and explain those statistical results by exploring participant views in greater depth [39,40].

During Phase I, we will carry out a cross-sectional survey, in the Portuguese and Swiss contexts, to assess the psychological responses of higher-education students during the COVID-19 pandemic using an anonymous online questionnaire.

In Phase II, a qualitative approach will be used to understand the psychological stress experienced by students due to the COVID-19 pandemic, focusing on their perceptions, attitudes, and experiences. Information will be collected from online focus group discussions (FGDs). According to Liamputtong [41], this methodology is appropriate for sensitive topics and vulnerable populations. The FGDs will be useful for exploring differences of opinion and will provide an opportunity to delve deeper into the phenomena under study through an interactive discussion of participant experiences and attitudes, in a group context.

Recruitment and Sampling

Data will be collected in two stages. All potential participants will be given written information on the study and asked to provide their informed consent. Participants will include adults at any level of education beyond high school, including undergraduate and graduate programs. Students participating in Erasmus or other mobility programs will be excluded.

First, we will collect data using an online survey created by the researchers specifically for this purpose, including its items, protocol, and variables. We will contact the deans of each institution to present our research and obtain authorization to disseminate our online survey to students. A convenience sampling method will be used to collect information from potential participants. We will use mailing lists to send individual emails containing our questionnaire, an explanation of our research, and the results of our research. The assumption of nonduplication of response will be taken into account by limiting one response per email account.

For Portugal, sampling will take place in four higher-education institutions (ie, universities and polytechnic institutes). Given a total population of 40,000 students—an average of 10,000 students per institution—our sample size should include 381 students, for a confidence level of 95%.

For Switzerland, sampling will occur within the HES-SO (Haute école spécialisée de Suisse occidentale) University of Applied Sciences and Arts of Western Switzerland, covering the cantons of Vaud; Neuchâtel, a French-speaking region; Fribourg; and Valais, where French is the co-official language. According to a recent survey, the total student population was approximately 21,000 in the 2019-2020 academic year [42]. The size of our sample should, therefore, include 377 students, for a confidence level of 95%.

After the online surveys, we plan to carry out at least two online FGDs in each context (ie, Portuguese and Swiss). Participants who complete the anonymous online survey will have the option to provide their contact information (eg, phone number or email). The participants representing diverse backgrounds, in terms of gender, education, and geography, will be selected using a maximum-variation sampling method. Eligible students will be contacted by email, and we will send them the documentation concerning the informed consent and the interview guides. If they are interested in participating in the FGDs, we will schedule appointments with the student groups. The FGDs will take place using the Microsoft Teams videoconferencing platform in groups of 6 to 10 participants, with facilitation by the researchers. This will give a total sample of 24 to 40 participants. The sample size should provide sufficient data to meet our aims and cover a range of views. Data collection and analysis will continue until thematic saturation is reached in the inductive analysis of qualitative interviews. A key advantage of the Microsoft Teams platform is its ability to securely record and store sessions without recourse to third-party software [43].

Data Collection and Instruments

Phase I: Survey

The e-questionnaire constructed by our project team will be based on FAQ (frequently asked questions) found on the World Health Organization official website [44].

Our questionnaire will include questions related to eight items. The first series of questions, pertaining to items 1 to 4, will have to be developed for, and linguistically adapted to, both countries. Linguistic discrepancies that might arise when ensuring cross-cultural congruency or equivalency between the two languages will be solved by a bilingual research team member. The second series of questions pertain to items 5 to 8. The eight items are as follows:

1. Sociodemographic and health information, including variables such as gender; age; geographical region; education; marital status; employment, if applicable; household size; perceived health status; and history of chronic disease.

2. Contact history, including close contact with a person with confirmed COVID-19 infection, indirect contact with a person with confirmed COVID-19 infection, and contact with a person with suspected COVID-19 infection or infected materials.
3. Knowledge and perceptions of COVID-19, including (1) knowledge of transmission routes, level of satisfaction with COVID-19 health information, trends in new cases and deaths, and potential treatment of COVID-19 infection; (2) sources of information; and (3) concerns about COVID-19 variables, such as COVID-19 infection of self and other family members and chances of survival if infected.
4. Protective measures against COVID-19, including (1) avoiding the use of shared utensils during meals, conduct in case of coughing and sneezing, and hygiene rules and (2) individual and social measures to avoid COVID-19.
5. Mental health status, which will be measured using the 21-item Depression, Anxiety, and Stress Scale (DASS-21) developed by Lovibond and Lovibond [45]. The total depression subscale score was divided into scores for normal depression (0-9), mild depression (10-12), moderate depression (13-20), severe depression (21-27), and extremely severe depression (28-42). The total anxiety subscale score was divided into five score categories: normal (0-6), mild anxiety (7-9), moderate anxiety (10-14), severe anxiety (15-19), and extremely severe anxiety (20-42). The total stress subscale score was divided into scores for normal stress (0-10), mild stress (11-18), moderate stress (19-26), severe stress (27-34), and extremely severe stress (35-42). The DASS-21 has been shown to be a reliable and valid measure for assessing the mental health of the Portuguese-speaking [46] and French-speaking [47] populations.
6. The psychological impact of COVID-19, which will be measured using the Impact of Event Scale–Revised (IES-R) developed by Weiss and Marmar [48]. The IES-R is a self-administered questionnaire that has been validated in the Portuguese population to determine the extent of psychological impact after exposure to a public health crisis [49]. A French version of the scale is also available [50]. This 22-item questionnaire is composed of three subscales and aims to measure average avoidance, intrusiveness, and hyperarousal. The total IES-R score was divided into the following score categories: normal (0-23), mild psychological impact (24-32), moderate psychological impact (33-36), and severe psychological impact (>37) [51].
7. Coping strategies, which will be measured using the Brief Resilient Coping Scale developed by Sinclair and Wallston [52]. This is a 4-point measure designed to assess an individual's tendency to cope adaptively. The cutoff point categories are low resilience (4-13), medium resilience (14-16), and high resilience (17-20). The Portuguese version was validated by Pais-Ribeiro and Morais [53], and the French version was translated by Ionescu [54].
8. Hope levels, which will be assessed using the Herth Hope Index (HHI) created by Herth [55]. Hope has been recognized in all disciplines as an important motivational state for overcoming adversity or life-threatening situations. The HHI measures different dimensions of hope using a 4-point Likert scale, ranging from 1 (strongly disagree) to 4 (strongly agree). The scale has an overall score ranging from 12 to 48, as well as individual scores ranging from 1 to 4. A higher score indicates a higher level of hope. The Portuguese version was validated by Viana et al [56]. No translation or cross-cultural evaluation of the HHI into French has yet been published. Therefore, we will conduct a methodological validity study of the instrument following the COSMIN (Consensus-Based Standards for the Selection of Health Measurement Instruments) guidelines [57] and by using a reverse method for transcultural validation [57]. A pilot study will be carried out prior to data collection and will include two phases: Phase I will comprise the adaptation of the scale, including translation and back translation, an expert evaluation, and a pretest [57], and Phase II will involve validation of the translated scale, including assessment of reliability and factorial validity of all the scale's items. To establish the initial psychometric properties of the HHI, at least 120 higher-education students will be recruited. According to the general rule of thumb, the sample size should be at least 10 individuals per item for an exploratory factor analysis or principal component analysis [58].

Phase II: Focus Group Questions

Findings from the online survey will serve as a basis to develop questions to facilitate discussion in the focus groups, as demonstrated in Multimedia Appendix 1. A qualitative description provides a straightforward, rich account of experiences to understand the perspective of individuals, as well as the rationale for their actions [39].

Two key considerations in cross-national focus group research is that questions asked in each country cover the same themes and be understood similarly by participants in each country [59]. We will define a fixed number of broad questions to be discussed for 20 to 30 minutes each. An initial 5-minute icebreaking round of introductions will force every participant to say something early on, preventing people from remaining silent throughout the discussion. Furthermore, moderators in both countries will be instructed to simply refer participants back to the question asked, limiting follow-up questions to the clarification of opinions. In each country, the same nondirective moderating style will be followed to promote interaction between focus group participants. Standardizing the moderating style will also improve the cross-national comparability of the discussions.

Interviews will be structured to identify participant perceptions and attitudes about the determinants of psychological stress, strategies adopted by students to promote better psychological adjustment during the pandemic crisis, and students' opinions and feelings about the teaching-learning process during quarantine. At this point and based on the current state of evidence [21,60,61], certain external and environmental variables have been identified as relating to mental health, as follows: (1) new forms of academic work organization (eg, distance education and evaluation), (2) personal working conditions and study strategies, and (3) perceived social isolation

and interactions with others (eg, classmates and educational staff).

Data Analysis

Quantitative Measures

Quantitative data from the standardized measures will be entered into SPSS Statistics, version 27 (IBM Corp), for analysis. Parametric and nonparametric techniques—as appropriate, depending on the nature and distribution of the data—will be used to estimate and explain changes in primary and secondary outcomes. Descriptive data analysis will be performed using absolute and relative frequencies, mean and standard deviation, and median and interquartile range. The appropriate techniques will analyze the association and/or differences between groups according to the conditions (chi-square tests, *t* tests, analyses of variance, etc). Associations between variables will be determined with univariable and multivariable analyses, using simple linear regression and general linear regression analyses, respectively. The significance level will be set at α=.05.

Qualitative Measures

The interviews will be audio-recorded and transcribed in full, with all personal and place identifiers removed. Data will be managed and analyzed with the aid of the computer-assisted qualitative data analysis software package ATLAS.ti (Scientific Software Development GmbH). The data from FGDs will be coded and inductively analyzed using a thematic analysis approach [62]. Inductive codes will be created and used to identify and link segments of data in a variety of meaningful ways. Verbatim quotes from participants, translated from the original Portuguese and French versions into English, will be used as examples when presenting results. Categories will be represented visually using diagrams to illustrate the conceptual relationship between the emerging categories. Data analysis will be guided by the COREQ (Consolidated Criteria for Reporting Qualitative Research) guidelines [63].

Results

This study is currently ongoing and the results, using the recruitment, data collection, and data analysis methodology described above, are expected to be available no later than the end of 2021.

Triangulation of Quantitative and Qualitative Data Findings

According to the sequential explanatory design discussed in Multimedia Appendix 1, an initial data analysis will be undertaken when completing Phase I (ie, quantitative data extracted from e-questionnaires). The results of Phase I will help develop an interview guide for the FGDs with students. In Phase II, qualitative data will be analyzed using thematic analysis, and the results of this phase will be integrated with the previous analysis to obtain a broader and more accurate picture describing psychological needs during the COVID-19 pandemic among higher-education students. In this study, both quantitative and qualitative cultural data sets will be collected independently and researchers in each study will integrate data sets into four stages: (1) data collection, by designing qualitative interview questions based on the results of the quantitative survey instrument; (2) sampling, by selecting interviewees for the qualitative phase from among participants in the quantitative phase; (3) coding process (ie, hierarchical tree); and (4) inferential stage, by jointly discussing the results from both quantitative and qualitative approaches and comparing the corresponding analysis maps generated in the study.

As noted previously, ensuring the conceptual equivalence of constructs, the functional and linguistic equivalence of instruments, and the authentic comparability of translated data are critically important issues for all cross-cultural research [64]. The presence of a bilingual researcher on our team constitutes a linguistic advantage to actively intervene in data integration, by systematically establishing lexical equivalence across languages in the online survey (ie, quantitative) and capturing authentic oral meanings and articulating them in transcriptions (ie, qualitative).

The criteria of trustworthiness and authenticity will be taken into account [65]. Trustworthiness will be provided by elements such as the study's duration and the use of triangulation of sources, methods, and researchers. To ensure study reliability, the researchers will be deeply involved in data handling and will maintain transparency while they analyze the data. The research team includes six nurses involved in academic teaching and with expertise in nursing practice (AQ, CL, MD, FSM, TC, and ZC), as well as a psychologist (DA).

Qualitative data from both countries will be shared, and procedural similarities and differences in each context will be discussed. Field and self-reflective notes will be taken during data collection and analysis to enhance transparency and provide an audit trail of context and on how key decisions on interpretation were made [64]. For that purpose, we will use qualitative coding techniques (ie, interrater reliability) to ensure study trustworthiness, because multiple researchers will be involved with coding. Multiple competing realities and perspectives may differ across time and context, and our findings will be limited to the time and context of this study. Transferability of findings is nonetheless maximized by triangulation to ensure the inclusion of different perspectives. Findings will be used to produce recommendations and best practices.

Ethical Considerations

Ethical rules and considerations will follow the international Declaration of Helsinki guidelines [66]. Requests for ethical approval differ between the two countries participating in this research. For Portugal, this study was formally approved by the local ethics committee (CE/IPLEIRIA/22/2020). For Switzerland, ethics approval was given by the Swiss Association of Research Ethics Committees, swissethics (CER-VD-2020-02889).

Personal data will be processed in accordance with the European Union General Data Protection Regulation (GDPR2016/679) and, until the end of the study, only the research manager will have access to data identifying the participants. All participants will be informed of the purpose of the study, that participation is voluntary, that they can leave the study at any time, and that

all data are handled confidentially. By responding to and submitting the e-survey, participants will give their consent to participate in the study. Similarly, an independent informed consent form will be presented to the students participating in the focus groups, stating the same principles and reinforcing the anonymization and confidentiality of the information shared during the FGDs.

Quantitative data processing and analysis will be carried out by the research team, and the use of files will be the responsibility of the two main researchers. Data transfer will respect the Swiss federal law on data protection, as well as the law of the canton of Fribourg [67] and regulation No. 2016/679, known as the General Data Protection Regulation for Portugal. A contract between the two parties supports these elements.

Discussion

Study Rationale

As with any other type of natural disaster, the risk of a pandemic cannot be eliminated. Despite prevention efforts, pandemics will continue to occur and will, at times, overwhelm the systems in place to mitigate health, societal, and economic effects [68]. As stated in Madhav et al, "Unlike most other natural disasters, pandemics do not remain geographically contained, and damage can be mitigated significantly through prompt intervention. As a result, there are strong ethical and global health imperatives for building capacity to detect and respond to pandemic threats, particularly in countries with weak preparedness and high spark and spread risk" [68]. There is no single, optimal response to a public health emergency; strategies must be tailored to the local context and to the severity and type of pandemic [68].

Considering the relevance of global warming and the increase in frequency and magnitude of natural disasters, mental health assessments should be extended to impacts caused by the pandemic. There is little understanding of mental well-being assessment under pandemic scenarios involving social isolation and lockdown. This study will enable us to conduct a multisite survey in Portugal and Switzerland on the perception of the psychosocial impact of the COVID-19 pandemic among higher-education students, using the same research instruments. By studying and comparing the current situation in both countries, this study could provide empirical evidence for psychiatric symptoms and coping strategies. Thus, the results could inform the development of psychosocial interventions to minimize psychological impact, anxiety, depression, and stress due to the COVID-19 pandemic [69] and provide a baseline for evaluating prevention and control efforts for future biological catastrophes.

This mixed methods international study will also contribute to the development of pedagogical strategies and good practices to reinforce positive mental health strategies, hope, and adaptive coping during catastrophes and traumatic events. These elements would enable institutions to be recognized as mental health friendly.

Conclusions

In any biological disaster, themes of fear, uncertainty, and stigmatization are recurrent and may act as barriers to appropriate medical and mental health interventions [12]. Based on experience from past, serious, novel pneumonia global outbreaks and the psychosocial impact of viral epidemics, the development and implementation of mental health assessment, support, and services are crucial and pressing goals for a health care response to the COVID-19 pandemic [69]. The recognition that the academic community's recovery after a disaster will need to include resilience and mental health promotion can do much to improve our understanding of mental health and its determinants more broadly. We expect that our findings will promote other multicenter studies in other contexts, based on our Portuguese and Swiss partnership.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Summary of the sequential explanatory mixed methods research design.
[DOCX File , 23 KB - resprot_v10i6e28757_app1.docx]

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Abbreviations

COREQ: Consolidated Criteria for Reporting Qualitative Research
COSMIN: Consensus-Based Standards for the Selection of Health Measurement Instruments
DASS-21: 21-item Depression, Anxiety, and Stress Scale
FAQ: frequently asked questions
FGD: focus group discussion
HES-SO: Haute école spécialisée de Suisse occidentale
HHI: Herth Hope Index
IES-R: Impact of Event Scale–Revised

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Proposal

Clustering of Unhealthy Behaviors: Protocol for a Multiple Behavior Analysis of Data From the Canadian Longitudinal Study on Aging

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Abstract

Background: Health behaviors such as physical inactivity, unhealthy eating, smoking tobacco, and alcohol use are leading risk factors for noncommunicable chronic diseases and play a central role in limiting health and life satisfaction. To date, however, health behaviors tend to be considered separately from one another, resulting in guidelines and interventions for healthy aging siloed by specific behaviors and often focused only on a given health behavior without considering the co-occurrence of family, social, work, and other behaviors of everyday life.

Objective: The aim of this study is to understand how behaviors cluster and how such clusters are associated with physical and mental health, life satisfaction, and health care utilization may provide opportunities to leverage this co-occurrence to develop and evaluate interventions to promote multiple health behavior changes.

Methods: Using cross-sectional baseline data from the Canadian Longitudinal Study on Aging, we will perform a predefined set of exploratory and hypothesis-generating analyses to examine the co-occurrence of health and everyday life behaviors. We will use agglomerative hierarchical cluster analysis to cluster individuals based on their behavioral tendencies. Multinomial logistic regression will then be used to model the relationships between clusters and demographic indicators, health care utilization, and general health and life satisfaction, and assess whether sex and age moderate these relationships. In addition, we will conduct network community detection analysis using the clique percolation algorithm to detect overlapping communities of behaviors based on the strength of relationships between variables.

Results: Baseline data for the Canadian Longitudinal Study on Aging were collected from 51,338 participants aged between 45 and 85 years. Data were collected between 2010 and 2015. Secondary data analysis for this project was approved by the Ottawa Health Science Network Research Ethics Board (protocol ID #20190506-01H).

Conclusions: This study will help to inform the development of interventions tailored to subpopulations of adults (eg, physically inactive smokers) defined by the multiple behaviors that describe their everyday life experiences.

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KEYWORDS

health behaviors; multiple behaviors; cluster analysis; network analysis; CLSA

Introduction

Two-thirds of all annual deaths in Canada are caused by 4 noncommunicable chronic diseases: cancer, cardiovascular disease, diabetes, and chronic respiratory disease [1]. Approximately 12% of Canadians 65 years or older have lived with 2 or more of these chronic diseases, also known as multimorbidity [2]. Health behaviors such as physical inactivity, unhealthy eating, smoking tobacco, and alcohol use are leading risk factors for chronic diseases and play a central role in health status and quality of life [3]. The prevalence of risky health behaviors is high, with approximately 4 in 5 Canadian adults reporting at least one of these modifiable risk factors for noncommunicable chronic diseases [2].

Although the risk factors and consequences of multimorbidity have been studied extensively [4-6], much less attention has been paid to understanding how different combinations of multiple behaviors influence individuals' life satisfaction and health. Our everyday lives are defined by multiple co-occurring health, social, family, personal, and work-related behaviors, each vying for the limited time, energy, and motivation available [7]. In spite of this, health behaviors tend to be studied and promoted largely separately from each other, resulting in guidelines and interventions for healthy aging siloed by specific behaviors. For example, Canada has distinct sets of guidelines for physical activity and sleep [8] and alcohol consumption [9]. In addition to focusing on single health behaviors, guidelines often do not consider the interconnectedness—or co-occurrence—of the various other family, social, work, hobby, and other behaviors that characterize daily life. Understanding how behaviors cluster and how such clusters are associated with physical and mental health, life satisfaction, and health care utilization may provide new opportunities to leverage this co-occurrence to promote multiple health behavior change interventions tailored to which behaviors co-occur for whom, thus better reflecting the real-world complexity of health care for aging Canadians.

International population data support the co-occurrence and clustering of health behaviors. For instance, Irish national data collected in the 2007 National Survey of Lifestyle, Attitudes, and Nutrition investigated the co-occurrence of smoking, alcohol use, physical inactivity, and unhealthy eating in adults aged 18 years and older [10]. In this cross-sectional analysis, the authors identified 6 clusters of behaviors to describe the population, which were labeled as (1) *healthy lifestyle* (characterized by people who had never smoked, high physical activity, highest healthy eating, and moderate alcohol use), (2) *former smokers* (former smokers who reported high physical activity, moderate alcohol use, and healthy eating), (3) *temperate* (moderately active and moderate drinkers who had never smoked), (4) *physically inactive* (people with low levels of physical activity, poor eating habits, and who reporting some smoking and high alcohol use), (5) *mixed lifestyle* (those who had never smoked and reported moderate physical activity and variable alcohol consumption), and (6) *multiple risk factor* (moderate physical activity, moderate to high alcohol use, and variable healthy eating). Although the cluster labels do not directly convey the co-occurrence of the behaviors, definitions of each label describe which behaviors co-occur most in each group in terms of the extent of the performance of each behavior. Beyond defining how behaviors cluster, they also showed that membership in each cluster was associated with demographic factors and health and well-being outcomes: those in the *healthy lifestyle* cluster were more likely to be women 65 years or older, be in the highest socioeconomic status (SES) group, and exhibit low psychological distress; those in the *former smokers* cluster were more likely than the healthy lifestyle cluster to be men and be in a lower SES group; the *temperate* cluster was associated with being male and being in a lower SES group as well as being younger; the *physically inactive* cluster was associated with being male aged 18 to 29 years and being in a lower SES group and having higher psychological distress; the *multiple risk factor* cluster had lowest reported energy and vitality, highest distress, lowest self-reported health, and lowest quality of life; and the *mixed lifestyle* cluster was associated with being male and younger and being in a lower SES group, with highest distress and lower energy and vitality. These findings show how the population can be segmented by the multiple health behaviors that characterize their lives and that these segmented clusters are socially patterned and associated with different health outcomes. It remains to be seen how such clusters may hold when focusing on adults aged 45 to 85 years and extending the behaviors under consideration beyond health behaviors. Identifying these clusters and their associations with demographic factors, general health, and health care utilization can inform the tailoring of future interventions targeting multiple behavior change.

In another study, Buck and Frosini [11] used data from the Health Survey for England to investigate the clustering of smoking, excessive alcohol use, unhealthy eating, and physical inactivity among adults aged 16 to 74 years between 2003 and

2008. They showed that in 2008, only 7% of people engaged in none of the behaviors and only 5% engaged in all 4; 63% of people engaged in 1 or 2, with the remaining 25% engaging in 3 or more behaviors. The most common co-occurring behaviors included either unhealthy eating and physical inactivity (more prevalent in women) or alcohol use, unhealthy eating, and inactivity (more prevalent in men). Men were more likely than women to have 3 co-occurring unhealthy behaviors, and those 65 years and older were more likely to have 2 co-occurring unhealthy behaviors than any other age group (16-24, 25-44, 45-64, and ≥65 years).

Although the importance of co-occurring health behaviors is clear, the role of nonhealth behaviors should not be overlooked. Using Australian population survey data collected in 2007 and 2009 in the Household Income and Labour Dynamics of Australia survey, we showed that other behaviors co-occurred with healthy eating and to some extent differed between men and women aged 18-65 years [12]. For Australian women, some family behaviors (caring for young children) and work behaviors (being employed in a managerial position) were associated with healthy eating, whereas not working was negatively associated with healthy eating. For men, the co-occurrence of work-related behaviors with healthy eating depended on the type of job category (positive for managers and negative for laborers). The findings highlight that nonhealth behaviors also co-occur with health behaviors and underscore the connectedness of the multiple behaviors in daily life.

The examples discussed so far have examined co-occurring health behaviors in the general population. However, some studies have focused on adults aged 50 years and older. For example, one study specifically focusing on older adults involved cross-sectional data collected in Germany in 2006, involving 982 men and 1020 women aged 50 to 70 years [13]. The authors investigated how 4 health behaviors (tobacco use, alcohol use, unhealthy eating, and physical inactivity) clustered in the population of adults in one German state and reliably grouped individuals by the unhealthy behaviors that they engaged in: 25% were defined by the lack of unhealthy behaviors, 21% as inactive, 18% as low fruit and vegetable eaters, 13% as smokers with other risk behaviors, and 23% as drinkers with other risk behaviors [13]. Although some adults were only described using one unhealthy behavior, over one-third had multiple unhealthy behaviors that clustered together. Furthermore, membership in each cluster was also patterned in terms of sociodemographic factors: those with multiple co-occurring unhealthy behaviors tended to be men, living alone, and of a lower SES. This study focused on a limited set of unhealthy behaviors, and it remains unclear which other behaviors characterizing daily life may also co-occur.

A different methodological approach was taken by Shaw and Agahi [14], who used baseline data from the 1998 Health and Retirement Study [15], which collected data from adults older than 50 years, to form *health behavior profiles*. In total, 12 health behavior profiles were constructed based on combinations of smokers versus nonsmokers, physically active versus inactive, and those who reported no versus moderate versus heavy alcohol consumption. Profiles varied widely in the percentage of participants captured in each profile. The 6 most prevalent profiles included the following: (1) *physically inactive, nondrinkers, who do not smoke* (6702/19,662, 34.1%); (2) *physically active, nondrinkers, who do not smoke* (4662/19,662, 23.7%); (3) *physically active, moderate drinkers, who do not smoke* (1986/19,662, 10.1%); (4) *physically inactive, moderate drinkers, who do not smoke* (1684/19,662, 8.6%); (5) *physically inactive, nondrinkers, who smoke* (1274/19,662, 6.5%); and (6) *physically active, nondrinkers, who smoke* (820/19,662, 4.2%).

Taken together, population survey data worldwide are converging on the idea that health behaviors cluster differently across the population and that the resulting clusters have distinct sociodemographic and health outcome patterns. However, to our knowledge, this has only been explored to a limited extent in Canadian data. Canadian National Population Survey data have shown that physical inactivity, alcohol use, and smoking co-occur [16,17]. Understanding how behaviors co-occur at a population level may provide novel ways of developing support and guidance for patients and clinicians and preventing noncommunicable chronic diseases in the general population using a multiple behavior approach.

To this end, we aim to leverage cross-sectional baseline data from the Canadian Longitudinal Study on Aging **(**CLSA) [18]. By 2031, 1 in 4 Canadians will be aged 65 years or older, and the CLSA aims to understand the determinants of health and wellness as people age [19]. For our purposes, we will use CLSA baseline data to address the following objectives: (1) describe how health behaviors cluster, (2) describe how other behaviors of everyday life (family, work, hobby, and community behaviors) cluster, (3) identify sociodemographic factors (sex, age group, marital status, income, country of birth, and social support availability) associated with cluster membership, (4) examine whether life satisfaction and health differ across clusters, (5) examine whether and which clusters of behavior are associated with health care utilization, and (6) examine whether clusters of health behaviors are associated with nonhealth behaviors.

Methods

Overview

The CLSA is a national longitudinal study designed to assess the biological, physical, societal, and psychosocial factors involved in healthy aging [18]. CLSA baseline data collection was conducted between 2010 and 2015 and involved 2 approaches: (1) a *tracking* cohort (n=21,241) that responded to questions administered by a 60-minute computer-assisted telephone interview and (2) a *comprehensive* cohort (n=30,097) that involved a 90-minute in-person interview and a data collection site visit. A 30-minute *maintaining contact questionnaire* was also administered by telephone to both cohorts 18 months after the initial contact to collect supplementary data from the same cohort (all of which form the baseline data collection used in our planned analysis).

Participants

Participants were recruited through random-digit dialing, provincial health registries, and the Canadian Community Health Survey on Healthy Aging [19,20]. Exclusion criteria for the

CLSA included residents living in 3 territories and First Nations reserves, full-time members of the Canadian Armed Forces, people living with cognitive impairments, and individuals living in institutions (including 24-hour nursing homes) [21]. This study included 51,338 French- and English-speaking Canadians (26,155/51,338, 50.95% female) aged between 45 and 85 years at the time of enrollment. The average participant age was 62.98 years (SD 10.43), with 26.15% (13,427/51,338) aged between 45 and 54 years, 31.98% (16,420/51,338) aged between 55 and 64 years, 23.37% (11,996/51,338) aged between 65 and 74 years, and 18.5% (9495/51,338) aged between 75 and 85 years. A full description of demographic characteristics of the sample as well as summary data across all measured variables is available in the CLSA baseline data report [19].

Variable Selection

Selection Approach

Variable selection can be performed by *objective* or *subjective* approaches. Objective methods rely on data-driven techniques (eg, forward or backward selection) and techniques such as factor analysis and principal component analysis for dimension reduction to arrive at a parsimonious set of features for inclusion in a model [22]. In contrast, subjective approaches are generally driven by expert opinions and/or theory-driven research questions. Due to the manageable number of variables in the CLSA related to our research question, objective or data-driven approaches to feature selection were not required. Rather, based on our research objectives and the data collected by CLSA, we identified by group consensus an initial set of variables assessing health behaviors, nonhealth behaviors, sociodemographic indicators, general health and well-being, and health care service utilization. Our decisions were also shaped by issues of survey design (eg, skip questions), knowledge of basic summary statistics for baseline CLSA data [19], and our own supplementary summary statistics on the baseline data. Multimedia Appendix 1 provides a description of variables in each category (eg, health behaviors and nonhealth behaviors) to be used in the analyses, along with example items.

Health Behaviors

Physical activity and *sedentary behavior* were measured using the Physical Activity Scale for the Elderly [23], which assesses the frequency of sedentary behavior, walking, light physical activity, moderate physical activity, strenuous physical activity, and exercise. The items asked participants to report on their activity levels over the previous 7 days on a scale of 1 (never) to 4 (often, 5-7 days). A recent report published by Statistics Canada focusing on the relationship between physical activity and lung functioning [24] merged light and moderate physical activity together and merged strenuous physical activity and exercise together based on issues with question prompts and conceptual overlap between question items. To facilitate dimension reduction, we opted for a similar approach in which the Physical Activity Scale for the Elderly subscale items were merged to represent sitting, walking, light or moderate physical activity, and strenuous physical activity or exercise.

Fruit and vegetable consumption was assessed using one item from the Seniors in the Community Risk Evaluation for Eating and Nutrition questionnaire [25]. The item asks respondents how many servings of fruits and vegetables they eat in a day. The original scale was reverse coded such that higher scores indicate more fruit and vegetable consumption.

Smoking behavior was measured using a skip-question framework in the CLSA. Participants who answered "no" to the question "have you smoked at least 100 cigarettes in your life" and responded "yes" to the question "have you ever smoked a whole cigarette" were subsequently asked whether they smoke occasionally, daily, or not at all in the past 30 days. Next, only participants who reported smoking occasionally or daily were asked follow-up questions pertaining to the frequency and types of tobacco products used. A descriptive analysis of the last 2 items showed that only a small minority of respondents (4845/51,338, 9.44%) engaged in occasional or daily smoking, with the majority (30,558/51,338, 59.52%) not engaging in smoking behavior in the past 30 days. Although the frequency of smoking would be a more informative metric, any cluster analysis with smoking frequency would reduce the sample size to 4845 and would only represent people who have smoked within the past 30 days. In addition, we will assign a value of 0 to each respondent who responded "no" to the question "have you ever smoked a whole cigarette," as these individuals also did not smoke in the past 30 days. A similar approach has been applied to skip structure data when missing data represent the absence of a behavior or psychological feature [26]. Ultimately, this creates 4 levels distinguishing between people who have never smoked and people who have smoked occasionally, daily, or not at all during a 30-day window.

Alcohol use was assessed with a single item asking participants how often they drank alcohol in the past 12 months on a scale from 1 (almost every day) to 7 (less than once a week). Responses will be reverse coded so that higher values indicate greater alcohol consumption.

Finally, *sleep* was also measured with a single item. Participants were asked how many hours of sleep they get, on average, during the past month and could respond with any value between 0 and 24.

Nonhealth Behaviors

Two items representing participation in *hobbies* were selected from the general health module. One item asked how much time participants spent playing board games, crossword puzzles, cards, sudoku, or jigsaw puzzles. The second question asked how much time participants spent singing in a choir or playing a musical instrument. Both items were originally scored on a scale from 1 (every day) to 5 (once a year or less); we will reverse code these variables so that higher values represent higher frequencies.

A social participation module was included in the CLSA baseline data collection that asked respondents about their tendencies to engage in various *community activities*, including church or religious activities; attending concerts, watching plays, or visiting museums; service club or fraternal organization activities; community or professional association activities; volunteer or charity work; participation in activities with family or friends outside the household; participation in sports or

physical activities with others; participation in educational or cultural activities; and participation in other recreational activities. The CLSA contains 2 derived variables in the social participation module, one binary variable reflecting whether participants engaged in any social activities and another reflecting the frequency of participation in any activity over the past 12 months (0=no activities, 1=yearly, 2=monthly, 3=weekly, and 4=daily). We will use only the latter in our analysis.

The *caregiving* module contained questions pertaining to assisting others, how many others were assisted, the type of assistance, the people who the respondents help most often, and the personal and professional impacts of providing care to others. To reduce the number of items included in the analysis, we will use a derived variable in the CLSA data set, which indicates whether the respondent provided assistance to any person in the past 12 months (excluding aid rendered as part of a paid job or volunteer work). According to the descriptive analysis from CLSA baseline data [19], 44.4% (22,805/51,338) of participants reported aiding another person due to health conditions or other limitations. This variable will be recoded as 0 (did not provide assistance) or 1 (did provide assistance).

Finally, the CLSA participants were asked whether they used any *social networking sites* (eg, Facebook, LinkedIn, MySpace, MSNGroups, and Twitter). Our preliminary descriptive analysis showed that 44.7% (22,959/51,338) of the participants reported using social networking sites, whereas 38.0% (19,518/51,338) of the participants were not social networking site users, and 17.3% (8861/51,338) of responses were either missing or nonresponses. Although more detailed follow-up questions were subsequently posed to respondents, including these items would substantially reduce the sample size available for analysis. Given the skip-question structure of the CLSA social networking site module, we will include a binary variable representing the use (1) or nonuse (0) of social networking sites.

Sociodemographic Indicators

We will use several sociodemographic indicators in our analysis. These include age, as grouped in the CLSA data set (45-54, 55-64, 65-74, or 75-85 years); sex (male or female); country of birth (recoded as 0=Canada or 1=other); marital status (single, married or common-law, widowed, divorced, or separated); household income (five income levels); retirement status (completely retired, partly retired, or not retired); and working status (yes or no to the question “are you currently working at a job or business.” In addition, participants responded to 19 questions from the Medical Outcomes Study (MOS) Social Support Survey [27]. The MOS is scored according to 5 subscales: tangible social support, affection, positive social interaction, emotional support, and informational support. The MOS overall support index is also scored in the CLSA baseline data set. To reduce the number of constructs in our analyses, we will use the overall support index, scored from 0 (low support) to 100 (high support).

General Health and Life Satisfaction

Three single-item measures were selected from the CLSA’s general health module. These include an indicator of general health (“in general, would you say your health is excellent, very good, good, fair, or poor?”), mental health (“in general, would you say your mental health is excellent, very good, good, fair, or poor?”), and perceptions of healthy aging (“in terms of your own healthy aging, would you say it is excellent, very good, good, fair, or poor?”). Items were originally scored from 1 (excellent) to 5 (poor) but will be reverse coded. In addition, a composite score from the Satisfaction With Life Questionnaire [28] will be used in the analysis. The Satisfaction With Life Questionnaire is scored according to Deiner [29] on a scale ranging from 1 (extremely dissatisfied) to 7 (extremely satisfied). Finally, BMI will be used as an indicator of physical health.

Health Care Utilization

Three single-item questions were selected from the CLSA’s health care utilization module. These items represent emergency department visits (“Have you been seen in an Emergency Department during the past 12 months?”), hospital admittance (“Were you a patient in a hospital overnight during the past 12 months?”), and nursing home use (“Were you a patient in a nursing home or convalescent home during the past 12 months?”). All responses will be coded as yes (1) or no (0).

Cluster Analysis Overview

We will use cluster analysis to cluster *individuals* based on their behaviors and network community detection algorithms to cluster *variables* based on the strength of conditionally independent pairwise relationships between variables.

Classifying data through the assignment of classes to objects in a data set is a common application of machine learning (ie, “set of methods that can automatically detect patterns in data, and then use the uncovered patterns to predict future data” [30]). Classification algorithms fall into 3 categories: supervised learning, semisupervised learning, and unsupervised learning. In supervised learning, the relationships between the input and target variables are known. An algorithm is *supervised* in that it can be trained on a data set that contains correct classifications. Data sets containing these correct classifications are referred to as *labeled data*, in contrast to *unlabeled data*, in which the correct classifications are not known. In semisupervised learning, a combination of labeled and unlabeled data is used to model the data, whereas in unsupervised learning, the model works on its own to discover patterns in unlabeled data [31].

Cluster analysis is a type of unsupervised machine learning that comprises a set of methods for identifying distinct characteristics in heterogeneous samples and clustering them into homogenous groups [32]. When the target number of clusters (k) is known, partitioning-based clustering arguments such as k-means, k-medoids, or model-based clustering approaches are appropriate. However, when k is unknown, as is the case with clusters of Canadians based on health and nonhealth behaviors, hierarchical clustering is a suitable method [32].

The hierarchical structure of the data can be obtained by clustering individual data points in a bottom-up approach (ie, agglomerative clustering) or by partitioning a single cluster into smaller clusters until each cluster is a single observation through

a top-down approach (ie, divisive clustering). Divisive methods are rarely used in practice owing to their heavy computational requirements [33]. In agglomerative hierarchical clustering, each individual data point is initially treated as its own cluster. The methodological process is as follows [34]: each data point is assigned to its own cluster, the distance (ie, the similarity or dissimilarity between each cluster) between each cluster is calculated, the pair of clusters with the shortest distance between them is selected and merged into a single cluster, the distances between the new cluster and all other clusters are recalculated, and these steps are repeated until only one cluster remains. However, a single cluster (k=1) is unlikely to be informative; researchers can identify the number of clusters that best describe the data (eg, k=5) through subjective criteria and/or with the aid of statistical tests that have been developed for this purpose.

Several measures of *distance* are widely used in practice, although the Gower distance [35] is appropriate for mixed data (binary, ordinal, and continuous). In addition to selecting a measure of distance, hierarchical agglomerative clustering also requires a linkage method to be specified to define how the distance between clusters is calculated. Different methods exist for specifying the anchor points used to calculate the distance between clusters (ie, how the distances between clusters are *linked*). For example, *single or minimum linkage* calculates the minimum distance between data points in each cluster, whereas *centroid linkage* calculates the distance between the center of each cluster [31]. No consensus exists as to which linkage method is superior, although it is recognized that final clustering solutions may differ based on the linkage method selected [33].

Network Analysis and Community Detection Overview

Another method for clustering data is through network community detection. In contrast to cluster analysis, which clusters *people* based on similarity or dissimilarity of selected features (eg, health behaviors), network community detection identifies groups of *highly connected variables* based on the strength of the connections. Before conducting the community detection analysis, a network must first be estimated. Networks consist of nodes and edges. In psychological networks, nodes represent psychological attributes (eg, emotions, behaviors, and symptoms) and edges represent relationships between nodes (eg, partial correlations) and can indicate the presence of a positive or negative relationship and the direction of the effect. Psychological networks are commonly estimated using a pairwise Markov random field (PMRF) [36,37]. In a PMRF, edges represent the conditional independence between a pair of connected variables. For cross-sectional data, the underlying models for the PMRF vary depending on the type of data. For example, a Gaussian graphical model is appropriate for multivariate normal continuous data, whereas Ising models are used for binary data, and mixed graphical models (MGMs) [38] have been developed for mixed data. Due to the large number of parameters often estimated in a PMRF, researchers often compute a regularized network by applying, for example, the least absolute shrinkage and selection operator [39] to produce a sparse or conservative network that reduces weak connections between nodes to 0, resulting in a more interpretable network. However, recent work has questioned whether regularization is required for low-dimensional data with large sample sizes [40].

Once a network has been estimated, an additional analysis can be conducted. For example, node centrality, a family of measures meant to indicate the importance of nodes within a network [37], can be computed. Other analytical options include calculating the explained variance and performing network comparison tests. In the cross-sectional data, a network is estimated by regressing all nodes onto each other. This enables the explained variance for each node to be calculated and visualized within the network itself [38]. Network comparison tests are permutation-based hypothesis tests that allow comparisons between 2 networks (eg, health behaviors for those aged 45-54 years and 55-64 years) based on their global structure, global strength (a measure of centrality), and differences between individual edges [41].

Finally, community detection algorithms can be applied to the network. Commonly used community detection methods in psychology include the spinglass algorithm [42], the walktrap algorithm [43], leading eigenvector [44], exploratory graph analysis [45], and the clique percolation algorithm [46,47]. When compared with alternative methods, the clique percolation algorithm addresses a central challenge in identifying communities within a network, namely, the ability to assign a node to multiple communities. Overlapping communities enable the identification of *bridge nodes* (nodes that connect 2 otherwise distinct clusters) and are therefore important for hypothesis generation [48]. Cliques are fully connected networks. The number of nodes (k) that must be connected can vary, with the smallest clique being k=3 (a closed triangle). When more than one set of cliques are adjacent in a network, they are said to form a community. In psychological networks, where edges are weighted (eg, representing correlations), only edges that surpass a certain threshold (I) are considered when identifying cliques [46,47,49].

Proposed Analysis

Survey Weights

The CLSA baseline data set contains sample weights (to ensure representativeness of the sample), inflation weights (to improve the precision of estimates), and analytic weights (to estimate the relationships among variables) [50]. The CLSA recommends the use of inflation weights for the estimation of descriptive parameters and analytic weights for exploring the relationships among variables at a national or provincial level [50]. However, the statistical packages we have selected in our planned cluster analysis method do not have the option to include survey weights and will, therefore, not be applied. Given the relative novelty of network analysis methods in psychology, the appropriate role of survey weights in network methodology is unknown. To our knowledge, the only study that addresses this issue is the study by Lin et al [51], who opted not to include survey weights due to “a lack of established methods to do so for network models.” Therefore, weights will not be applied for the network analysis.

Preprocessing and Descriptive Statistics

All analyses will be conducted in R (R Core Team) [52]. Selected variables from the tracking (TRM) and comprehensive (COM) data sets will be merged and coalesced (eg, ALC_FREQ_TRM and ALC_FREW_COM coalesced into ALC_FREQ) using the tidyverse package [53]. Raw data will be visualized to inspect the univariate outliers. Means and SDs for all variables will be computed for continuous data, and frequencies and percentages will be computed for categorical data, overall and by sex and age group. Missing data will be handled with listwise deletion.

Cluster Analysis

Step 1

Variables will be reverse coded, when necessary, such that higher scores indicate greater frequency. Subsequently, all continuous and ordinal variables will be mean centered using the scale function in base R [52].

Step 2

We will run cluster analyses on the overall CLSA sample (all age groups) using 5 linkage methods (eg, complete linkage, single linkage, average linkage, centroid linkage, and Ward method). The research team will decide which method produces the most interpretable clustering solution; the selected linkage method will then be applied to all subset analyses grouped by age.

Step 3

Cluster analysis will be performed on health behavior variables for 5 groups (overall sample, 4 age groups) using the base R *hclust* function supported by the package *fastcluster* [54] to optimize performance. Gower distance will be computed using the *daisy* function in the *cluster* package [55].

Step 4

Once agglomerative cluster analysis has been performed, the next step is to determine the most interpretable number of clusters to represent the data. The cluster analysis literature has produced several competing methods to accomplish this task. To navigate these analytical options, we will use the NbClust package [56]. This approach allows for a consensus approach to determine the number of clusters, which best fits the data by computing 30 different indices and reporting the level of agreement between them. The output of this analysis is a list showing the agreement between statistical tests for various clustering solutions (eg, "10 indices propose 2 as the best number of clusters" and "7 indices propose 3 as the best number of clusters"). To allow for the synthesis of data-driven and expert consensus approaches, the research team will select the most interpretable clustering solution via a majority vote from the top 3 solutions identified via NbClust. In instances of an equal number of indices recommending the same cluster solution and/or disagreement within the research team, we will follow the advice of the NcClust package authors who recommend considering indices, which have performed the best in a seminal simulation study [57].

Step 5

When the optimal clustering solution has been identified, the clusters can be characterized by the number of individuals assigned to each cluster and by mean scores on each health-related variable via one-way analysis of variance tests to determine whether the mean levels of the health behaviors vary by cluster.

Step 6

Next, multinomial logistic regression will be used to determine whether clusters are associated with sociodemographic variables, indicators of physical and mental health (eg, life satisfaction), nonhealth behaviors, and health care utilization. Multinomial logistic regression is similar to logistic regression but is appropriate when the dependent variable has more than 2 levels (which will likely be the case for the number of identified clusters). The dependent variable will be the clusters we identify in the cluster analysis. To perform the analysis, we will use the *multinom* function from the *nnet* package [58].

Network Analysis

Step 1

Networks of health behaviors will be estimated using an MGM using the MGM package [38]. To the best of our knowledge, an MGM is the only available method for estimating a psychological network with mixed data. In the mixed model, the edges between nodes represent pairwise interactions and can be interpreted as the strength of conditional dependence [38]. A total of 5 networks will be estimated (all age groups, 45-54, 55-64, 65-74, and 75-85 years). In the mixed model, we will specify *lambdaSel=EBIC* to use the Extended Bayesian Information Criteria [59] for selecting the tuning parameter controlling regularization. The hyperparameter γ in the Extended Bayesian Information Criteria will be set to the default *lambdaGam=0.25*, and only pairwise interactions will be included in the model through setting k=2.

Step 2

For each network from step 2, networks will be visualized with qgraph [60] using the *averageLayout* function to compute a joint layout across networks.

Step 3

The NetworkComparisonTest package [41] will be used to conduct permutation-based hypothesis tests to determine whether networks differ from one another based on sociodemographic variables. We will specify *it=1000* to run 1000 iterations or permutations and will plot the results from the network structure invariance test.

Step 4

Next, community detection analysis will be performed on each network estimated in step 1 using the CliquePercolation package [49]. Although multiple options are available, we will detect overlapping communities by optimizing k and I, where k represents the minimum clique size and I represents the strength of the relationships between nodes required for classification as a community. Following the study by Blanken et al [61], we will determine the optimal threshold I for the fixed values of

k=3-6 and will set the clique percolation algorithm to search through ranges of *I* from 0.01 to the largest edge weight in each network through increments of 0.001. We will choose the value of *k* that allows for the broadest community structure, and *I* will be selected based on the largest chi-square value for intensities with a ratio threshold over 2. The resulting networks will be visualized with colored nodes indicating community structures.

Steps 5 to 8

The processes described in steps 1 to 4 will be repeated for nonhealth behaviors and health behaviors in the same model. A summary of the proposed analysis and its connections with research questions is presented in Table 1. Further graphical representations of the analytical steps are provided in Multimedia Appendices 2 and 3.

Table 1. Overview of research questions and planned analysis.

Research questions	Planned analyses				
	Cluster analysis (analysis 1)	Multinomial logistic regression (analysis 1)	Network analysis (analysis 2)	Network community detection (analysis 2)	Network comparison tests (analysis 2)
Describe how health behaviors cluster in Canadians aged 45-85 years	✓	—	✓	✓	—
Describe how nonhealth behaviors cluster in Canadians aged 45-85 years	—	—	✓	✓	—
Identify sociodemographic factors associated with cluster membership; identify sociodemographic factors associated with network structures	—	✓	—	—	✓
Examine whether cluster are associated with health indicators	—	✓	—	—	—
Examine whether clusters are associated with health care utilization	—	✓	—	—	—
Examine whether clusters are associated with nonhealth behaviors	—	✓	—	—	—

Data Availability

Data are available from the CLSA for researchers who meet the criteria for access to deidentified CLSA data. We will make R scripts public so that any researcher who independently gains access to data can reproduce the results. In addition, we will publish R Markdown documents so that the code and outputs of analysis can be viewed publicly on the Open Science Framework. Deviations from the protocol plan will be noted in the final report. Any additional analysis, not specified here, will be labeled as such and published in web-based supplemental materials.

Results

Baseline data for the CLSA were collected from 51,338 participants aged between 45 and 85 years. Data were collected between 2010 and 2015. Secondary data analysis for this project was approved by the Ottawa Health Science Network Research Ethics Board (protocol ID #20190506-01H).

Discussion

The scope, size, and rigor of the CLSA data set will provide us with an unprecedented opportunity to investigate how behaviors cluster. The findings will allow us to assess alignment with findings from other countries, while extending findings in novel ways by investigating how social, family, and work behaviors cluster alongside health behaviors typically investigated. Perhaps most importantly, this study will help to inform the development of novel health behavior change interventions tailored to subpopulations of adults defined by the behaviors that cluster within them. If behaviors co-occur, intervening on one may impact—or be impacted by—the others [62]. Interventions that target only one behavior may thus be undermined by the impact of a conflicting co-occurring behavior or miss an opportunity to leverage the enabling nature of a positively co-occurring behavior. In addition, targeting multiple co-occurring behaviors simultaneously has potential practical benefits, such as reduced expenses for intervention providers and reduced time commitments for those receiving the intervention. Understanding which behaviors co-occur and for whom is an important first step toward developing health behavior change interventions that address people's actual challenges. In the context of a behavioral intervention development and testing framework [63], the proposed analysis will inform the foundational *basic behavioral science*—regarding patterns of co-occurring risky health behaviors and their associated outcomes—which precedes early phase behavioral trials.

This study will ultimately help to develop and evaluate more targeted interventions to support healthy aging and well-being in adulthood by identifying how clusters of co-occurring health behaviors are associated with sociodemographic factors, general health, and health care utilization. However, the proposed analyses are not without limitations. For example, many of the items selected for planned analysis are self-report, which have inherent strengths and weaknesses [64]. In addition, there are several points in the proposed analysis that require subjective decision making on behalf of the research team (eg, selecting variables for inclusion in models, data preprocessing decisions, selecting missing data procedures, and interpreting and selecting

clustering solutions). We have sought to document these here to provide a clear explanation of decision processes, while acknowledging where and how researcher degrees of freedom are used to ensure transparency. Finally, we recognize that the analyses proposed are, to some extent, limited by their cross-sectional nature. Nevertheless, given the longitudinal nature of CLSA and planned future data releases, the proposed analyses have a number of novel implications and set the stage for planned future longitudinal analyses that extend the research questions to investigate changes in behavior clusters as a function of time both between and within individuals. Thus, this proposed study will establish the foundation for future analyses. More broadly, the methodological approaches proposed for this analysis lend themselves to replication in other similar data sets internationally, and we hope that the sharing of R code will help to enable this.

Finally, we emphasize that our choices of analytic methods are hypothesis generating, not hypothesis testing. However, if replicated, such findings may ultimately find their way into clinical practice guidance and public health guidance.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Variables to be included in the analysis.
[DOCX File , 19 KB - resprot_v10i6e24887_app1.docx]

Multimedia Appendix 2
Graphical representation of the cluster analysis and multinomial logistic regression analytical process.
[DOCX File , 145 KB - resprot_v10i6e24887_app2.docx]

Multimedia Appendix 3
Graphical representation of the network analysis and community detection process.
[DOCX File , 266 KB - resprot_v10i6e24887_app3.docx]

Multimedia Appendix 4
Peer-review report by the Canadian Institutes of Health Research.
[PDF File (Adobe PDF File), 100 KB - resprot_v10i6e24887_app4.pdf]

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Abbreviations

ADAPT: Artificial Intelligence–Driven Digital Content Technology
CIHR: Canadian Institutes of Health Research
CLSA: Canadian Longitudinal Study on Aging
FRQS: Fonds de Recherche du Québec–Santé
MGM: mixed graphical model
MOS: Medical Outcomes Study
PMRF: pairwise Markov random field
SES: socioeconomic status

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Corrigenda and Addenda

Correction: Disparities in Care Outcomes in Atlanta Between Black and White Men Who Have Sex With Men Living With HIV: Protocol for a Prospective Cohort Study (Engage[men]t)

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In "Disparities in Care Outcomes in Atlanta Between Black and White Men Who Have Sex With Men Living With HIV: Protocol for a Prospective Cohort Study (Engage[men]t)" (JMIR Res Protoc 2021;10(2):e21985) the authors noted one error.

In the originally published manuscript, one author was inadvertently not displayed in the authorship list. Author Jodie L Guest was uploaded in the manuscript file, but inadvertently not entered in the online metadata. In the corrected manuscript, the order of authorship has been updated as follows:

Patrick Sean Sullivan; Jennifer Taussig; Mariah Valentine-Graves; Nicole Luisi; Carlos Del Rio; Jodie L Guest; Jeb Jones; Greg Millett; Eli S Rosenberg; Rob Stephenson; Colleen Kelley

The correction will appear in the online version of the paper on the JMIR Publications website on June 3, 2021, 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

Automation of Article Selection Process in Systematic Reviews Through Artificial Neural Network Modeling and Machine Learning: Protocol for an Article Selection Model

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Abstract

Background: A systematic review can be defined as a summary of the evidence found in the literature via a systematic search in the available scientific databases. One of the steps involved is article selection, which is typically a laborious task. Machine learning and artificial intelligence can be important tools in automating this step, thus aiding researchers.

Objective: The aim of this study is to create models based on an artificial neural network system to automate the article selection process in systematic reviews related to “Mindfulness and Health Promotion.”

Methods: The study will be performed using Python programming software. The system will consist of six main steps: (1) data import, (2) exclusion of duplicates, (3) exclusion of non-articles, (4) article reading and model creation using artificial neural network, (5) comparison of the models, and (6) system sharing. We will choose the 10 most relevant systematic reviews published in the fields of “Mindfulness and Health Promotion” and “Orthopedics” (control group) to serve as a test of the effectiveness of the article selection.

Results: Data collection will begin in July 2021, with completion scheduled for December 2021, and final publication available in March 2022.

Conclusions: An automated system with a modifiable sensitivity will be created to select scientific articles in systematic review that can be expanded to various fields. We will disseminate our results and models through the “Observatory of Evidence” in public health, an open and online platform that will assist researchers in systematic reviews.

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KEYWORDS

deep learning; machine learning; systematic review; mindfulness

Introduction

Background

A systematic review (SR) [1] can be defined as a summary of the evidence found in the literature. Unlike classic reviews, specific and described methods are used in the literature search to reach certain results using scientific articles [2]. Essentially, a systematic review consists of a thorough and extensive survey of all published studies on a topic combined with a thorough analysis of the results. In addition, an SR is an extensive systematized survey on a specific subject in which a careful analysis of the evaluated outcomes is performed in an attempt to reach a single conclusion based on all included studies [2]. Reviews are increasingly common; it is estimated that 11 new reviews have been published per day since 2010 [3].

The SR should be conducted considering the factors of Population, Intervention, Control, and Outcome (PICO) [4]. In some cases, it is possible to combine the data in the articles included in an SR and perform a group analysis. This is called the statistical meta-analysis method, in which the variables that are common through similar outcomes can be analyzed in group order to synthesize the effect seen in the studies [5,6]. A meta-analysis is a mathematical calculation that combines the results of several related studies. There are cases in which it is not possible to conduct a meta-analysis, so an SR would be limited to qualitative comparisons [7].

In addition to the systematized search, specific criteria are used to evaluate the methodological quality of each selected article. These measurements are made using scores that vary according to the design of the study in question [8-10]. The search is conducted in various databases to reach the largest number of scientific articles and reduce the risk of failing to include a study that could potentially affect the final result. Thus, once the studies are combined, potential articles that have not been identified are searched in the so-called gray literature.

The literature search using the chosen keywords should be described such that any other researcher could reproduce the same results as the authors, proving that the search was systematized, and the included articles were not preselected, avoiding a selection bias in the final result. However, after combining the results found in the databases, the article selection process according to the PICO criteria can be laborious and time consuming.

According to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [4], the recommended approach is for two investigators to perform the same search and compare the final result. If there is disagreement regarding the selected studies, the senior investigator should make the final decision. The selection is made by reading the titles and abstracts, excluding irrelevant articles, duplicates, letters to the editor, reviews, and other publication types.

When researchers start an SR, most of the time they find a large volume of data, requiring time for a selection of articles based on their design and theme. Researchers have estimated that a systematic review can take 1046 hours or up to 26 weeks to perform [11].

Thus, to speed up the article selection process, it is possible to automate this process through a semiautomatic computer system that contains a machine learning method. The topic is broad, but if we were to restrict the idea to searching and learning with written words, the ideal model for automating article selection is artificial neural networks (ANNs) [12].

Similar to the biological model, ANNs are networks formed by several interconnected units. These connections are associated with synaptic weights that are responsible for learning on the network. The learning capacity of the network is directly linked to the number of neurons and connections. Even formed by simple units, ANNs intelligence emerges from its (network) connectivity.

One of the future goals of ANNs is to replace manual design features, which were believed to be subjective, via efficient algorithms for learning and decision making without continuous human guidance.

There are some published studies that have tested the use of artificial intelligence to improve systematic reviews. A system created by Cochrane with machine leaning algorithms enabled the identification of randomized clinical trials [13], just as Cohen and collaborators [14] launched a tool to estimate this probability from PubMed articles.

Other published articles attempted to automate the selection of studies in systematic reviews. Wallace et al [15] developed Abstrackr based on an active learning system (Active Learning) and used PubMed as a database, unlike our project that will cover other databases, using ANN. Another platform, RobotAnalyst, was created by Przybyła et al [16], but it presents a search and use methodology for artificial intelligence different from this study.

An article reading and selection system for SRs must be specialized to each field of interest and consider all selection stages. Generic software may not be sufficiently sensitive to achieve the accuracy of results afforded by using a complex tool.

Objective

The objective of this study is to develop a semiautomatic, dynamic, and open source computer system which will carry out the selection of scientific articles in SR, specifically in the area of “Mindfulness and Health Promotion,” after deleting duplicate articles and cleaning the data.

Methods

Overview

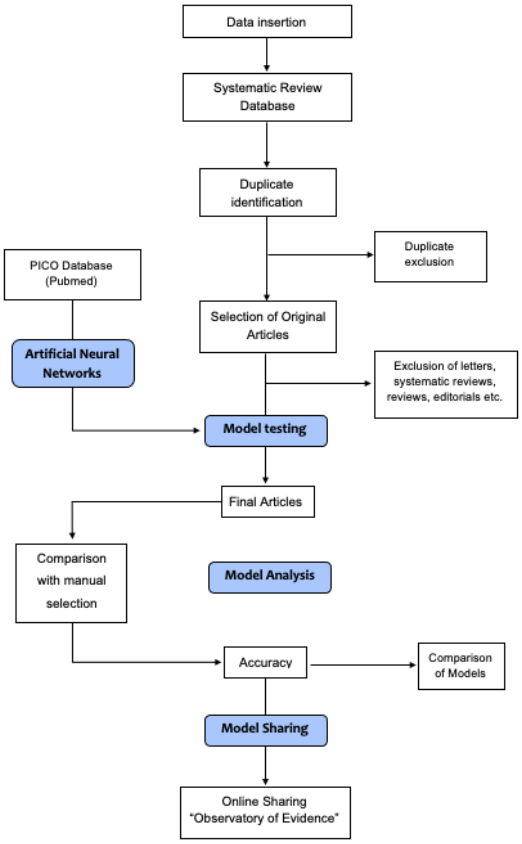
The study was approved by the local ethics committee (Federal University of São Paulo – Number 9425030220-2020). The project will be conducted using Python programming software and packages. Both Python and packages are freely available online.

The system will be constructed based on the search and selection structure of the 10 most cited SRs in Scopus in two different

fields: “Mindfulness and Health Promotion” and “Orthopedics” (control group), a specific area of knowledge for the authors. We will extract the PICO elements from each published SR and reperform the search in PubMed, Web of Science, and Embase. Next, articles will be manually selected for use as a template and metric for comparing the results.

A database will be created with the returned search results for each SR. The search results will be individually introduced into the selection system. Each published SR will have its own specific database and will be run in the system. Next, comparative analyses will be performed within the same field (intergroup comparison) and between two different fields (intragroup comparison). The system flowchart is shown in Figure 1.

Figure 1. Flowchart of the automated steps in the article selection system for systematic reviews. PICO: Population, Intervention, Control, and Outcome.



The system will consist of six main steps: (1) data import, (2) exclusion of duplicates, (3) exclusion of nonarticles, (4) article reading and model development in ANN, (5) comparison of models, and (6) system sharing. The ANN will only be used in the fourth step. Search models simpler than the ANN will be used in other steps to prevent data loading and processing from slowing down and destabilizing the system.

The steps will be performed for each of the SR databases included in this study (for a total of 20 reviews). The steps used to implement this protocol are described in the following sections.

Data Import

Data will be imported for each search return of the SRs. The data will be imported directly from the database of the research platforms and converted into a data frame. We will use all available data: title, abstract, year, authors, journal, and other information.

Exclusion of Duplicates

The data must be cleaned before the articles found in the search are read. In this step, we will exclude all types of duplicate documents. We will use the digital object identifier for initial filtering and exclusion. Subsequently, the title and abstract of the articles will be compared to reduce the risk of nonidentification.

Exclusion of Nonarticles

After the exclusion of duplicates, the data must be cleaned to exclude documents types found in the search that are not relevant to the required format and, at this time, the content. These document types include, among others, editorials, comments, author responses, reviews, and systematic reviews.

We have chosen not to build a neural network model, which would make the system slow and cumbersome. We consider that all these document types can be located and excluded through the search for regular expressions. Conducting manual article selection in parallel will provide a list of regular expressions related to each irrelevant document type to add to an SR.

Article Reading and Model Development in ANN

Learning the documents returned from the search databases will yield only articles potentially includible in the SRs. The article titles and abstracts will be read during the manual search.

The objective is to find studies that meet the criteria included in the SR design through the PICO elements. Thus, we intend to mimic this step by creating an ANN model.

Within PICO, only Population requires an understanding of the text, because there are several ways of describing a group of patients or samples. The terms generally used for Intervention, Control, and Outcome do not necessarily need a context, as they are often names of surgical techniques, medications, or scores. We believe that the search for the exact term will be appropriate.

Thus, the neural network will be automatically created with training on understanding Population. In each tested SR, the system will search PubMed for a MeSH (Medical Subject Headings) term (related to Population) for use as a database to develop an understanding of the text. The MeSH (Population) will be selected by the authors according to the design of each SR.

In addition to this database, we will add a MeSH search on the respective field to counteract and contextualize the creation of the neural network. Other fields, such as Intervention, Control, and Outcome, will be used in the form of tags to complement the article selection.

This specific model will be configured using the characteristics given in the following sections.

Network Configuration and Algorithm

The creation of the artificial neural network should be done through the Keras package, but there are other types of tools that we can use depending on the results found. The selection of scientific articles by reading the abstracts and title does not seem to require reading with semantic interpretation in which the word order is relevant, but rather with a selection of phrases that indicate a specific context. The word vectorization process is fundamental in the study design, impacting the final result of the model.

Thus, we will initially choose the *word2vec* and bag-of-words to capture a broad topical similarity through crosswords, but we will also test the Bidirectional Encoder Representations from Transformers [17]. The word classification will be done by multilayer perceptron (MLP) [18]. MLP is an analog of the artificial neural network, well known for its generalization and predictive capacity.

A neural network is created by stacking layers, and it is necessary to establish two main decisions in the model architecture. First, we will define how many layers will be required for the model. The second important decision to be made will be the number of hidden units used for each layer.

Regarding the model architecture, we will perform empirical adjustments of the hyperparameters during the execution. However, depending on the need, we can use some metaheuristics to optimize them, or even use an automated machine learning technique.

In addition, it will be essential to determine the parameters of the training algorithm and activation functions. This step will have a significant impact on the performance of the resulting system.

Loss Function and Optimizer

A model needs a loss function and an optimizer for training. The project in question will select the relevant and irrelevant articles for the outcome; thus, we can consider it a binary classification problem, and the model will generate a probability (a single-unit layer with sigmoid activation). The method used will be stochastic optimization by the Adam algorithm [19].

Model Training

Training will be controlled based on the model's accuracy with out-of-sample data, creating a validation set by separating samples from the original training data. During training, model loss and accuracy will be monitored in the samples from the validation set.

In this step, we will adjust the weights of the connections, where it is essential to consider factors such as network initialization, training mode and training time. The training time has some variables that may influence the duration; therefore, a stopping criterion must be chosen, such as the average error rate per cycle or the generalizability of the network. Training will be interrupted when the network demonstrates an ideal generalizability and when an appropriate moment to stop with little error and maximum generalizability is found.

Model Testing

In this step, we will observe how the model behaves. This evaluation will be performed according to two returned values: the loss (a number representing the error) and the accuracy. The test set is used to determine the network's performance with data not previously used. The network performance determined in the testing step will be a good measure of its actual performance. Other tests may also be used, such as network behavior analysis, through special inputs and analysis of current weights. If the values are very small, the connections can be considered insignificant and thus be eliminated.

Comparison of Models

At the end of each model test, we will evaluate the model accuracy to assess whether the model contributed significantly to the final result. The model accuracy is defined as the measured difference between the final results of each SR reconstructed using manual selection. This assessment will determine whether it is necessary to use separate fields while searching for articles for the SR.

To elucidate this measurement, comparative analyses will be conducted for models created for the same field (intergroup comparison) and for two different fields (intragroup comparison). The receiver operating characteristic curve appears to be the best option for these analyses.

System Sharing

The last step will be to share and test the system created for article selection in other fields. We will disseminate our project widely through the internet by creating the "Observatory of

Evidence" in public health. In this location, other researchers with the same interest in improving the SR automation model will be able to include their searches, after internal validation, and thus expand and improve the created system. Authors should upload the results of their searches on the platforms, insert them into the system together with PICO, and choose the corresponding MeSH (Population).

The objective will be to publicize the observatory, promote the improvement of the automation system, and increase the capacity of the neural network model with more previously performed searches. In addition, this open platform will assist new studies in the field of public health, stimulating new systematic reviews.

Results

Data collection will begin in July 2021. We estimate that data collection should be completed in December 2021, and the results should be available in March 2022.

Discussion

Our aim is to disseminate scientific evidence through the "Observatory of Evidence" in public health that will be free and open to researchers. The authors will be able to upload the database returned from the search on the chosen platforms and add information, such as the respective field, types of studies to be selected by reading the abstracts, and inclusion criteria through the PICO strategy. After the researcher runs the model, the platform will return a list of suggested articles that meet predetermined criteria. The selection sensitivity will be modifiable.

This important tool for facilitating the creation of SRs will be made available through the platform. SR creation is often difficult because the large quantity of data involved can prevent potential reviews from being carried out. Most researchers perform article selection entirely manually or through reference management systems that only identify duplicate articles and do not perform abstract selection and reading.

Once the platform is operational, we intend to openly and freely disclose all the SRs generated through our automatic selection tool to all interested researchers. The system must routinely monitor performance and maintain the network when necessary. Some other improvements can be made based on researchers' use of the SR automation, allowing the release of new versions with updates to better meet the needs of researchers.

The study has some limitations. The first and most important is that the system will depend on a corresponding MeSH or similar term for the study population for each systematic review. Another limitation is the use of three research databases (PubMed, Embase and Web of Science). Finally, the results will be studied for two areas of knowledge, limiting the generalization to other areas.

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Authors' Contributions

GFF and MD designed the protocol. All authors contributed to the planning of the protocol and reviewed and provided comments. The authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ANN: artificial neural networks
MeSH: Medical Subject Headings
MLP: multilayer perceptron
PICO: Population, Intervention, Control, and Outcome
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SR: systematic review

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Protocol

Defining the Scope of Digital Public Health and Its Implications for Policy, Practice, and Research: Protocol for a Scoping Review

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Abstract

Background: There has been rapid development and application of digital technologies in public health domains, which are considered to have the potential to transform public health. However, this growing interest in digital technologies in public health has not been accompanied by a clarity of scope to guide policy, practice, and research in this rapidly emergent field.

Objective: This scoping review seeks to determine the scope of digital health as described by public health researchers and practitioners and to consolidate a conceptual framework of digital public health.

Methods: The review follows Arksey and O'Malley's framework for conducting scoping reviews with improvements as suggested by Levac et al. The search strategy will be applied to Embase, Medline, and Google Scholar. A grey literature search will be conducted on intergovernmental agency websites and country-specific websites. Titles and abstracts will be reviewed by independent reviewers, while full-text reviews will be conducted by 2 reviewers to determine eligibility based on prespecified inclusion and exclusion criteria. The data will be coded in an iterative approach using the best-fit framework analysis methodology.

Results: This research project received funding from the British Columbia Centre for Disease Control Foundation for Population and Public Health on January 1, 2020. The initial search was conducted on June 1, 2020 and returned 6953 articles in total. After deduplication, 4523 abstracts were reviewed, and 227 articles have been included in the review. Ethical approval is not required for this review as it uses publicly available data.

Conclusions: We anticipate that the findings of the scoping review will contribute relevant evidence to health policy makers and public health practitioners involved in planning, funding, and delivering health services that leverage digital technologies. Results of the review will be strategically disseminated through publications in scientific journals, conferences, and engagement with relevant stakeholders.

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KEYWORDS

digital health; public health; prevention; scoping review; protocol

Introduction

Over the past 2 decades, there has been rapid development and proliferation of digital technologies and their concomitant application to achieve health objectives [1,2]. Their applications offer great potential to transform the speed, efficiency, capacity, and impact of health services and programs, including in public health [3-5]. In May 2018, the World Health Organization Member States acknowledged this reality by unanimously approving the World Health Assembly Resolution on Digital Health [1]. This resolution recognized the potential value of digital technologies in achieving universal health coverage and

the health-related aims of the United Nations Sustainable Development Goals [1].

Many public health initiatives and systems have integrated digital technologies in their operations. For instance, the Global Public Health Intelligence Network, maintained by the Public Health Agency of Canada, has leveraged big data capacity for global infectious disease surveillance [6]. Health prevention and promotion programs have leveraged social media strategies with the aim of expanding their reach [5]. Health services across the continuum of care, from clinical services to community prevention services, have adopted digital technologies. In 2019, the United Kingdom's National Health Service launched a digital-first primary health strategy to increase health care coverage by securing online access to health records for all patients by April 2020 and access to virtual consultations for all patients by 2021 [7].

The term "digital public health" was first mentioned in Public Health England's digital strategy in 2017 [8]. This term was used to refer to a re-imagination of public health that blends established public health wisdoms with new digital concepts and tools. However, digital public health is not a field well conceptualized and is characterized by ambiguity and confusing terminologies in the literature [9-11]. For example, digitization, digitalization, and digital transformation of public health services have often been used in varied contexts to refer to digital public health. However, these terms refer to distinct processes in many fields [11]. Further, despite the high proliferation of publications related to digital public health, especially in light of COVID-19, consensus on the definition, based on evidence, is yet to be achieved [1,4]. More specifically, the scope of digital public health needs to be clearly defined, including the technologies applied and the potential benefits, harms, and unintended or negative consequences of adopting digital technologies in population and public health. Similarly, the human resource and systems capacities required to fully take advantage of digital technologies in population and public health remain to be laid out [1,2].

Rather, enthusiasm for the application of digital technologies in public health has stimulated the proliferation of multiple, but often fleeting, digital health interventions. This proliferation increasingly diversifies the field, but very few interventions have been adopted at a large scale (eg, at a state or national level) where their potential benefits can become reality [1,12]. Complex issues regarding the impact of digital health interventions on reducing or widening health equity disparities and their ethical implications remain unresolved [13]. Evidence on these issues is crucial to thoughtfully implement and evaluate digital technologies and prevent unnecessary diversions of support and funding from other well-established, nondigital interventions.

As a first step, conceptualizing the scope of "digital public health" is necessary to clearly understand the field and to create appropriate policies and operational environments required to ensure the realization of its potentials. The European Public Health Association (EUPHA) has taken great strides to address this issue, recently creating a framework that conceptually defines digital technologies, their features, and the potential benefits of digitalization in public health [10]. However, the framework does not specifically describe how digital technologies may be deployed in specific public health domains; how we may consider foundational principles of public health, including health equity and social justice in this process [14]; or how to identify relevant challenges in digital public health and potential solutions. It may also benefit from additional domains and benefits of digitalization in public health as this field rapidly evolves. While other conceptual frameworks on digital health exist from a health systems perspective and the application of digital technologies restricted to specific public health domains [15], to the best of our knowledge, none other than the EUPHA framework broadly conceptualize a consolidated approach to digital technologies across the domains of public health.

Through this scoping review, we aim to conceptualize "digital public health" and to expand on the EUPHA's conceptual framework by examining how the scope of digital health is described by public health researchers and practitioners within published and grey literature. We also seek to outline relationships between digital technologies and the public health domains, identifying the benefits, challenges, and potential solutions to these challenges within the domains of digital public health.

Methods

Project Design

This scoping review will utilize the framework proposed by Arksey and O'Malley [16] for scoping reviews, while integrating improvements to the framework as suggested by Levac et al [17]. Scoping reviews have been suggested as a useful method for clarifying complex concepts [17]. The framework recommends organizing the scoping review into 5 compulsory stages and an optional sixth stage.

Stage 1: Identifying the Research Question

A preliminary review of literature in the field suggests that the conceptualization of "digital public health" is relatively recent [10,18-20]. Therefore, this scoping review will be more broadly focused on how "digital health" and closely related domains (eg, virtual health, mobile health [mHealth], eHealth) have been conceptualized and characterized within public health research and practice discussions. Our main research question is therefore: "How is digital health described, understood, and applied by public health researchers and practitioners within the context of public health?"

We anticipate that selected literature may include: conceptual descriptions of digital health in relation to public health practice, goals or purpose of applying digital technologies in public health, types of digital technologies applied in public health, amenability of various public health domains to digital health approaches, and potential benefits and challenges of digital technologies in public health.

Stage 2: Identifying Relevant Literature

To comprehensively identify literature relevant in conceptually defining "digital public health," we will employ a broader

analytical lens and search strategy that will enable us to capture the main defining issues, developments, and debates that shape this rapidly evolving field.

We recognize that public health and clinical medicine are distinct practices with significant areas of overlap. Therefore, we will restrict our scoping review to the application of digital health in public and population health, with accommodations for areas of overlap including disease prevention and control, quality of care, ethics, research, guidelines, decision support, training, and management [21]. However, facets of digital health as applied exclusively within clinical medicine will not be assessed in the review.

We will adopt the following working definitions of "digital health" and "public health" to guide the search strategy.

The World Health Organization defines digital health as "the field of knowledge and practice associated with the development and use of digital technologies to improve health. This is a broad umbrella term encompassing eHealth (including mHealth) and emerging areas such as the use of advanced computing sciences in big data, genomics, and artificial intelligence" [3].

We will apply the Canadian Public Health Association's (CPHA) definition of public health as "an approach to maintaining and improving the health of populations that is based on the principles of social justice, attention to human rights and equity, evidence-informed policy and practice, and addressing the underlying determinants of health. Such an approach places health promotion, health protection, population health surveillance, and the prevention of death, disease, injury and disability as the central tenets of all related initiatives" [14]. This definition is illustrated in the CPHA's framework (Figure 1).

Figure 1. Canadian Public Health Association framework for public health.

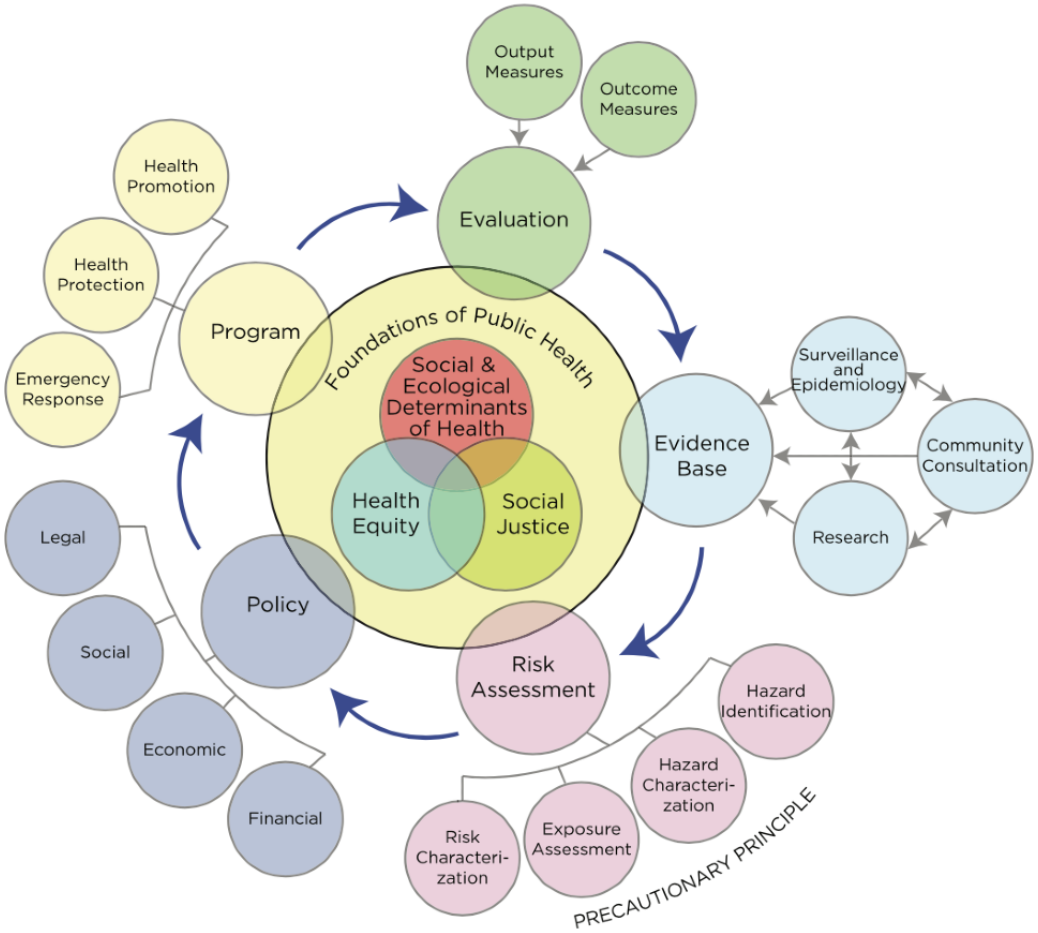


Table 1 describes the inclusion and exclusion criteria that will be adopted for this scoping review. Publications that conceptually describe digital technologies or identify goals, benefits, challenges, and components of digital health from a public health or population health perspective will be included in this study. We will focus on the time period between January 2000 and June 2020 because our preliminary searches reveal that discussions about innovative health care services delivery in the internet age have proliferated within this timeframe.

We will search MEDLINE (Ovid) and Embase (Ovid) as bibliographic and citation databases for relevant literature on digital health. Grey literature searches will be conducted using Google Scholar and other agency or country websites as shown in Table 2.

Table 1. Eligibility criteria.

Parameter	Inclusion criteria	Exclusion criteria
Phenomenon of interest	Publications that broadly conceptualize and/or analyze digital health from a public health perspective	Publications evaluating or describing specific digital health programs or interventions
Health context	Publications that focus on health issues at the population level or population health outcomes, with a focus on preventive, community medicine, or public health (eg, environmental health, obesity, diabetes, stigma, antibiotic resistance, prevention of sexually transmitted and blood-borne infections)	Publications solely focused on the application of digital health in clinical contexts
Language	English	Not in English
Publication status	Published and grey literature	No full text, only abstract or short summary <500 words published
Year of publication	January 2000 and June 2020	None

Table 2. Agency and country websites searched for grey literature.

Country or jurisdiction	Agency
Intergovernmental	World Health Organization
Europe	European Public Health Association
Australia	Public Health Association of Australia, Government of Canada
Canada	Government of Canada, Public Health Agency of Canada, Canadian Institutes of Health Research, Canadian Public Health Association, National Collaborating Centres for Public Health, National Collaborating Centres for Determinants of Health, Canadian Agency for Drugs and Technologies in Health
United States of America	US Centers for Disease Control and Prevention, American Public Health Association
United Kingdom	UK Public Health Association, National Health Service

This strategy will aim to identify the intersection between terms related to “digital health” and “public health.” In consultation with a UBC librarian, we will determine a combination of keywords, Medical Subject Heading (MeSH) terms, and filters to maximize the comprehensiveness of our search. Preliminary keywords that have been proposed to be searched in title, abstract, and keyword database fields include the following for digital health: digital public health, digital health, mHealth, virtual health*, mobile health, e-health/ehealth, online health, internet-based health, web-based health/web*, computer-based health, digitalization/digit*, electronic health, health informatics, digital tools, digital technologies, telehealth/telemedicine, health informatics, social media, predictive algorithms, or connected care devices, artificial intelligence, machine learning methods, big data. Similarly, the following preliminary keywords have been proposed for public health: public health, health promotion, health prevention, health protection, health policy, health determinants, surveillance, health evaluation, public health ethics, health economics, risk assessment, epidemiology, community health, emergency preparedness, emergency response, health equity, social justice, social determinants.

The final search strategy (Multimedia Appendix 1) will be informed by a pilot search of Ovid MEDLINE and Ovid Embase. The intersection between digital health and public health will be identified using Boolean terms such as “and” to identify literature relevant to digital public health. Using the finalized search terms and strategy, returns will then be retrieved from each database.

Grey literature searches will be conducted using simpler search terms: “digital” and “public health.” This search will be conducted on Google Scholar. We will review the first 100 returns to identify relevant literature. Further, we will apply the same search strategy on government-specific websites and intergovernmental agency websites. To standardize searches across country and agency websites, we will parse our search through Google to each website. For example, to search the Government of Canada website [22], we will apply the search terms: “digital “public health” site:canada.ca” on Google to identify relevant publications from the website. We will review the first 100 returns for each search for grey literature. All retrieved publications will be exported to Covidence for citation management and review.

Stage 3: Study Selection

Study selection will be conducted in 2 phases. In phase 1, titles and abstracts of all literature retrieved from the searches will be reviewed to determine eligibility for full-text review based on the inclusion and exclusion criteria. To ensure reliability of the review process, 25% of titles and abstracts will be independently assessed by 2 members of the research team (II and AX), who will meet to discuss discrepancies and establish a consensus for the study selection protocols.

In phase 2, 2 members of the research team will independently review all full texts of publications and gray literature included from phase 1 using a structured framework (Multimedia Appendix 2). Reviewers will have access to the list of full texts selected by other members of the team where discrepancies will be appropriately discussed to establish consensus. A

comprehensive list of literature reviewed, included, and excluded will be compiled and used to create a flowchart that describes the literature selection process.

Stage 4: Charting the Data

Our methodological approach will be based on the best-fit framework analysis as described by Carroll et al [23]. This method offers a pragmatic way of conducting qualitative evidence synthesis that builds on existing theoretic or conceptual frameworks to address "policy-urgent" questions. It involves prior selection of a conceptual model, reduction of the model to variables that form the a priori framework, and coding new data against the a priori matrix framework, while making additional themes where appropriate, to inform a resultant framework [23].

Our a priori framework will be informed by the EUPHA conceptual framework on digitalization in public health and the CPHA framework for public health. We will finalize an initial matrix codebook (Multimedia Appendix 3) to support data extraction. Definitions of each of the codes in the matrix will be discussed among the authors based on existing literature and agreed on before commencement of coding, which will be conducted using QSR NVIVO version 12. Data from the selected literature will be coded against themes of the a priori framework using an iterative approach [24]. Publication details will be recorded including article type, author(s), publication year, country, and continent. Themes included in the a priori framework as informed EUPHA and CPHA frameworks will include the digital technology discussed, features of digital health, foundations of public health considered, public health domains, and potential benefits of digital public health. We will also code challenges and recommendations. Where applicable, new themes will be added to the a priori framework based on inductive interpretation and constant comparison of new themes across reviewed publications.

Initial data familiarization and coding will be completed by 2 members of the research team. As recommended by Levac et al [17], 10% of the full texts will be initially coded into the a priori framework, and findings will be discussed to ensure consistency of the charting process and allow for refinement of the codebook as appropriate. Intersections between digital technologies and public health domains will be double coded to relevant codes. This will allow us to identify dominant technologies that have been applied in specific public health domains. Matrix coding summaries will be produced and used to visually map related findings to aid interpretation.

Stage 5: Collating, Summarizing, and Reporting the Results

Data organized in the charting process will be thematically analyzed. Heatmaps will be generated to identify the extent to which the literature has documented the application of digital health technologies in the various domains of public health and its public health benefits. This will further inform analyses.

The analyses will inform the consolidation of a working conceptual framework of digital public health that includes the public health foundations, domains of public health, digital technologies applied to the domains, features of the digital technologies, and potential benefits of digital technologies in each domain. Further, practice and research gaps, challenges, and potential recommendations to address these gaps will be identified in the literature.

Reporting will follow the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement - Scoping Reviews (PRISMA-ScR) [25]. As advocated by Levac et al [17], data from the analysis will be presented as descriptive numerical summaries (frequency tables and charts) including article type, country and continent of the first author, year of publication, and public health domain discussed. The data will also be presented as narrative syntheses and conceptual maps as appropriate depending on the research question. Differences in perspectives across years of publication, country and regions, and fields of practice will also be presented as narratives and tables.

Stage 6: Consultation With Stakeholders

Finally, we will consult with population and public health stakeholders to validate our conceptual framework for digital public health and identified research and practice gaps. We will convene a workshop with public health stakeholders, including individuals with and without expertise in the application of digital technologies to public health (eg, public health nurses and physicians, social media and communications staff, health promotion leads, virtual health representatives, public health researchers). Using a World Café method, where small groups rotate through tables on different discussion topics, we will facilitate discussions about various aspects of the framework and will document feedback as required. These discussions will also inform a working understanding of policy implications tied to the framework. All of this information will be used to finalize our working conceptual model of digital public health and will inform ongoing collaboration to further explore this emergent field.

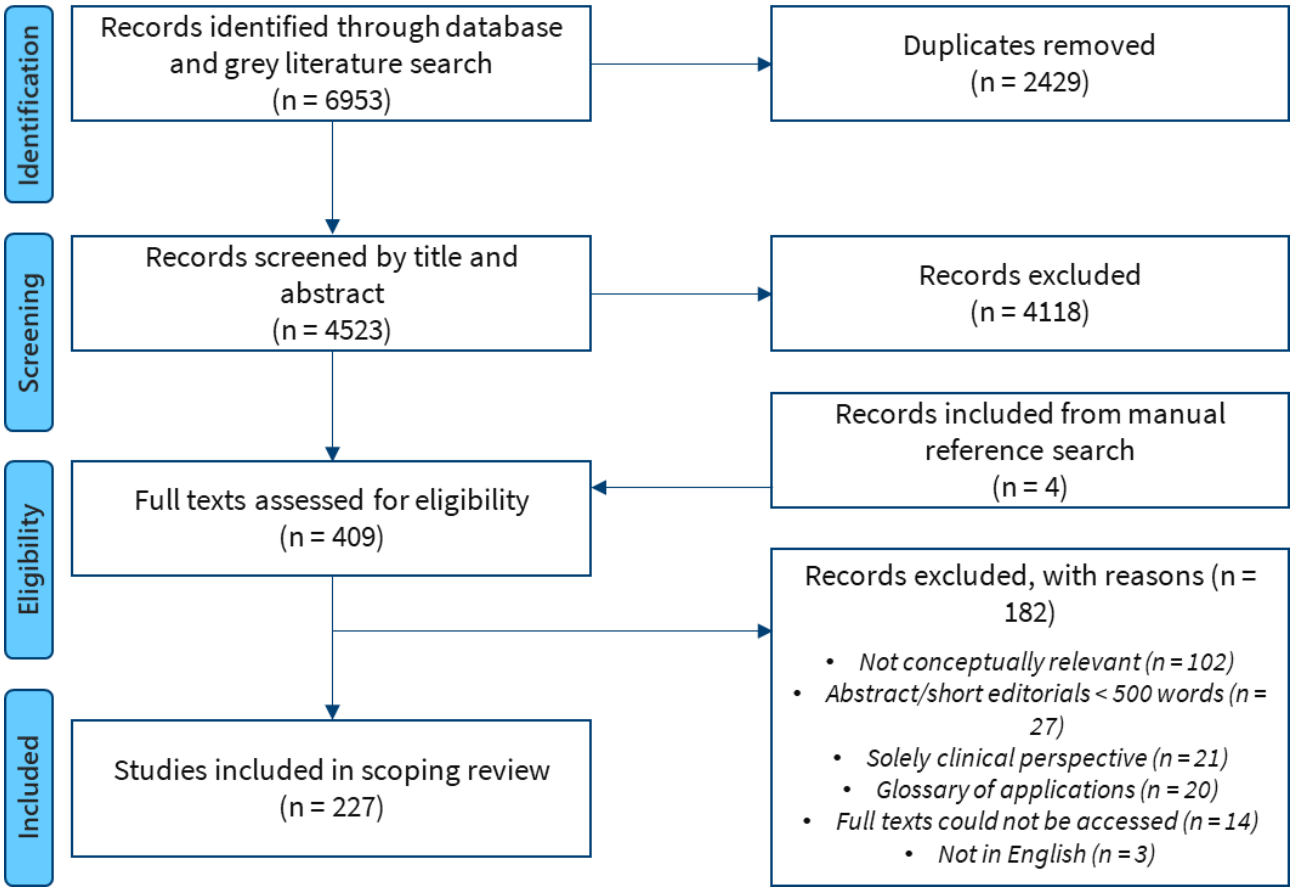
Ethics and Dissemination

Ethical approval was not required for this scoping review as it is a synthesis from publicly available publications. Data generated from the review will, however, be stored in a secured network drive. Findings from the scoping review will be shared with relevant stakeholders including leaders of the CPHA and academia through targeted consultations as has been described, to consolidate a conceptual framework for digital public health and inform policy and practice. Findings will also be published as a final report and in peer-reviewed journals and scientific conferences. Finally, members of our research team will utilize output from this scoping review to directly facilitate the development of public health initiatives and strategies within British Columbia, Canada, and beyond.

Results

This research project received funding from the British Columbia Centre for Disease Control (BCCDC) Foundation for Population and Public Health on January 1, 2020. The initial search was conducted on June 1, 2020 and returned 6953 articles in total (Figure 2). After deduplication, 4523 abstracts were reviewed, and 227 articles have been included in the review.

Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Reviews (PRISMA-ScR) flow diagram of the search and study selection process.



Discussion

Digital public health continues to gain popularity as an emergent field of practice, especially in the context of COVID-19 [26]. As multiple public health initiatives integrate digital technologies to advance their objectives, effort is required to understand the scope of field, prevailing challenges, and potential solutions if public health researchers and practitioners are to appropriately support its ongoing development.

We envisage that the findings of the scoping review will contribute relevant evidence to health policy makers and public health practitioners involved in planning, funding, and delivering health services that leverage digital technologies. Given the broad scope of the review, we anticipate that we can potentially highlight already known fields and emergent and promising public health functions that can benefit from digital technologies, especially at scale.

This scoping review will focus on literature published between January 2000 and June 2020, excluding more recent articles. We acknowledge the recent upsurge in articles describing digital technologies in relation to public health emergency preparedness and response in the context of the COVID-19 pandemic. However, we consider it more relevant to focus on a more balanced view of digital public health that is not skewed by the discourse on the pandemic. Finally, given that our review strategy utilizes a nonspecific collection of publications, we have not undertaken a quality assessment of included articles in line with the framework for this scoping review [16].

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 17 KB - resprot_v10i6e27686_app1.docx]

Multimedia Appendix 2
Full paper review framework.
[DOCX File , 19 KB - resprot_v10i6e27686_app2.docx]

Multimedia Appendix 3
Initial codebook.
[DOCX File , 26 KB - resprot_v10i6e27686_app3.docx]

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Abbreviations

BCCDC: British Columbia Centre for Disease Control
CPHA: Canadian Public Health Association
EUPHA: European Public Health Association
MeSH: Medical Subject Heading
mHealth: mobile health
PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses statement – scoping reviews
UBC: University of British Columbia

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