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A Smartphone-Based Intervention for Anxiety and Depression in Racially and Ethnically Diverse Adults (EASE): Protocol for a Randomized Controlled Trial

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Abstract

Background: Clear health disparities have emerged in the rates of COVID-19 exposure, hospitalization, and death among Black, Hispanic, and American Indian (BHAI) individuals, relative to non-Hispanic White (NHW) individuals. BHAI populations have been disproportionately affected by lower behavioral health access and heightened negative mental health outcomes during the pandemic.

Objective: This project directly addresses health disparities in access to behavioral health care during the COVID-19 pandemic among BHAI populations via an adaptation of the established, initially validated, low-cost, mobile app Easing Anxiety Sensitivity for Everyone (EASE) among individuals with symptoms of elevated anxiety or depression or both.

Methods: The EASE trial is a 2-arm, prospective, randomized, blinded-assessor study with intention-to-treat analysis. Participants (N=800; n=200, 25%, Black; n=200, 25%, Hispanic; n=200, 25%, American Indian; and n=200, 25%, NHW) are randomized to receive either EASE or an active comparison condition for anxiety and depression. Participants compete an online prescreener, an enrollment call to provide informed consent, a baseline survey, a 6-month intervention period, and 3- and 6-month postbaseline assessments. Select participants also complete a 3- and 6-month postbaseline qualitative interview via phone or an online platform (eg, Zoom). Participants complete 2 scheduled daily ecological momentary assessments (EMAs) during the 6-month study period. These twice-daily EMAs guide a just-in-time approach to immediate, personalized behavioral health care.

Results: Outcomes include reductions in anxiety and depressive symptoms and functional impairment at 3 and 6 months postrandomization. We also will examine putative mechanisms (eg, anxiety sensitivity [AS] and COVID-19–specific stress and fear) of the intervention effects. Further, as treatment effects may differ across sociocultural factors, perceived discrimination,

social support, and socioeconomic status (SES) will be evaluated as potential moderators of treatment effects on the primary outcomes. Process evaluation using data collected during the study, as well as individual interviews with participants, will complement quantitative data.

Conclusions: Data from this efficacy trial will determine whether EASE successfully improves symptoms of anxiety and depression and whether these improvements outperform an active comparison control app. If successful, findings from this study have the potential to decrease anxiety and depression symptoms among vulnerable populations determined to be most at risk of exacerbated, long-lasting negative health sequelae. Data from this study may be used to support an implementation and dissemination trial of EASE within real-world behavioral health and social service settings.

Introduction

Significant racial/ethnic health disparities have been identified in the United States [1] related to COVID-19 [2]. Indeed, the rates of COVID-19 infection, hospitalizations, and death are disproportionately higher among Black, Hispanic, and American Indian (BHAI) individuals relative to non-Hispanic White (NHW) persons [1,3-6]. BHAI individuals are also more likely to experience COVID-19–related stress relative to NHW persons [7]. Recent data from April 27 to May 9, 2022, indicate that 31.2% of Black and 34.7% of Hispanic individuals report current symptoms of an anxiety or depressive disorder [8]. These estimates are in stark contrast to the estimated 11.3% of Black and 10.3% of Hispanic individuals who reported symptoms of an anxiety or depressive disorder prior to the COVID-19 pandemic from January to July 2019 [8]. Although NHW individuals experience comparable, albeit slightly lower, rates of anxiety or depression (30.0% from April 27 to May 9, 2022) [8], the racial/ethnic disparity gap for mental health outcomes is widening. To illustrate, data from January to July 2019 found a 0.2%-1.2% difference in elevated anxiety or depression symptoms between NHW and Black and Hispanic persons, with NHW individuals evincing higher prevalence rates of these symptoms (11.5%) [8]. The inverse pattern is now prevalent, with Black and Hispanic persons reporting higher rates of these symptoms by 1.2%-4.7% [8,9]. Although postpandemic onset mental health data for American Indians in the United States is lacking, American Indian community leaders have expressed continued concern for the health of their constituents, given their propensity for worse physical and mental health outcomes related to COVID-19 [10,11]. Pre-existing inequities related to social determinants of health (eg, lower access to mental health care and therefore less treatment engagement [12,13]) and the effects of racism [14] have likely contributed to and exacerbated these disparities and may compound the severity of emerging COVID-19–related mental health disparities [7]. Emerging COVID-19–related disparities in mental health symptoms are likely to widen without proper early intervention tactics.

The ongoing COVID-19 pandemic has led to increases in stress, including stress related to unemployment, homelessness, food insecurity, and lack of adequate health care resources. The COVID-19 stress burden may have a particularly pernicious influence in persons already struggling with greater stress exposure and pre-existing psychopathology [15]. Theoretically, higher degrees of COVID-19 stress may influence patterns of social, emotional, and neurobiological development, facilitating the rapid detection of potential threats, and, by extension, increase the risk for multiple forms of psychopathology. A transdiagnostic approach to intervention development and deployment could serve as an effective treatment method. This approach relies on identifying the fundamental processes underlying multiple psychopathologies [16] and may be particularly effective and efficient at mitigating emerging mental health disparities arising from the pandemic.

Anxiety sensitivity (AS), defined as the fear of anxiety symptoms, including bodily sensations [17], has been identified as a key vulnerability factor for anxiety [17-20], depression [21-23], substance use [24-26], and other psychopathology symptoms [27-29]. Theoretical models posit that individuals with high AS are more likely to attend to bodily sensations that are associated with anxiety, such as respiratory symptoms, stomach distress, fatigue, and body aches, and to misinterpret these symptoms as dangerous or catastrophic [30,31]. These interpretations of bodily sensations can lead to increased anxiety and perpetuate a cycle of increased attention to and misinterpretation of bodily cues [31-33]. This process may eventually lead to avoidance and increased symptoms of anxiety, stress, and depression, with potential to exacerbate stress on the body systems, further compromising the immune system and placing certain individuals at greater risk for more severe psychopathology [34]. This maladaptive cycle may be particularly relevant to BHAI populations during and following the pandemic, given their increased likelihood of COVID-19 exposure [5,35-39], challenges with enacting behaviors to reduce the likelihood of infection, concerns about the increased likelihood of worse outcomes if infected, and greater pandemic-related stressors (eg, job loss [40], income reduction [41-43], childcare needs [44,45], and discrimination). Further, because it has been shown previously that some minority groups experience higher levels of distress expressed somatically [46], AS is particularly relevant because it could amplify the threat response to somatic perturbation.

Importantly, AS is malleable in response to psychosocial interventions [47], making it a prime mechanism to target in prevention/intervention programs. Reductions in AS improve clinical outcomes among clinical and nonclinical populations [47], reductions in AS have been shown to be associated with positive outcomes in smokers who are motivated to quit [48], and AS can be effectively engaged through in-person and digitally delivered methods [49,50]. This is a critical consideration, given the overwhelming stress that the pandemic has placed on the health care system and the current paradigm shift toward providing care remotely [51,52]. In the context of mental health, digital health (eg, mobile health [mHealth]), telemedicine/telehealth, and health IT (eg, mobile phones, wearable sensors) can be used to develop scalable interventions that offer mental health care that is personalized to meet the unique needs of patients [53-55] and thus reduce the burden on the health care system. Indeed, mHealth interventions have strong potential for a broad reach, high accessibility, and widespread dissemination and serve as a potential vehicle to provide access to evidence-based mental health treatments.

A recent meta-analytic review found that mHealth interventions for anxiety and depression reduction may lead to significant within-person reductions in anxiety and depression, and the reduction in anxiety was greater than what was reported by control participants [56]. The majority of the reviewed mHealth apps (67%), however, focused on strict cognitive behavioral therapy (CBT) and did not consider the potential of using a transdiagnostic approach to negative affective symptom reduction. Using an mHealth framework to deliver mHealth AS reduction treatment could address both individual- and system-level barriers to accessing effective mental health treatment during and after the pandemic and result in reduced anxiety and depressive symptoms by effectively engaging an underlying mechanism implicated in both conditions.

This study capitalizes on our expertise in mHealth interventions, mental health treatments, and health disparities research. We propose to test an accessible mHealth AS reduction treatment that incorporates a just-in-time treatment approach to address the mental health sequelae resulting from the COVID-19 pandemic. The primary aim of this study is to test the effects of a novel, smartphone-delivered intervention (Easing Anxiety Sensitivity for Everyone [EASE]) aimed at reducing mental health disparities across racial/ethnic minority groups that have been exacerbated by the COVID-19 pandemic in a large, racially/ethnically diverse sample of adults with clinically significant anxiety or depression. The comparison condition is a time-matched real-world treatment (mindfulness/relaxation-based therapy). Our primary outcomes are reductions in anxiety and depression symptoms and functional impairment at 3 and 6 months postrandomization. Recognizing the clinical importance of mechanistic research to optimize interventions [40], we will also examine putative mechanisms (eg, AS and COVID-19–specific stress and fear) of the intervention effects. Moreover, as treatment effects may differ across sociocultural factors, perceived discrimination, social support, and socioeconomic status (SES; indexed by monthly income) will be evaluated as potential moderators of treatment effects on the primary outcomes.

Methods

Ethical Considerations

All participants provide written informed consent electronically after reviewing consent documents with research staff. To protect participant privacy and confidentiality, phone-based appointments are completed by research staff in a secure office at 1 of the 2 collaborating sites. Additionally, participants are assigned an ID number that is used to identify their data throughout the study. Only trained research staff have access to the key that can match participant data to the participant's name. The key is password-protected on a secure server housed at the collaborating institutions. Participants are compensated up to US $410 for participating in the study and receive compensation via a GreenPhire [57] Mastercard gift card that is loaded by research staff. The Institutional Review Board (IRB) at the University of Houston approved the study (IRB approval no. STUDY00002802) and serves as the Relying IRB for all sites under the National Institutes of Health (NIH) Single IRB policy, and a Data Safety and Monitoring Board provides ongoing oversight.

Study Design

Adults who report clinically significant anxiety or depression (N=800; racial breakdown: n=200, 25%, Black/African American; n=200, 25%, Hispanic; n=200, 25%, American Indian; and n=200, 25%, NHW individuals) are being recruited and enrolled to participate in a trial on the effects of a novel, smartphone-delivered intervention to address negative mood symptoms and reduce COVID-19–related mental health disparities. Participants are recruited via community organizations and social media and internet outlets (eg, Craigslist, Facebook). Interested individuals complete an online prescreener assessment, where they are asked to answer basic demographic questions, questions about their phone use, and levels of anxiety and depression they are experiencing via the Overall Anxiety Severity and Impairment Scale (OASIS) [58] and the Overall Depression Severity and Impairment Scale (ODSIS) [59]. Those eligible at the prescreener complete an enrollment call to assess for full eligibility and receive instructions on how to download the app to their smartphone to complete the baseline assessment. Participants who do not own a smartphone that is compatible with the Insight app [60] are mailed a study phone and contacted by study staff once the study phone arrives. Following completion of the baseline assessment, research staff contact participants to schedule their randomization phone call. During the randomization call, research staff randomly assign the participant to either the (1) EASE or the (2) mindfulness/relaxation-based comparison condition. Participants then engage with the assigned intervention for 6 months following randomization. Participants complete follow-up assessments at 3 and 6 months postrandomization, which includes self-report measures, and a randomly selected subset of the sample completes a qualitative interview focused on app use and experiences with the app. Additionally, participants are prompted to complete ecological momentary assessments (EMAs) twice daily throughout the 6-month postrandomization period. See Figure 1 for the participant flow diagram.

Figure 1. Participant flow diagram.
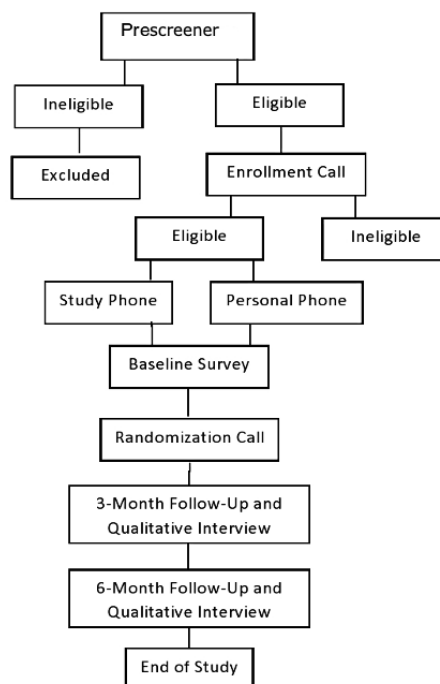
Specific Aims and Hypotheses

This study has 2 specific aims:

- To use a randomized controlled trial (RCT) design to compare the effects of EASE to a mindfulness/relaxation-based comparison group on anxiety and depression symptoms, and functional impairment at 3-month and 6-month follow-up. We hypothesize that those assigned to EASE will show greater reductions from baseline to follow-ups in OASIS [58] and ODSIS [59] scores and also greater reductions in functional impairment in daily responsibilities (eg, work performance, household maintenance, social interactions, and relationships) [61] relative to the comparison group (hypothesis 1 [H1]). We also hypothesize that the effectiveness of EASE (as assessed by slope changes from baseline to follow-ups in outcomes listed in H1) will be similar across racial/ethnic groups (H2).
- To examine the mechanisms of action at 3- and 6-month follow-ups (H3) and moderators of treatment outcomes at 3- and 6-month follow-ups (H4). In testing the putative mechanisms of action, we hypothesize that the intervention effects on study outcomes will be mediated by reductions in AS and changes in COVID-19–related stress and fear. To determine possible moderators, we will test whether treatment effects vary as a function of perceived discrimination (worse intervention outcomes), social support (better intervention outcomes), or SES (lower SES associated with worse outcomes).

This study has 2 exploratory aims:

- To identify opportunities to improve the efficacy, reach, and adoption of EASE through qualitative interviews
- To use daily EMAs to obtain a granular understanding of the course (eg, changes in anxiety/depression symptoms

and fear of COVID-19) and sequelae (eg, employment status, daily activities, substance use) of the COVID-19 pandemic and health behaviors affected by COVID-19 (ie, physical activity, pain experience, sleep) among those who do and do not contract the virus

Participants

Participants will be 800 adults (n=200, 25%, Black/African American; n=200, 25%, Hispanic; n=200, 25%, American Indian; and n=200, 25%, NHW individuals) who report current clinically significant anxiety or depression. All participants must meet the following eligibility criteria: (1) have clinically significant anxiety or depression symptoms, as evinced by a score of 8 or higher on OASIS [58] or a score of 8 or higher on ODSIS [59]; (2) be aged 18 years or older; (3) self-identify as Black, Hispanic, American Indian, or NHW (singular or multiracial identification); (4) be willing to complete all study surveys/assessments; and (5) score 4 or more on the Rapid Estimate of Adult Literacy in Medicine-Short Form (REALM-SF) indicating an English literacy level higher than the sixth grade. Exclusion criteria include the following: (1) identifying with a race/ethnicity for which the corresponding study cell has been filled, (2) significant cognitive impairment evinced by a score of 8 or higher on the 6-Item Cognitive Impairment Test (6CIT) [62], and (3) inability to read or understand English at the sixth-grade or higher level.

Procedures

Enrollment to the RCT began in December 2021 and, as of this writing, is in the recruitment phase. Enrollment, randomization, intervention delivery, and assessments (EMAs and follow-ups) are completed remotely via a smartphone or phone call with trained research staff. Both study conditions receive the same set of questionnaires at each assessment (see Tables 1 and 2 for a full list and timeline of study measures). These questionnaires assess anxiety or depression symptoms, functional impairment,

general and COVID-19–specific affect constructs, and sociocultural factors.

Interested individuals complete an initial 5-minute online screener via Research Electronic Data Capture (REDCap; Vanderbilt University) to assess age, racial/ethnic identity, clinical anxiety and depression, state of residence, and willingness to complete study assessments. Those deemed eligible at the online screener complete an enrollment call with research staff that lasts approximately 30 minutes. During the enrollment call, participants provide informed consent and are informed of the purpose, goals, and procedures of the study. Participants are also further assessed for eligibility (ie, English literacy and fluency, and cognitive impairment). Those found eligible are instructed on how to download the smartphone-based

app that will administer assessment and intervention content (ie, Insight app) [60] during the enrollment call. Eligible participants who do not have a smartphone that is compatible with the study app are mailed a study smartphone to use during study participation and are contacted by study staff once the phone is received. After participants download the study app to their personal or study-provided phone, they are oriented on how to use the app to complete the baseline assessment and instructed to complete it within the next 7 days. The smartphone-based baseline assessment takes approximately 20 minutes to complete. Participants who have not completed the baseline assessment within 48 hours are contacted by study staff via text, phone, or email to remind them to complete the assessment.

Table 1. List and timeline of study measures.

Measure	Screener	Enrollment	Baseline	Follow-ups
Demographic Questionnaire	X[a]	N/A[b]	X	N/A
6CIT[c] [62]	N/A	X	N/A	N/A
REALM-SF[d] [63]	N/A	X	N/A	N/A
Demographic/Background Information Questionnaire	X	N/A	N/A	N/A
Functional Impairment Related to Anxiety and Depression	N/A	N/A	X	X
EDS[e] [64]	N/A	N/A	X	X
CRBS[f] [65]	N/A	N/A	X	X
F-SozU K-6[g] [66]	N/A	N/A	X	X
OASIS[h] [58]	X	N/A	X	X
ODSIS[i] [59]	X	N/A	X	X
SSASI[j] [67]	N/A	N/A	X	X
Fear of COVID-19 [68]	N/A	N/A	X	X
COVID-19 Psychological Impact Survey	N/A	N/A	X	X

[a]X: applicable.

[b]N/A: not applicable.

[c]6CIT: 6-Item Cognitive Impairment Test.

[d]REALM-SF: Rapid Estimate of Adult Literacy in Medicine-Short Form.

[e]EDS: Everyday Discrimination Scale.

[f]CRBS: Coronavirus Racial Bias Scale.

[g]F-SozU K-6: 6-Item Perceived Social Support Questionnaire.

[h]OASIS: Overall Anxiety Severity and Impairment Scale.

[i]ODSIS: Overall Depression Severity and Impairment Scale.

[j]SSASI: Short-Scale Anxiety Sensitivity Index.

Table 2. List and timeline of EMAs[a].

Assessment	Daily diary	Sunday morning diary	Report distress	COVID-19 symptoms
Sleep	X[b]	N/A[c]	N/A	N/A
Alcohol consumption	N/A	N/A	N/A	N/A
Cigarette consumption	X	N/A	N/A	N/A
Marijuana use	X	N/A	N/A	N/A
Fast-food consumption	X	N/A	N/A	N/A
Other substance use	X	N/A	N/A	N/A
SSASI[d]	X	N/A	N/A	N/A
Prescription medication consumption	X	N/A	N/A	N/A
Discrimination experience				
Affect	X	N/A	X	N/A
Pain level	X	N/A	X	N/A
Ability to cope with stress	X	N/A	X	N/A
Social support	X	N/A	N/A	N/A
Physical activity	X	N/A	N/A	N/A
Location	N/A	N/A	X	N/A
Self-rated health questionnaire	N/A	X	N/A	N/A
OASIS[e]	N/A	X	N/A	N/A
SSASI	N/A	X	N/A	N/A
Current COVID-19 symptoms	N/A	N/A	N/A	X
Exposure to someone with COVID-19	N/A	N/A	N/A	X

[a]EMA: ecological momentary assessment.

[b]X: applicable.

[c]N/A: not applicable.

[d]SSASI: Short-Scale Anxiety Sensitivity Index.

[e]OASIS: Overall Anxiety Severity and Impairment Scale.

Research staff are automatically notified via an encrypted email once a participant completes the baseline assessment. Once notified, research staff call the participant and complete the randomization process with the participant. During the randomization call, participants are randomly assigned to an intervention condition: (1) EASE or (2) mindfulness-based comparison; see Table 3 for a comparison of treatment components. Specifically, participants are randomized using permuted block randomization to allocate them to a treatment condition within each racial/ethnic category (EASE=100, 12.5%, per racial/ethnic group; mindfulness/relaxation-based comparison=100, 12.5%, per racial/ethnic group). The study statistician (author MWG) set up the randomization schema tables (stratified by racial/ethnic identity and sex assigned at birth) in REDCap and has no contact with participants, thereby preventing experimenter bias in randomization. Only the study project manager can see and access the tables once uploaded to REDCap; all other study team members use the REDCap randomization module, which hides the allocation until randomization is prompted.

Following randomization, research staff provide participants with a code that enables them to access condition-specific intervention materials. Next, trained research staff provide a brief app orientation to the participant on how to use the app and its components, and answer any questions the participant may have. Research staff also provide a brief orientation on how to report distress and COVID-19 symptoms via the app (both groups). The day after the randomization call, all participants begin to receive 2 prompts to complete daily EMAs, one 30 minutes after waking and one 75 minutes before bedtime. Daily EMAs take approximately 2 minutes to complete. Research staff monitor participant EMA completion rates weekly. When a participant's completion rate significantly decreases, a staff member contacts the participant via text, phone, or email to remind them of the importance of completing the daily EMAs. Participants are informed that they can contact study staff at any point during the trial by pressing the "Call Staff TX" button at the top of the app home screen if they experience technical difficulties (see Figure 2). Participants are encouraged to use the app daily for 6 months, particularly when they are experiencing distress.

Participants complete follow-up smartphone-based, self-report assessments at 3 and 6 months postrandomization. Additionally, research staff contact participants selected through a modified

quota sampling strategy [69] at 3 and 6 months postrandomization to complete a brief qualitative interview to assess their experience with the app and to solicit suggestions on ways to improve the app content, delivery, or reach potential. The qualitative interview uses a semistructured interview guide and is audio-recorded for transcription. The 3- and 6-month self-report assessments each require approximately 20 minutes to complete, and the 3- and 6-month qualitative interviews take approximately 30 minutes to complete. Data gathered through the qualitative interviews will be used to identify opportunities to improve the efficacy, reach, and adoption of the EASE app.

Regarding compensation, all participants who enroll in the study receive a GreenPhire [57] Mastercard gift card to facilitate paying them for completing study surveys. GreenPhire offers an auditable mechanism for all study payments. Participants receive US $20 for completing the baseline assessment and US $50 for completing each of the 3- and 6-month follow-ups. Additionally, participants are compensated for completion of EMAs (2 per day × 30 days = 60 monthly EMAs). Specifically, those who complete 50%-74% of prompted EMAs each month receive US $20, those who complete 75%-89% of assessments receive US $30, and those who complete 90% or more of their EMAs receive a total of US $40 for that month. Participants can click the "Payment" button on the app home screen at any time for an up-to-the-moment summary of EMAs presented and completion rate (see Figure 2). Payments for completing EMAs are loaded onto GreenPhire cards each month. Participants are not compensated for accessing on-demand app features or completing treatment components. Following completion of study participation, participants who borrowed a study smartphone are mailed a prepaid envelope and instructed to return the phone.

Table 3. Comparison of treatment components.

App components	EASE[a]	Control
EMA[b]	X[c]	X
COVID-19 monitoring and intervention	X	X
Distress reporting	X	X
App instructions	X	X
AS[d] psychoeducation	X	N/A[e]
Interoceptive exposure exercises	X	N/A
On-demand tips and exercises		
General relaxation tips	X	X
Coping with mood	X	N/A
Coping with stress and anxiety	X	N/A
Coping with COVID-19	X	N/A
Coping with loss and grief	X	N/A
Coping with discrimination	X	N/A
Videos for distraction	X	N/A
Interoceptive exposure	X	X
Guided relaxation exercises	X	N/A
Inspirational messages	N/A	
Challenge unhelpful thoughts	N/A	
Tailored treatment messages in real time	X	N/A
State and national resources for needs	X	N/A
Compensation earned	X	X

[a]EASE: Easing Anxiety Sensitivity for Everyone.

[b]EMA: ecological momentary assessment.

[c]X: applicable.

[d]AS: anxiety sensitivity.

[e]N/A: not applicable.

Figure 2. EASE app home screen. EASE: Easing Anxiety Sensitivity for Everyone; TX: Texas.
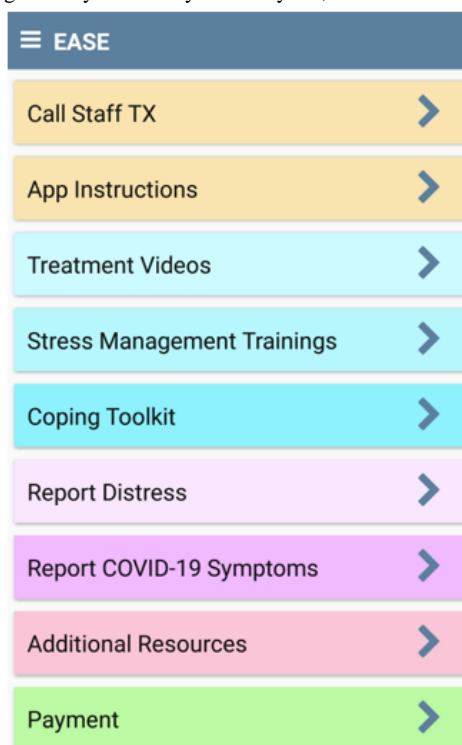
Event-sampling EMAs are self-initiated by the participant. Specifically, all participants are instructed to self-initiate an event-sampling EMA to record distress and new COVID-19 symptoms. Participants are instructed to answer questions based on immediate thoughts/feelings when they initiate an event-sampling EMA. EASE participants receive unique intervention content when they report elevated depression or anxiety symptoms. Further, our previously developed COVID-19 risk assessment and detection algorithm [70] automatically advises participants in both conditions to get a test for COVID-19 when elevated risk is detected. In addition, the app immediately triggers an automated and encrypted email to study staff to call the participant and assist with obtaining a COVID-19 test (if desired by the participant). All EMAs are date-, time-, and location-stamped for future analyses.

Study Conditions

Easing Anxiety Sensitivity for Everyone

EASE integrates standard CBT with AS reduction. EASE provides (1) standard treatment on a schedule, (2) scheduled and cued interoceptive exposure sessions, (3) on-demand intervention content (ie, ways to cope with symptoms of anxiety and depression, cognitive restructuring exercises, guided relaxation videos), (4) tailored treatment messages based on responses to EMA items, and (5) additional resources. All interactions with the app are date-, time-, and location-stamped for future analyses.

Treatment on a Schedule

EASE includes 18 four- to six-minute intervention videos (adapted from our previous interventions [71-75] and recorded by racially/ethnically diverse actors) that are delivered via a smartphone over the first 3 months of the intervention period. Specifically, new videos become available during the morning daily EMAs on Mondays and Thursdays. Participants have the option to watch the videos immediately or later by clicking the "Treatment Videos" button (see Figure 2). Videos can be watched as many times as desired, and the app records the date/time/location when each video is watched (both initiation and completion).

The videos cover topics including the role of AS in interoceptive stress, the CBT model of anxiety/depression and interoceptive stress, procedures for each intervention module, coping mechanisms for negative emotions (eg, chronic stress due to sociocultural stressors), fear avoidance hierarchy for specific stressors (eg, bodily stress or stress burden due to experiences of racism or discrimination), interoceptive exposure techniques, the relationship between COVID-19 and anxiety/depression, and use of AS reduction strategies to mitigate the impact of COVID-19–related stress on mental health. Videos also present known disparities regarding COVID-19 and the potential impact on mental health disparities. Finally, several videos focus on relaxation training to help mitigate the impact of stress related to discrimination, general life events, and COVID-19–specific stressors on heightened symptoms of anxiety and depression. See Table 4 for a list of video titles.

Table 4. List of video titles.

EASE[a] group		Active comparison group	
Video number	Title	Video number	Title
1	Introduction to the Program	1	What Is Mindfulness
2	CBT[b] Model & Example	2	Mindfulness vs Meditation
3a	General Stressors	3	Levels of Mindfulness
3b	Race/Discrimination Stressors	4	The WHAT Skills
4	AS[c] & Interoceptive Stress	5	The HOW Skills
5	Interoceptive Exercises	6	Living Mindfully
6	Present-Focused Exercise	7	Mindfulness and Acceptance
7	Interoceptive Exercises (CON'TD)	8	Diaphragmatic Breathing Exercise
8	Unhelpful Thinking	9	Body Scan Exercise
9	Thinking Flexibly	10	Walking Mindfully Exercise
10	Avoidance & Exposure	11	Eating Mindfully Exercise
11	Opposite Action	12	Sleep and Mindfulness Exercise
12	Diaphragmatic Breathing	13	Science of Mindfulness
13	Values	14	5-4-3-2-1
14	Grief/Loss and Control	15	STOP Practice
15	Grounding	16	Leaves on a Stream
16	Self-Care & Compassion	N/A[d]	N/A
17	Review Video	N/A	N/A
18	Next Steps	N/A	N/A

[a]EASE: Easing Anxiety Sensitivity for Everyone.

[b]CBT: cognitive behavioral therapy.

[c]AS: anxiety sensitivity.

[d]N/A: not applicable.

Exposure Exercises

To target AS, graduated exposure to anxiety and distress-provoking situations and response prevention is introduced, reviewed, and practiced via EASE videos and the "Stress Management Trainings" button. Participants learn to manage negative affect, stress, and uncomfortable physiological symptoms during exposure exercises without acting on acute motivation to suppress distress. These exposure exercises were created and pilot-tested as part of our previous work on smartphone-delivered AS reduction [72]. The exercises include overbreathing, straw breathing, running in place, chair spinning, and head rush. EASE participants are reminded to practice the interoceptive exercises during treatment videos and are asked whether they would like to practice stress management training 2 times per day (during morning and evening EMAs). Participants can access the exposures by clicking the "Stress Management Trainings" button on the app home screen (see Figure 2). When this button is clicked, the app explains the purpose of the exercise and assesses the current level of distress (0-100 scale) and physical sensations (1-7 scale). Next, the app randomly selects 1 of the 5 exercises and explains how to complete it. A 1-minute countdown timer is initiated, and the participant completes the exercise. Following the exercise, the app reassesses the level of distress and physical sensations. The app suggests repeating the exercise up to 3 additional times if the current reported distress is greater than 50 on a 1-100 scale. This strategy aims to increase habituation to feared sensations. Participants are encouraged to continue practicing these exposures daily.

On-Demand Features

Participants have access to a "Coping Toolkit" menu of on-demand intervention content (see Figure 3). Specifically, participants can access (1) suggestions on ways to cope with stress and anxiety, (2) guided relaxation exercise videos, (3) exercises focused on challenging automatic thoughts, (4) suggestions for coping with COVID-19–related stress, (5) coping with loss and grief, (6) coping with discrimination, and (7) coping with sadness and depression. In addition, participants are instructed to click the "I'm Bored, Distract Me" button to gain access to brief funny or cute videos. Further, participants are prompted to press the "Report Distress" button when they experience elevated stress, anxiety, or depression (see Figure 2). The Report Distress assessment includes questions about mood and feelings, and the app provides tailored content based on current anxiety, depression, and self-reported ability to cope with current emotions. The "Report COVID-19 Symptoms"

button assesses symptoms that are consistent with COVID-19. When symptom clusters that are consistent with COVID-19 are reported, participants are informed that they should get tested and asked whether they would like help with finding a testing center. An encrypted email is sent to study staff in real time when participants report symptoms consistent with COVID-19. The "Additional Resources" button contains links to state and federal resources focused on COVID-19, housing, food, and job placement.

Figure 3. "Coping Toolkit" menu of on-demand intervention content.
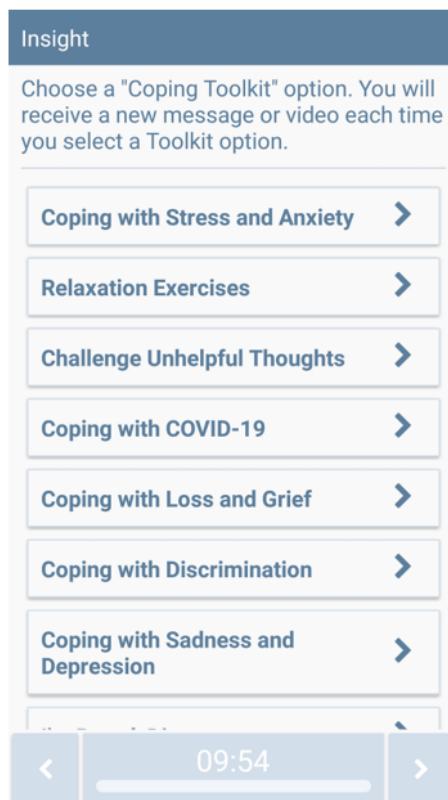
EMAs With Tailored Real-Time Treatment Messages

During the 6-month intervention period, a tailored message is delivered at the end of each scheduled EMA (2 per day). Specifically, when participants provide a pattern of responses that are suggestive of heightened emotional distress (eg, current depression or anxiety/stress score>5 on a 1-10 scale), they receive a coping message that attempts to address current symptoms (eg, "If you are feeling stressed, take a moment to breathe. Breathe in for 5 seconds, hold it, and breathe out. Stress and bad moods are temporary." or "Research shows that sunlight can help reduce feelings of depression. Take some time for a walk today.").

Mindfulness-Based/Relaxation-Based Comparison

Participants randomized to the mindfulness/relaxation-based comparison condition have access to some app components that are similar to EASE. The comparison intervention emphasizes the importance of mindfulness in the larger context of mental and physical health and specific skills to improve mindfulness and promote relaxation/stress reduction [76-78]. The 16 treatment videos selected for this treatment were chosen based on their relevance to the target population and potential to offer a real-world comparison. Topics covered in the videos include an introduction to the concept of mindfulness, the difference and similarities between mindfulness and meditation, guided meditations, and guided mindfulness-based exercises (ie, 5-4-3-2-1 exercise, leaves on a stream thought, diaphragmatic breathing). Similar to EASE, during the Monday and Thursday morning EMAs, comparison group participants are asked whether they would like to watch 1 new 5-10-minute mindfulness-based psychoeducation and skill-building videos. Videos also become available weekly via the "Treatment Videos" button. The comparison group does not have access to the stress management training exercises, and EMAs are not paired with tailored real-time treatment messages. The "Report COVID-19 Symptoms" button is fully functional and identical to the EASE version of this feature. The "Report Distress" button is available, but tailored messaging is not delivered at the end of the Report Distress assessment.

Assessments

Prescreen and enrollment call data are collected via REDCap. Baseline, EMA, and follow-up data are collected using smartphones through the Insight mHealth platform app software [60]. Qualitive follow-up data are collected via phone calls. This approach reduces data entry errors and the need to retain paper copies of raw data. Each question appears on the smartphone screen, and the participant responds by touching their answer on the touch screen. Data are collected via self-report, with the exception of the REALM-SF [63] and the 6CIT [62], which are administered via interviews during the

enrollment phone call. See Tables 1 and 2 for a schedule of study measures.

Demographics and Screener Questions

Participants are asked to provide standard demographic information (ie, name, contact information, age, sex, race/ethnicity, monthly income used as a measure of the SES [79-83], level of education), current state of residence, comfort with the English language, information about the type of phone they have, and whether they would like to download the app to their personal phone or be provided with a phone with the app predownloaded to it.

English Literacy

The REALM-SF [63] is an interviewer-administered checklist in which individuals are asked to read and pronounce 9 common medical terms. Individuals who pronounce ≥4 words correctly are considered to be reading at a reading level higher than the sixth grade (an English literacy level higher than the sixth grade is required to complete EMAs). The REALM-SF is administered by trained research staff during the enrollment call.

Cognitive Functioning

The 6CIT is a brief cognitive function test that takes less than 5 minutes to complete and is widely used in primary care settings [62]. The scale uses an inverse score, and questions are weighted to produce a total out of 28. Participants with scores in the normal range (ie, 0-7) are eligible for study participation. Individuals with scores of 8 or higher (ie, mild-to-severe impairment) are excluded from participating in this study.

Anxiety

OASIS [58] is a 5-item measure that has demonstrated strong psychometric properties to identify those with clinically significant anxiety symptoms [58]. A score of 8 or higher is indicative of clinically significant anxiety. OASIS is administered during the REDCap prescreen (to screen for eligibility), baseline assessment, and 3- and 6-month postrandomization assessments.

Depression

ODSIS [59] is a 5-item measure that has demonstrated strong psychometric properties to identify those with clinically significant depression symptoms [59]. A score of 8 or higher is indicative of clinically significant depression. ODSIS is administered during the REDCap prescreen (to screen for eligibility), baseline assessment, and 3- and 6-month postrandomization follow-up assessments.

Functional Impairment

The research team developed items to assess functional impairment related to experiencing anxiety and depression. These items assess the extent to which a person's relationships, work performance, household maintenance, and social interactions have been negatively affected by depression and anxiety. These items are administered at baseline and 3- and 6-month postrandomization follow-up assessments.

Anxiety Sensitivity

The Short-Scale Anxiety Sensitivity Index (SSASI) [67] is a 5-item brief measure of AS derived from the Anxiety Sensitivity Index-3 (ASI-3) that has demonstrated excellent psychometric properties. The SSASI is administered at baseline and 3- and 6-month postrandomization follow-up assessments.

COVID-19–Related Stress and Fear

The Fear of COVID-19 [68] scale is a 6-item validated measure to assess emotional fear and the somatic expression of fear related to COVID-19. The COVID-19 Psychological Impact Survey is a 4-item self-report measure of the psychological impacts of COVID-19 and associated risk factors [84]. The survey asks (1) the extent to which participants agree with the statement "I worry about the coronavirus all of the time" (1=strongly disagree to 7=strongly agree), (2) how sad participants feel when they think about coronavirus (0=not at all to 100=extremely), (3) how stressed participants feel when they think about coronavirus (0=not at all to 100=extremely), and (4) the degree to which the participant is stressed due to the COVID-19 pandemic (0=no stress to 100=extreme stress). The Fear of COVID-19 and COVID-19 Psychological Impact Survey measures are administered at baseline and 3- and 6-month postrandomization follow-up assessments.

Perceived Discrimination

The Everyday Discrimination Scale (EDS) [64] is a 6-item validated measure of discrimination. The Coronavirus Racial Bias Scale (CRBS) [65] is a 9-item Likert-type scale designed to assess disparities in COVID-19, including the likelihood of contracting COVID-19, lack of appropriate health care, and viewing negative social media posts against certain racial groups. Both measures are administered at baseline and 3- and 6-month postrandomization follow-up assessments.

Social Support

The 6-Item Perceived Social Support Questionnaire (F-SozU K-6) [66] is a self-report measure of the perceived availability of social support [66]. This measure is administered at baseline and 3- and 6-month postrandomization follow-up assessments.

Ecological Momentary Assessments

The EMA methodology used for this study is similar to that used in our previous studies and by other researchers [74,75,85-95]. Each EMA asks about current emotional, physical, and behavioral symptoms and takes approximately 2 minutes to complete. Two types of EMAs are used: time-based sampling (ie, daily diary) and event sampling. Time-based EMAs are prompted and initiated by the smartphone 2 times per day during the 6-month study period (ie, morning daily diary 30 minutes after the participant's preset wake time, end-of-day daily diary 75 minutes before the participant's preset bedtime). The phone rings and vibrates to cue these EMAs for 5 minutes (ie, alternating between 30-second alerting and silence periods). If the participant does not respond to the daily diary prompts, the EMA is automatically rescheduled (up to 3 times during morning assessments and twice during evening assessments) 15 minutes later. EMA questions ask about current symptoms of anxiety and depression, medication use, current

thoughts/affect/behaviors, social support, discrimination experiences, sleep quality, substance use, fast-food consumption, current location, fear of COVID-19, employment status, daily activities, and current COVID-19 symptoms. Participants are asked to rate their emotional state by indicating the extent to which they agree or disagree with each of 15 statements (using a 5-point scale from strongly disagree to strongly agree): I feel stressed, happy, angry, tired, afraid, relaxed, sad, bored, worried, lonely, calm, depressed, overwhelmed, energetic, and anxious (from the circumplex model of affect) [96]. Participants also indicate their current environment/social setting. In addition, participants are prompted to watch treatment videos twice per week ("A great way to get your day started is to watch a NEW short video that provides information and tips for handling stress. Would you like to watch the brief new video now? Note: Each video provides new information.") and complete stress management exercises in the app ("Would you like to complete an exercise right now?").

Data Analysis

Overview

Hypotheses for aims 1 and 2 will be examined using latent growth models (LGMs) [97], multilevel structural equation models (MSEMs) [98], and latent difference score models [99] using MPlus 8.0 [100]. Data will first be examined for multivariate normality and outliers to determine the most appropriate estimator. The maximum likelihood (ML) estimator will be used if data are approximately normal. Robust maximum likelihood (MLR) will be used if the data are not multivariate normal. LGMs will generally be used to model outcomes collected at major assessments. MSEMs will be used to further examine the longitudinal course of outcomes and hypothesized mechanisms of action as an MSEM is ideally suited for disentangling within and between individual variance in order to more precisely estimate main effects, lagged effects, and indirect effects in intensive longitudinal designs. Evaluation of the model fit in the LGMs/MSEMs will be examined using fit diagnostics (ie, standardized residuals) and common fit statistics (ie, root-mean-square error of approximation) following the associated cut-off criteria recommended by Hu and Bentler [101]. We will assess the equivalence of the treatment groups on key baseline variables (demographics and psychological variables); variables on which the groups differ will be used as covariates in the final analyses. We will also examine attrition from the study as a dichotomous outcome and use logistic regression to determine whether treatment assignment predicts attrition.

Aims

Aim 1

- H1: Participants randomized to the EASE intervention will have greater reductions in anxiety, depression, and functional impairment at 3- and 6-month follow-ups compared to those randomized to the mindfulness/relaxation-based comparison intervention. Multiple approaches to modeling changes in primary outcomes will be used to evaluate our hypothesis that the EASE app will result in greater reductions in the primary

outcomes relative to the comparison app and that reductions will be similar across racial/ethnic groups. We will first estimate between-group differences by calculating Cohen d effect sizes (with a 95% CI) for anxiety, depression, and functional impairment at each major follow-up assessment. We will then conduct a series of conditional LGMs to examine the impact of the treatment condition on the trajectories of primary outcomes from baseline to the end of the follow-up period. First, an LGM will be specified using the assessments of primary outcomes at major assessments: baseline, 3 months, and 6 months. A dummy code representing the treatment condition will be included in the model as a predictor of the intercept and slope factors to quantify the effect of the EASE program on the longitudinal course of outcomes relative to the comparison group. The statistical significance (and magnitude of the effect size) of the main effect of treatment condition will test H1 (the EASE app will show greater reductions in anxiety [OASIS] and depression [ODSIS] symptoms and improved functional impairment). Separate models will be specified for anxiety, depression, and functional impairment.

- H2: Intervention effects of EASE relative to mindfulness/relaxation-based comparison will be equivalent across racial/ethnic groups. We will next conduct similar effect size and LGM analyses within each of the 4 racial/ethnic groups in order to test H2 (the effectiveness of EASE will be similar across racial/ethnic groups). We will then use MSEMs to examine the effects of the EASE app on the longitudinal course of outcomes, as measured by the EMA daily diary data. MSEM analyses will also be conducted both across and within the racial/ethnic groups to evaluate how effects vary across groups.

Aim 2

- H3: Intervention effects on study outcomes listed in aim 1 will be mediated by reductions in AS and changes in COVID-19–related stress and fear. Similar modeling procedures will be used to determine the impact of the treatment condition on AS and COVID-19–related stress and fear and whether improvements in primary outcomes are mediated by reductions in AS and the secondary mechanisms. We will first conduct separate LGMs for AS and the secondary mechanisms using methods such as those described for the primary outcomes. After conducting univariate LGMs to explore changes in AS and secondary mechanisms as a function of treatment condition, we will conduct a series of parallel process LGMs to examine how changes in AS and secondary mechanisms relate to changes in the primary outcomes. The effects of changes in AS and secondary mechanisms on changes in the primary outcomes will be examined by specifying the slope factor for each potential mechanism as a predictor of the slope factor for each outcome. Separate parallel process LGMs will be conducted for each primary outcome, and a series of parallel process LGMs will be evaluated to determine the unique effect of each mechanism when modeled simultaneously. The indirect effects of treatment on primary outcomes via AS and other potential mechanisms will be evaluated by calculated bootstrapped CIs of the indirect effect using the

MODEL indirect command in MPlus. These parallel process LGMs will not provide formal tests of mechanisms of change, as these models will be examining concurrent changes across the 6 months of assessment, but if the results from these models are promising, they will be followed by analyses that include the EMA measures of outcomes and mechanisms and will use models that permit more fine-grained examinations of temporal dependencies of change (ie, mediation models in MSEMs and latent difference score models).

- H4: Perceived discrimination (worse intervention outcomes), social support (better intervention outcomes), or the SES (lower SES associated with worse outcomes) will moderate intervention effects on study outcomes listed in aim 1. The moderating influence of discrimination, social support, and SES will be evaluated using conditional LGMs in which condition, moderator, and condition×moderator interaction terms will be specified as predictors of the slope factor for primary outcomes using the XWITH command in MPlus. Separate models will be specified for each hypothesized moderator, and conclusions will be based on the CIs of the interaction terms.

Exploratory Aims

The brief qualitative interviews will be transcribed following completion and read to ensure accurate transcription. The transcribed interviews will be coded using NVivo v.12 (QSR International). The study team (2-3 project staff) will create the initial codebook and then code 2 interviews together. The codebook will then be revised (if needed), and a third interview will be coded as a team. If there is high coding agreement between team members, the remainder of the interviews will be coded independently by the staff and then checked by author MC. The team will meet to discuss any disagreements in coding and to create a final coded version for thematic analysis. Themes will be determined within and across codes. Comparisons will also be made across racial/ethnic groups and between the intervention and comparison groups. An additional team member will then review the coding and analysis for confirming and disconfirming evidence for the themes [102]. Participant responses will be integrated with quantitative usage data to identify inconsistencies in the participant's perceptions and actual engagement with the app [103,104]. The team will make recommendations that can be used to improve app engagement and modifications for specific racial/ethnic groups. MSEMs will then be used to further explore temporal patterns of COVID-19 outcomes and health behaviors using daily EMA data. Specifically, we will specify a series of models to examine interrelationships and concurrent and lagged effects among COVID-19 experiences (eg, treatments received, duration of symptoms), sequelae (eg, job loss, eviction, reduction in unemployment benefits), and health behaviors affected by COVID-19 (ie, physical activity, pain experience, sleep) among those who do and do not contract the virus.

Missing Data

We anticipate some participant attrition during the trial. Missing data will be handled in all analyses using direct ML techniques within MPlus under a missing-at-random (MAR) assumption

[105]. Modern missing data techniques, such as direct ML, increase statistical power and provide more accurate estimates of model parameters and standard errors and are the recommended intent-to-treat approach for clinical trials.

Statistical Power

We calculated the sample size required to detect the treatment effect of EASE on the primary outcomes of anxiety, depression, and functional impairment at 3 and 6 months both across and within the racial/ethnic groups, the treatment effect of EASE on the longitudinal course of AS and secondary mechanisms, and the indirect effects of EASE on primary outcomes via the hypothesized mechanisms. Based on our pilot data and prior published research, we hypothesize moderate-to-large (d>.50) effects of EASE on primary outcomes and the hypothesized mechanisms and moderate-to-large associations (r>.30) between changes in mechanisms and primary outcomes. Power determinations based on these hypothesized effect sizes were conducted using GPower, RMASS [106], and simulation studies identifying the sample sizes needed to detect indirect effects [107]. Power analyses indicated that the targeted sample size of 200 participants for each of the 4 racial groups would yield greater than 80% power to detect effects for each study aim at α=.05, resulting in the overall target sample size of 800. Stratified block randomization was used to ensure equal allocation of adults across sex and racial/ethnic groups across treatment conditions.

Results

The study was funded by the National Institute of Mental Health (NIMH) in May 2021. The smartphone app was finalized in December 2021, and data collection began on December 22, 2021. Study staff have since been engaged in activities associated with study enrollment and data collection, including ordering and monitoring of gift cards and supplies; screening, consenting, and enrolling participants; dispersing intervention incentives; follow-up tracking/calls; maintaining an up-to-date Institutional Review Board (IRB) protocol and associated documents; and monitoring incoming data to identify and resolve problems early (ie, both EMA and traditional questionnaire data). As of June 17, 2022, 217 participants have been recruited into the study.

Discussion

Principal Results

Mental health disparities across racial/ethnic groups are projected to become more pronounced as a result of the COVID-19 pandemic [9]. Emerging evidence points to the utility of a digitally delivered, mobile transdiagnostic intervention that engages AS for ameliorating anxiety and depression [49]. Integrating theoretical and empirical models with a practical approach to treatment delivery, the proposed study aims to address emerging and downstream mental health disparities among BHAI populations by testing whether our novel intervention (EASE) outperforms an active, credible comparison group. Data from this efficacy trial will determine whether EASE successfully improves symptoms of anxiety and

depression and whether these improvements outperform an active comparison control app. If successful, EASE may be ready for implementation and dissemination into real-world behavioral health and social service settings consistent with the 4 objectives outlined in the NIH's strategic plan [108]. Overall, this proposal has the potential to decrease anxiety and depression symptoms among all populations, including vulnerable populations determined to be most at risk of exacerbated, long-lasting negative health sequelae.

Notably, all study procedures are administered remotely. As such, this study may serve as a clinically important example for how to implement remote/virtual mental health research with BHAI individuals. Indeed, such flexible platforms for treatment delivery may have greater potential to reach and impact people of color, who constitute an underserved, hard-to-reach population. By providing a remote means of care, our study may be able to assess and assist a larger group of individuals who identify as BHAI and remove potential barriers to treatment access, such as money needed to commute into the office/clinic or the need to take time off from work to attend appointments.

Limitations

One notable limitation of our study is the reliance on Android smartphones to complete assessments and access app features. Study-provided Android smartphones will be loaned to eligible participants upon request; however, those who are unwilling to use a study-provided smartphone or their own personal Android smartphone will be unable to participate in the study. Additionally, recruitment of older populations may be hindered due to the lack of appropriate knowledge and familiarity with mHealth apps [109]. This study will focus on enrolling individuals who identify as either Black/African American, Hispanic, American Indian/Alaska Native, or NHW; therefore, those who identify their racial/ethnic identity as an identity other than Black/African American, Hispanic, American Indian/Alaska Native, or NHW, such as identifying solely as Asian, Native Hawaiian, or Other Pacific Islander, will be excluded from the study. Given that these groups have faced elevated levels of xenophobia [110] and discrimination (eg, microaggressions, hate crimes) [111] due to the COVID-19 pandemic, it is important that these groups—and the unique issues they face—be addressed in the development of future interventions. The experimental group targets 1 transdiagnostic factor (AS); however, future research would benefit from evaluating other factors associated with COVID-19–related anxiety, distress, and disability. Further, although the app includes videos on the disproportionate effect the pandemic has had on BHAI individuals, the cultural tailoring of the app and its features (ie, tailored treatment messages, resources) would benefit from further development. Finally, we will conduct exploratory analyses of how the frequency/duration of app feature use may relate to outcomes. Given that all app features are available simultaneously, these exploratory analyses will be confounded by the potential effect of using other app features. Future work would benefit from conducting a dismantling study of EASE to understand the potential for each component to improve outcomes.

Conclusion

Ultimately, the goal of this study is to target and reduce emerging and likely exacerbated mental health disparities among BHAI individuals. We aim to fill a void surrounding mental health treatment among all groups but particularly BHAI individuals by developing a digitally delivered, mobile, easy-to-use treatment for anxiety and depression. By addressing comorbid anxiety and depression symptoms through an intervention that targets an underlying transdiagnostic vulnerability factor (eg, AS), we hope that this intervention will help adults with anxiety or depression to reduce their symptoms.

Data Availability

The data sets generated and analyzed during this study will be available from the corresponding author on reasonable request following the completion of the trial and publication of the main outcomes paper. Deidentified data also will be made available via the National Institute on Mental Health (NIMH) Data Archive (NDA).

Conflicts of Interest

MSB and DEK are inventors of the Insight mobile health (mHealth) platform, and they receive royalties related to use of this platform by investigators external to the University of Oklahoma Health Sciences Center (OUHSC). However, because MSB is a multiple principal investigator (MPI) on this study, neither MSB nor DEK will receive royalties in this case.

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Abbreviations

6CIT: 6-Item Cognitive Impairment Test
AS: anxiety sensitivity
BHAI: Black, Hispanic, and American Indian
CBT: cognitive behavioral therapy
CRBS: Coronavirus Racial Bias Scale
EASE: Easing Anxiety Sensitivity for Everyone
EDS: Everyday Discrimination Scale
EMA: ecological momentary assessment
F-SozU K-6: 6-Item Perceived Social Support Questionnaire
LGM: latent growth model
mHealth: mobile health
ML: maximum likelihood
MSEM: multilevel structural equation model
NHW: non-Hispanic White
OASIS: Overall Anxiety Severity and Impairment Scale
ODSIS: Overall Depression Severity and Impairment Scale
RCT: randomized controlled trial
REALM-SF: Rapid Estimate of Adult Literacy in Medicine-Short Form
REDCap: Research Electronic Data Capture
SES: socioeconomic status
SSASI: Short-Scale Anxiety Sensitivity Index

<u>Protocol</u>

A Novel Remote Patient and Medication Monitoring Solution to Improve Adherence and Persistence With Inflammatory Bowel Disease Therapy (ASSIST Study): Protocol for a Randomized Controlled Trial

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Abstract

Background: Inflammatory bowel diseases (IBDs) are chronic inflammatory conditions of the gastrointestinal tract. Although adherence to IBD therapies is associated with improved clinical outcomes, overall adherence is poor. Consequently, there is a critical need to develop interventions that monitor adherence in real time and identify reasons for nonadherence to support clinical teams in initiating effective interventions. Recently, electronic- and web-based platforms have been developed to monitor adherence and guide interventions. A novel remote therapy monitoring (RTM) technology, the Tappt digital health system, has been developed to monitor real-time medication adherence patterns through smart label technologies, capture patient-reported outcomes and barriers to care, and process patient data through algorithms that trigger personalized digital and human touch points between clinical visits. Such a digital health solution enables care teams to proactively identify and mitigate nonadherence and worsening clinical outcomes.

Objective: We propose a 12-month multicenter randomized controlled trial to assess the effectiveness of the Tappt digital health system on adherence, clinical outcomes, and health care use among patients diagnosed with IBD starting a new oral or subcutaneous therapy.

Methods: The digital health system intervention will provide automatic measurement of medication adherence via smart labels for pill bottles or injectors as well as a monitoring platform for providers. The system will prompt patients to complete a two-item assessment of symptoms monthly using the PRO-2 scales for UC and Crohn disease, from which increased symptoms will be alerted to providers. Participants will be randomized 2:1 to the intervention group or the control group, which will receive standard of care. All participants are required to complete questionnaires at baseline as well as at 12, 26, and 52 weeks. Assuming an adherence rate of 0.65 and 0.9 among control and intervention participants, respectively, we will need to enroll 123 participants: 82 (66.7%) in the intervention group and 41 (33.3%) controls. We will compare adherence as measured by the medication

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possession ratio, defined as the number of days of supply of medication obtained during the observation period out of the total number of days in the observation period, in participants using the RTM versus those receiving standard of care. We will also compare clinical outcomes and health care use in participants using the RTM versus those receiving standard of care.

Results: We anticipate starting recruitment in December 2022.

Conclusions: Effective medication adherence monitoring and intervention programs need to be cost-efficient, pose little or no burden to the patient, record reliable data in real time, and provide actionable insights to the health care team. We anticipate the Tappt digital health system to improve the medication possession ratio, clinical outcomes, and health care use compared with standard of care.

Trial Registration: ClinicalTrials.gov NCT05316584; https://clinicaltrials.gov/ct2/show/NCT05316584

International Registered Report Identifier (IRRID): PRR1-10.2196/40382

KEYWORDS

Introduction

Background

Inflammatory bowel diseases (IBDs), comprising Crohn disease (CD) and ulcerative colitis (UC), are chronic, progressive, inflammatory conditions of the gastrointestinal tract that affect up to 3 million Americans [1]. IBD is thought to be driven by inappropriate immune responses to an altered gut microbiome, with a disease course characterized by remitting and relapsing episodes of inflammation, or flares.

Most patients with a chronic condition require long-term therapy. Evidence has demonstrated that suboptimal adherence is associated with poor clinical outcomes, including increased IBD activity and associated complications, worsened quality of life (QoL) [2], and higher health care use and costs [3]. In addition, nonadherence to biologic therapies may increase the risk for developing antidrug antibodies, leading to loss of response to therapy. Despite this, adherence to IBD therapies remains suboptimal. A recent survey administered to 322 patients with IBD found that 55% reported nonadherence, including forgetting or skipping medication owing to not feeling well [4]. Overall adherence to IBD medications ranges from 40% to 80%, depending on the patient population, medication class, data sources, and adherence quantification measures [5].

Adherence to oral IBD medications such as aminosalicylates and thiopurines ranges from 50% to 93% [6]. Studies evaluating adherence to biologic therapies are conflicting. Using a medication possession ratio (MPR)—calculated as the number of days of supply of medication obtained during the observation period out of the total number days in the observation period—of <100% as a definition of nonadherence in 365 patients with IBD treated with biologic therapies, adherence was highest for intravenous formulations (70%-83%) compared with subcutaneous biologics (47%-50%) [7]. Conversely, in a large multicenter prospective cohort study where adherence was defined as ≥80% using a visual analog scale, the majority of patients with CD and UC were considered adherent (88% and 86%, respectively) [8]. However, when comparing across medication classes, adherence was lowest for patients on rectal (68%) and oral (83%) therapies and highest for intramuscular

(88%) and parenteral (87%) therapies [8]. Similar results were found in a recent study of 112 patients with IBD in the Manitoba cohort: 81% of the patients were considered adherent to their therapy using an MPR cutoff value of ≥90% [9].

The variance in adherence is in part due to inconsistent measurement. Objective and validated approaches include pill counts, refill counts, and pharmacological or biochemical markers; subjective approaches include validated measures, visual analog scales, and patient interviews. Some approaches may work better in certain settings, given that they measure adherence in different ways and at different time points [10]; for example, although validated measures are effective in clinical trials, they can be burdensome and time consuming in real-world practice. Furthermore, they do not capture day-to-day variability in adherence because the adherence measure summarizes medication-taking behaviors over a designated period [3]. Similarly, pharmacy records and insurance databases provide data that can be used to calculate MPR and percentage of days covered by the prescriptions, but they do not provide information on medication intake patterns and do not capture use of samples [10,11]. Patient interviews are the most efficient way to gather a complete picture of patient adherence, but they can be unreliable, given that patients tend to overestimate their adherence [10].

In recent years, electronic- and virtual-based platforms have been developed to monitor adherence routinely and guide appropriate interventions. These remote therapy monitoring (RTM) systems include electronic pill caps, electronic pill and needle boxes, bidirectional SMS text message reminders, and patient-facing mobile apps [10,12-14]. Although some of these have been successful at monitoring and improving adherence, they are limited by their battery requirement and cost as well as the survey fatigue of respondents. Furthermore, these solutions and apps collect data inconsistently and are not synchronized with clinical teams' workflows in a real-time manner to identify patients at risk for nonadherence and drive actionable follow-up.

Synchronyx, which is based in Boca Raton, Florida, United States, has developed a scalable RTM and patient engagement solution called the Tappt digital health system. It consists of

smart battery-free labels affixed to medication packages that transmit encrypted adherence data from the patient's smartphone through a secure server; a patient-facing web application with access to personalized data and educational resources; and a centralized cloud-based and password-protected clinician portal that summarizes patients' medication intake behaviors in real time at individual and aggregate levels, collects patients' barriers to care and patient-reported outcomes (PROs), and triggers alerts to designated clinical teams.

Preliminary Work

IBD Home Automated Telemanagement

For patients with IBD, we previously developed the IBD Home Automated Telemanagement (HAT) system, which consists of a laptop computer, an electronic weighing scale, and a physician web portal. The laptop computer and scale made up the patient home unit. The laptop computer administered questions on patient symptoms, adherence, and medication side effects and delivered educational messages, whereas the scale was used to regularly measure body weight [15,16].

We performed a 6-month open-label trial to assess the feasibility and patient acceptance of the IBD HAT system in patients with IBD. We predetermined that ≥80% adherence with self-testing would demonstrate feasibility. Patient acceptance of the HAT system was evaluated using the IBD HAT attitudinal survey. In total, 27 patients with IBD were recruited from the University of Maryland and Veterans Affairs Hospital in Baltimore, Maryland, United States. Participants continued to receive standard IBD care in addition to the weekly HAT sessions.

Of the 27 participants, 25 (93%) successfully completed the 6-month study. During the study, 89% (22/25) of the participants were adherent with weekly self-testing, and 91% (23/25) said that self-testing was not complicated. Of the 25 participants, 18 (73%) reported that they felt safer using the system, and 23 (91%) stated that they would agree to use the self-testing program in the future. Self-reported adherence with IBD medications was 90% throughout the study. Clinical disease activity, disease-specific QoL, and patient knowledge improved compared with baseline [17].

We then pursued a 12-month randomized clinical trial to assess the effectiveness of the UC HAT system compared with best available care (BAC). We modified the symptom diary and alert criteria to make them specific to UC and added action plans and electronic messaging for participants to communicate with the research team. Adults with UC from the University of Maryland and Veterans Affairs Hospital in Baltimore were randomized to self-testing with the UC HAT system weekly or BAC. All participants underwent visits at baseline and every 4 months. Disease activity was measured using the Seo index [18,19], disease-specific QoL was measured using the Inflammatory Bowel Disease Questionnaire [20], and medication adherence was measured using a medication adherence scale [21]. We randomized 47 patients, and 29 (62%) completed the study. After adjustment for baseline QoL scores, participants in the UC HAT arm had a strong trend toward decreased Seo index scores from baseline (mean –11.9, SD 6.6; P=.08). Furthermore, after adjustment for baseline disease knowledge,

participants in the UC HAT arm had a significant increase in QoL scores from baseline (mean 12.5, SD 5.9; P=.04), whereas participants in the BAC arm had nonsignificant decreases in QoL scores from baseline (mean –3.8, SD 5.3; P=.47). The difference in change in QoL scores from baseline between the UC HAT and BAC arms at 12 months was significant. Self-reported adherence to medical therapy was low in both groups at baseline (BAC: 45% and UC HAT: 40%). Adherence rates increased in both groups but were not significantly different at any time point after baseline. Both arms had poor IBD knowledge at baseline, with improvement at the 12-month follow-up; however, there was not a significant difference between the UC HAT and BAC arms at the 12-month follow-up [22]. Our results suggested that the randomization process was inadequate because participants in the UC HAT arm had higher rates of immune suppression use and greater impairments in QoL than participants in the BAC arm. We suspect that the baseline differences in favor of the BAC arm impaired our ability to demonstrate a treatment effect of the UC HAT system. This hypothesis is supported by the findings of clinically important improvements in disease activity and QoL from the baseline to the 12-month visit in the UC HAT arm. Furthermore, after adjustment for baseline disease knowledge, a significant improvement in QoL was noted in the UC HAT participants.

Telemedicine for Patients With IBD

We then conducted a multicenter randomized controlled trial to assess the effectiveness of telemedicine for patients with IBD (TELE-IBD) weekly (TELE-IBD W) or every other week (TELE-IBD EOW) compared with BAC. Patients completed self-assessments via SMS text messages, assessment of weight was completed through use of an electronic scale and manually entered by the participant, and educational messages were sent either weekly or twice weekly throughout the trial. We recruited 348 participants (n=116, 33.3%, TELE-IBD W; n=115, 33%, TELE-IBD EOW; and n=117, 33.6%, BAC controls), including 236 (67.8%) participants with CD and 112 (32.2%) with UC or indeterminate colitis. Of the 348 participants, 259 (74.4%) completed the final 12-month visit. Clinical indices of CD activity using the Harvey-Bradshaw Index (HBI) decreased in the control, TELE-IBD EOW, and TELE-IBD W groups (P=.16). The decreases in HBI scores over time were significant in all groups (P<.001) but not different among the groups (P=.18). Clinical indices of UC activity using the Simple Clinical Colitis Activity Index (SCCAI) decreased in the control, TELE-IBD EOW, and TELE-IBD W groups (P=.41), but they were significant only in the controls (P=.01) and not different among the groups (P=.25). IBD QoL scores increased in the control, TELE-IBD EOW, and TELE-IBD W groups (P=.42) but were significant only in the TELE-IBD EOW group (P=.03) and not different among the groups (P=.95). However, use of health care resources was different among the groups, with participants in the TELE-IBD arms experiencing lower total and IBD-related hospitalization rates and higher number of noninvasive diagnostic tests, telephone calls, and electronic messages [23]. In addition, those in the TELE-IBD arms had a greater improvement in Crohn's and Colitis Knowledge scores [24] than those in the standard of care group. General self-efficacy scores improved in all arms during the trial but

were not different among the groups [25,26]. In an analysis of intervention participants only, adherence increased with depressive symptoms in those who were aged ≤40 years (*P*=.02), but there was no association between depressive symptoms and adherence in those who were aged >40 years (*P*=.53) [27]. A follow-up qualitative study demonstrated that participants identified clear benefits of the TELE-IBD system, including a better understanding of the disease process, monitoring of symptoms, and feeling of connection to the health care team. Both adherent and nonadherent participants preferred a flexible system that was personalized, included targeted education, and promoted self-management [28].

Aims

On the basis of the aforementioned preliminary work demonstrating that technology has the capacity to improve medication adherence and clinical outcomes, there is a critical need to integrate interventions that are affordable and practical to monitor adherence in real time. In addition, interventions that aim to identify reasons for nonadherence, intentional or unintentional, should be prioritized to support clinical teams in tailoring adherence interventions to each unique patient [10,29]. As such, we propose a 12-month multicenter randomized controlled trial to assess the effectiveness of an RTM solution, the Tappt digital health system, on adherence, clinical outcomes, and health care use among patients with IBD starting a new oral or subcutaneous therapy. Specifically, we will (aim 1) compare adherence as measured by the MPR in participants using the digital health system versus those receiving standard of care and (aim 2) compare clinical outcomes and health care use in participants using the digital health system versus those receiving standard of care.

Methods

Overview and Population

The proposed study is a multicenter randomized controlled trial to be conducted over 12 months. Participants in the intervention arm will be encouraged to verify medication adherence using the Tappt digital health system. This system will provide automatic measurement of medication adherence via smart labels for pill bottles or injectors as well as a monitoring platform for providers. In addition, the Tappt system will prompt patients to complete an assessment of symptoms monthly using the PRO scale, 2-item version (PRO-2) for UC and CD; if symptoms worsen, alerts will be triggered to providers. Participants randomized to the control group will receive standard of care. All participants are required to complete questionnaires at baseline and at 12, 26, and 52 weeks.

Study Schedule

All participants are required to complete electronic data entry forms at baseline and at 12, 26, and 52 weeks. Adherence, disease activity, QoL, PROs, IBD self-efficacy, and health care use will be measured at each time point during the 1-year study (Table 1). Demographic and clinical information will be collected at the baseline visit.

Table 1. Schedule of events for the study.

Instrument	Category	Source	Baseline	Week 12	Week 26	Week 52
Demographics	Demographics	Patient	✓			
Clinical history	Clinical information	Provider or site	✓			
Medication adherence	Adherence	Patient		✓	✓	✓
MARS-5[a]	Adherence	Patient	✓	✓	✓	✓
Health care use	Health care use	Patient	✓	✓	✓	✓
Modified Harvey-Bradshaw Index	Disease activity: CD[b]	Patient	✓	✓	✓	✓
Simple Clinical Colitis Activity Index	Disease activity: UC[c]	Patient	✓	✓	✓	✓
C-reactive protein	Disease activity	Provider or site	✓	✓	✓	✓
Calprotectin	Disease activity	Provider or site	✓	✓	✓	✓
Simple endoscopic score: CD	Disease activity	Provider or site	✓	✓	✓	✓
Mayo Endoscopic Score	Disease activity	Provider or site	✓	✓	✓	✓
PROMIS[d] Global Health Scale	Quality of life	Patient	✓	✓	✓	✓
PROMIS anxiety	Mental health	Patient	✓	✓	✓	✓
PROMIS depression	Mental health	Patient	✓	✓	✓	✓
PROMIS sleep disturbance	Mental health	Patient	✓	✓	✓	✓
PROMIS fatigue	Disease activity	Patient	✓	✓	✓	✓
PROMIS pain interference	Disease activity	Patient	✓	✓	✓	✓
PROMIS physical function	Frailty	Patient	✓	✓	✓	✓
IBD[e] self-efficacy	Self-efficacy	Patient	✓	✓	✓	✓

[a]MARS-5: Medication Adherence Report Scale-5.

[b]CD: Crohn disease.

[c]UC: ulcerative colitis.

[d]PROMIS: Patient-Reported Outcome Measurement Information System.

[e]IBD: inflammatory bowel disease.

Study Population

Patients will be recruited for this study from 5 clinical centers at the University of Maryland School of Medicine, University of Cincinnati School of Medicine, NYU Grossman School of Medicine, University of North Carolina School of Medicine, and Vanderbilt University School of Medicine.

Inclusion criteria will include (1) aged ≥18 years; (2) documented IBD based on usual diagnostic criteria, including clinical symptoms and findings from endoscopy, radiology studies, and histology [30]; (3) initiation of treatment with a new oral or subcutaneous treatment for IBD; (4) access to a smartphone with a reliable data plan or Wi-Fi access; and (5) ability to understand the protocol and provide informed consent in English. Exclusion criteria will include (1) inability to speak and read English or comply with the study protocol; (2) the presence of an ileostomy, colostomy, ileoanal pouch anastomosis, or ileorectal anastomosis; (3) initiation of oral corticosteroids only without concurrent use of an oral or subcutaneous maintenance therapy; (4) imminent surgery within the next 60 days; (5) history of short bowel syndrome; or (6) uncontrolled medical or psychiatric disease.

Study Conduct

Eligible patients will be approached by research staff at the time of routine clinical visits or via telephone and provide informed consent. All of the participants' concomitant medications will be continued during the study. Corticosteroids will be tapered at the discretion of the investigator. Addition of new IBD medications will be allowed during the study. If the new medication is an eligible oral or subcutaneous addition to existing therapy, this will be tracked using the approach that was used to track the original medication during the initial treatment. If the new medication replaces the initial therapy, the replacement medication will be similarly tracked.

Participants will be randomized 2:1 to receive either remote monitoring or standard of care using a random permuted block design with randomly varied block sizes. Participants will be stratified based on study site and disease subtype (CD vs UC or indeterminate colitis). We chose to stratify on these variables because they could affect the response to the intervention; stratification will ensure balance of these covariates among the study groups. The randomization order will be computer generated, and group assignment will be made when a new participant is enrolled into the study by the clinical site. The

site investigators and research staff will remain blinded to the randomization order. The participants and physicians will not be blinded to the group assignment; however, we will attempt to minimize measurement bias by collecting outcome data through electronic data capture directly from participants.

Intervention Group

Eligible patients will complete a baseline survey gathering demographic and clinical information. Upon enrollment, the intervention participants will activate their account to access the patient-facing Tappt web application, which includes the individual participants' medication regimen information, upcoming doses, and adherence data. The web application also includes a curated resource library with links to educational material on the Crohn's and Colitis Foundation website, expert-led video modules on each IBD medication class, and training videos on how to use the system and seek support. The web application also allows patients to respond to surveys related to nonadherence or PROs. The system uses algorithms to send participants personalized alerts and reminders for medication doses or survey completion through SMS text messages.

After providing training to the intervention participants on how to use the Tappt system, the research team will input into the system the intervention participants' deidentified information as well as the medication to be tracked, dose, and frequency of dosing. The research team will then assign smart labels to the participants' medication regimen, which will be used by the participants to record their medication use. The research team will also walk each study participant through the Tappt system and explain how to label and scan medication and how to complete all required surveys. Along with the first medication, the corresponding smart labels to be affixed to the pill bottle, pen, or syringe container of the newly prescribed medication will be shipped to the participants. Participants will receive sufficient labels for dosing of 90 days of the medication to be tracked, plus an additional 2 to 6 labels to account for lost or damaged labels and dose escalation. Participants will receive enough labels until their next assessment (ie, a participant on mesalamine 2.4 g daily will receive 90 labels). Changes in dose of medications for the intervention participants will be monitored on a weekly basis by study coordinators. Any change in dosing will be updated on the Tappt clinician portal; labels will be reassigned to the new dosing frequency, and a new set of smart labels will be sent to the participants for the next 90-day dosing period.

At the time of taking a medication dose, participants will scan the label with their mobile phone to verify that they are taking the medication. Upon scanning, participants will immediately receive a notification on their device indicating that the label was successfully scanned and that their medication adherence was updated in their profile. Each day that a medication is due to be taken, participants will receive a reminder through SMS text message notifying them of their medication schedule for the day. If participants fail to scan the label at a given time (as determined by their specific medication regimen), they will receive an SMS text message at the end of the day with a link to respond to a survey that captures reasons for nonadherence.

Participants will also complete a PRO-2 assessment at baseline and then monthly for the entire 12 months of the study triggered by the Tappt system through an HTML link sent to patients by SMS text message [31,32]. For participants with CD, the PRO-2 assessment includes abdominal pain and liquid stool frequency. For participants with UC or indeterminate colitis, the PRO-2 assessment includes rectal bleeding and stool frequency. The research team will also be able to send the PRO-2 survey to patients at any given time, at their discretion, if patients are experiencing a flare or at the time of a change in medication dose. Items for the PRO-2 assessment vary based on disease type (refer to the Outcomes and Outcome Measures section).

Clinical teams can review their participants' data in real time through the secure cloud-based provider-facing Tappt portal. To reduce monitoring burden among clinical teams, the system's algorithms prompt automated email alerts to the clinical team when participants' adherence or PROs fall below predetermined thresholds, when a participant's regimen is approaching refill date, or when a participant reports an error on their profile. These alerts can support clinical teams in following up with patients in a timely manner to reduce risk for poor outcomes (Figure 1).

For oral medications, mean adherence <80% in a 2-week period will trigger an alert. For subcutaneous medications, 2 missed doses of adalimumab and 1 missed dose of other biologics will trigger an alert. If alerts are triggered for nonadherence, a clinical nurse, pharmacist, or social worker will contact the participant to identify barriers to adherence; remediation will be initiated, if possible. For participants with CD, a PRO-2 abdominal pain score of 2 (moderate) or higher or a liquid stool frequency score of >4 will trigger an alert. For participants with UC or IBD type undetermined, a rectal bleeding score of 2 or a stool frequency score of 2 will trigger an alert (obvious blood most of the time or blood alone passes and stool frequency >2 stools more than normal, respectively). A clinical nurse will contact the participant if a symptom-based alert is triggered.

Figure 1. Study intervention: the Tappt remote therapy monitoring digital health system.
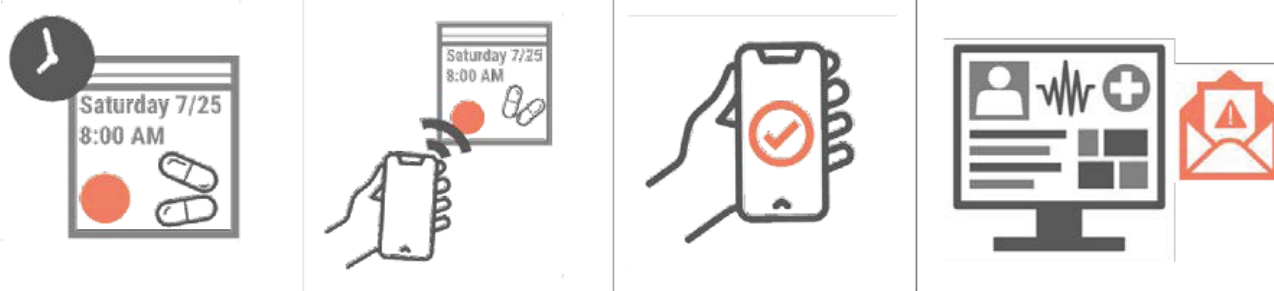
Control Group

The standard of care for participants in this study is modeled after the standard of care at all study sites. Standard of care is based on current evidence-based guidelines, including a comprehensive assessment, a guideline-concordant therapy plan, scheduled and as-needed clinic visits, scheduled and as-needed telephone calls, and administration of educational fact sheets about disease-specific topics when appropriate. Personnel used to provide standard of care at each site will vary and may include nurse coordinators, advanced practice providers, social workers, psychologists, dietitians, pharmacists, and other ancillary staff.

Outcomes and Outcome Measures

Overview

The outcome measures outlined in the following sections will be assessed at baseline and at 12, 26, and 52 weeks after initiating treatment. All outcome measures will be captured electronically and will not require a study or office visit.

The primary outcome of the proposed study will be the difference in mean MPR between the intervention and control groups during the 12-month study. The mean MPR will be calculated as follows:

MPR = number of days' supply of medication obtained during observation period / total number of days in observation period.

If a participant discontinues therapy but initiates treatment with another eligible medication, the MPR will continue to be calculated. Any delay in initiating new treatment will be adjusted for the total number of days in the observation period (ie, if drug A is discontinued and drug B is started 2 weeks later, the observation period will be 365 – 14 = 351 days); for example,

if a participant is prescribed oral mesalamine (1.2 g), 4 tablets daily, for 90 days (dispense 360) with 2 refills between months 6 and 12, the MPR would be 100%. Likewise, if a participant is prescribed ustekinumab 90 mg subcutaneous every 8 weeks (dispense 1 syringe) with 2 refills between months 6 and 12, the MPR would be 66%. Data on medication use will be self-reported by participants at each time point. However, we will randomly validate participant report via chart review of pharmacy data for 20% of the participants. Participants will report the date the medications of interest were filled as well as the number of days' supply of medications filled. Self-reported adherence will be assessed with the Medication Adherence Report Scale-5 questionnaire (Table 2). Scores for each item are summed to give a total score, with higher scores indicating higher levels of reported adherence [33].

The secondary outcome of the proposed study will be the difference in health care use between the intervention and control groups during the 12-month study. For health care use, we will use a composite end point, including counts of hospitalizations, urgent care or emergency room visits, IBD-related surgeries, telephone calls (primary care and IBD provider), endoscopic procedures, imaging examinations, and blood and stool testing. We will also assess new prescriptions for corticosteroids (prednisone and budesonide) at each time point during the study period. The total events will be adjusted per 100 patient years of follow-up because the 2 groups will be unequal in number. In addition, we will evaluate each outcome individually. The relatedness of hospitalization and urgent care or emergency room visits to IBD will be determined as well. Information will be obtained from patient self-report at each assessment. This approach has been validated in patients with IBD using a modification of the Canadian Community Health Survey [34]. However, we will validate participant self-report via chart review for 20% of the participants, randomly selected.

Table 2. Medication Adherence Report Scale-5 questionnaire.

Item	Scoring				
	Always	Often	Sometimes	Rarely	Never
I forget to take my medication	1	2	3	4	5
I alter my medication dose	1	2	3	4	5
I stop taking my medication for a while	1	2	3	4	5
I decide to miss out a dose of my medication	1	2	3	4	5
I take less medication than instructed	1	2	3	4	5

Assessment of Disease Activity

To measure disease activity in participants with CD, we will assess a modified HBI without including the item on the presence of an abdominal mass (Table 3). HBI scores of <5, 5 to 7, 8 to 16, and >16 correlate with symptomatic remission, mildly active symptoms, moderately active symptoms, and severely active symptoms, respectively. A decrease in the HBI score of 3 or 4 correlates well with a symptomatic response [35].

In addition to calculating clinical remission and response using the aforementioned measures, we will create an outcome of steroid-free remission or response based on whether the patient was on concurrent steroids at the time of assessment. In patients with UC and indeterminate colitis, disease activity will be assessed with the SCCAI (Table 4). An SCCAI score of <3 has been shown to correlate with symptomatic remission, whereas a decrease of 2 points has been shown to correlate with a symptomatic response [36].

Table 3. Modified Harvey-Bradshaw Index.

Item	Scoring
General well-being	Well: 0, fair: 1, poor: 2, terrible: 3
Abdominal pain	None: 0, mild: 1, moderate: 2, severe: 3
Number of liquid stools per day	Each liquid stool: 1
Arthralgia	Yes: 1, no: 0
Uveitis	Yes: 1, no: 0
Erythema nodosum	Yes: 1, no: 0
Aphthous ulcers	Yes: 1, no: 0
Pyoderma gangrenosum	Yes: 1, no: 0
Anal fissure	Yes: 1, no: 0
New fistula	Yes: 1, no: 0
Abscess	Yes: 1, no: 0

Table 4. Simple Clinical Colitis Activity Index.

Item	Scoring				
	0	1	2	3	4
Bowel frequency (day)	1 to 3	4 to 6	7 to 9	>9	N/A[a]
Bowel frequency (night)	None	1 to 3	4 to 6	N/A	N/A
Urgency of defecation	None	Hurry	Immediately	Incontinence	N/A
Blood in stool	None	Trace	Occasionally frank	Usually frank	N/A
General well-being	Very well	Slightly below par	Poor	Very poor	Terrible
Aphthous ulcers	None	Present	N/A	N/A	N/A
Uveitis	None	Present	N/A	N/A	N/A
Erythema nodosum	None	Present	N/A	N/A	N/A
Arthralgia	None	Present	N/A	N/A	N/A

[a]N/A: not applicable.

We will calculate steroid-free remission as described in the previous paragraph. To assess disease activity using the Tappt system, we will use the PRO-2 assessments for CD [31] and UC [32]. These measures of PROs have been validated in IBD and demonstrate an association between improvements in patient-reported symptoms and clinical remission and response [37,38]. For CD, the PRO-2 assessment comprises questions regarding the frequency of bowel movements in the prior week and the degree of abdominal pain (Table 5). PRO-2 scores of 8, 14, and 34 correlated with Crohn's Disease Activity Index

[39] scores of 150, 220, and 450, respectively. A Crohn's Disease Activity Index score of <150 is consistent with clinical remission, whereas a score of >220 is consistent with moderate to severe disease. In lieu of calculating a total score, an average liquid stool frequency per day of >4 or an average abdominal pain score of 2 (moderate) or higher will trigger an alert.

For UC and indeterminate colitis, a PRO-2 assessment specific for UC will be used. It comprises questions related to stool frequency and rectal bleeding (Table 6). A score of ≥2 for stool frequency or rectal bleeding will trigger an alert.

Table 5. Patient-reported outcome scale, 2-item version, for patients with Crohn disease.

Variable	Day							7-day average	Weighting factor	Total
	1	2	3	4	5	6	7			
Number of liquid or very soft stools	__a	—	—	—	—	—	—	—	× 2 = —	—
Abdominal pain (0=none, 1=mild, 2=moderate, 3=severe)	—	—	—	—	—	—	—	—	× 5 = —	—

aTo be filled in by health care staff.

Table 6. Patient-reported outcome scale, 2-item version, for patients with ulcerative colitis.

Stool frequency	Rectal bleeding	Score
Normal number of stools	No blood seen	0
1 to 2 stools more than normal	Streaks of blood with stool less than half the time	1
3 to 4 stools more than normal	Obvious blood with stool most of the time	2
≥5 stools more than normal	Blood alone passes	3

In addition, the results of quantitative C-reactive protein and fecal calprotectin tests, if available, will be extracted from the medical record at each time point. Research staff will use the value closest to the time of assessment within 30 days. C-reactive protein correlates well with endoscopic disease activity ($r=0.56$), and values <5 mg/dL have negative predictive values for endoscopic disease activity ranging from 29% to 61% [40-42]. Likewise, fecal calprotectin correlates well with endoscopic disease activity ($r=0.53$) but has better negative predictive values for endoscopic disease activity ranging from 71% to 97% using a value of <250 mcg/g [42,43]. Similarly, we will collect information on endoscopic disease activity, if available. For UC and IBD type undetermined, we will use the Mayo Endoscopic Score (MES; Table S1 in Multimedia Appendix 1). The MES assessment was modified to remove friability in the mild disease category. An MES of 0 to 1 is consistent with endoscopic remission [44].

For patients with CD, we will assess endoscopic disease activity with the Simple Endoscopic Score (Table S2 in Multimedia Appendix 1). A score of <3 is consistent with inactive disease, 3 to 6 mildly active, 7 to 15 moderately active, and ≥16 severely active [45,46]. We will also record new steroid use (oral or topical treatment) in the interval between assessments.

Assessment of QoL and PRO Measures

The Patient-Reported Outcome Measurement Information System is a National Institutes of Health–funded instrument that assesses patients' self-reported health over a 7-day period [47]. Patients report global health as well as different components of physical, mental, and social health, including physical function, anxiety, depression, fatigue, sleep disturbance, and pain interference; higher scores indicate poorer health (Tables S3-S9 in Multimedia Appendix 1). Patient-Reported Outcome Measurement Information System scores are standardized to the general population where a T-score of 50 is the standardized normal, with an SD of 10. Therefore, these measures can be considered within normal limits (<55), mild (55 to <60), moderate (60 to <70), and severe (≥70) based on domain scores measured in the general population in the United States. Minimally important differences of 2 to 6 points have

been reported for other disease states, including chronic pain, stroke, osteoarthritis, and cancer [48].

Self-efficacy

Self-efficacy is a perception of a patient's ability to engage in the skills necessary to master a new challenge when facing obstacles. An IBD-specific self-efficacy scale has been developed (Table S10 in Multimedia Appendix 1). The 29-item instrument includes questions on managing medical care, stress and emotions, and symptoms and disease, as well as maintaining remission. Responses range from 1=not sure at all to 10=totally sure. Scores range from 29 to 290, with higher scores correlating with greater self-efficacy [49].

Health Care Use

Health care use will be measured using the Canadian Community Health Survey (Table S11 in Multimedia Appendix 1).

Data Management

Outcome measures from participants will be collected via direct data capture through use of electronic data entry forms sent to participants via email. Information on health care use will be collected by research staff at each site and recorded in the source documents. The data will then be entered electronically into electronic case report forms. All data will be maintained, archived, retrieved, and distributed by a computer system.

Statistical Analyses

Baseline analyses will include tabulations of demographic and clinical variables of the study participants. Chi-square tests and 2-tailed *t* tests will be used to compare these groups to determine whether baseline differences exist. The distribution of each continuous variable will be inspected for outliers to determine whether a parametric or nonparametric approach should be applied. The Wilcoxon rank sum test will be used for any variable that does not meet the statistical assumptions of the *t* test. In addition, analyses will be conducted stratified by clinical site to determine whether the sites are comparable across the groups of interest. If differences are detected, these variables

will be evaluated as potential confounders in the regression models.

For study aim 1, we will compare the mean MPR ratio between the intervention and standard of care groups using *t* tests. For study aim 2, we will compare differences in health care use between the groups using the Wilcoxon ranked sum test because we expect that the data will not be normally distributed.

For the secondary aims of clinical outcomes and health care use, dichotomized outcomes will be compared in a similar fashion with bivariate analyses. For health care use, the outcome will be investigated in quartiles of health care use, and specific outcomes of interest selected a priori will be investigated (eg, need for hospitalization for IBD, need for IBD surgery, and initiation of corticosteroids).

All analyses will be completed using intention-to-treat principles. Assuming 2 intervention participants for every 1 control, with adherence rates of 0.65 among controls and 0.9 in intervention participants and with a type I error rate of 0.05 and power of 0.9, we will need to enroll 123 participants: 82 (67%) in the intervention group and 41 (33%) controls. We may enroll more patients pending our initial recruitment and data capture.

Although we will make every effort to obtain complete data from all randomized participants, we anticipate that there could be as much as 20% loss to follow-up by 12 months. To detect potential bias by analysis of only the collected data, we plan first to compare patients with data with those without data at a given time point on baseline characteristics to determine characteristics of those who do not provide complete data. We will also perform sensitivity testing to see whether estimates of intervention effects differ if only patients with complete data are analyzed. Depending upon the extent of missingness, we will also consider imputation methods that use multiple regression predictions for imputation.

Ethics Approval

We will seek approval for this study from the institutional review boards of each participating institution.

Results

We anticipate starting recruitment in December 2022.

Discussion

Study Expectations

The proposed study addresses 2 high-priority research areas in the field of IBD. First, it will assess a novel RTM digital health technology to improve adherence and clinical outcomes. Second, it will determine whether enhanced remote monitoring improves clinical outcomes compared with standard of care. As CD and UC are chronic illnesses that require continual medical management to prevent disease relapse and complications and

as nonadherence has been linked to poor clinical outcomes and greater health care use, interventions that improve adherence are greatly needed. If our RTM digital health system is effective at improving adherence as we anticipate, we expect superior clinical outcomes and decreased use of unnecessary health care use such as unplanned clinic visits, steroid prescriptions, emergency room visits, and hospitalizations. In addition, if a system is patient-centric, easy to use, and can interface with existing clinical workflows so that clinical team members can intervene in a timely fashion for patients at risk for poor outcomes, it will improve the care experience and lives of patients living with IBD.

The results of this study can lay the foundation for a larger study to input data from the Tappt digital health system into the electronic medical record so that all members of the health care team can easily view the results. A larger study would also facilitate inclusion of communities with more diverse study populations and populations with health disparities. In addition to advancing the science on remote monitoring in chronic illnesses and methods to improve adherence, the remote monitoring system could be accessed by patients not only to track adherence and symptoms but also as a link to vetted educational resources and their personalized data. Furthermore, the system might be useful to large integrated health systems and provider networks or to payers to improve adherence, reduce health care use, and contain costs. In addition, given the recent reimbursement expansion for RTM under Medicare, provider teams can benefit from generating recurring revenue and improve the patient care experience derived from RTM digital health systems.

Few Difficulties or Limitations Anticipated

We anticipate few difficulties or limitations in conducting the proposed study. Enrollment of 123 participants over 12 months among 5 sites (approximately 2 per site per month) is a very reasonable goal as each site is a large referral center for the care of patients with IBD. In addition, we are not restricting enrollment to patients initiating treatment with a biologic or small molecule, which will increase the pool of eligible patients. If recruitment is challenging, we can recruit additional sites to participate. We have included sites in the Northeast, mid-Atlantic, Midwest, and South, which should increase the diversity of the patient population studied. However, because IBD is underrepresented in populations consisting of people of color, our participants will not be as diverse as the general population at each site. Moreover, a digital platform may not benefit disadvantaged people with limited access to technology or technological literacy. Finally, although the COVID-19 pandemic seems to be easing, it is possible that new variants of the virus will emerge, resulting in restricted access for in-person visits. We do not anticipate that prescribing patterns will change if this occurs, and we have implemented remote consent and data collection to mitigate these barriers to enrollment and capture of outcome data.

Authors' Contributions

JA and RC, the guarantors, were responsible for the study concept and design as well as acquisition of data. JA wrote the first draft of the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version of the paper, including the authorship list.

Conflicts of Interest

JA reports research grants from BioFire Diagnostics and consultancy fees, honoraria or advisory board fees from BioFire Diagnostics, Bristol Myers Squibb, Janssen, and AbbVie. ML reports consulting fees from AbbVie, Takeda, Pfizer, Janssen, Lilly, Bristol Myers Squibb, Genentech, Roche, Prometheus, Theravance, and Target Pharmasolutions, as well as research support from Pfizer and Takeda. SH reports consulting fees from AbbVie, Takeda, Gilead, and Janssen. AA reports consulting fees from AbbVie, Takeda, Janssen, Bristol Myers Squibb, Pfizer, Eli Lilly, Gilead, DiaSorin, and TLL Pharmaceuticals, as well as speaking fees from AbbVie, Takeda, Janssen, Bristol Myers Squibb, and Pfizer. TS and KF are employed by Synchronyx. KDF reports speaking fees from AbbVie, Pfizer, Takeda, and Bristol Myers Squibb, as well as advisory board fees from Bristol Myers Squibb. RC reports research grants from Janssen and consultancy fees, honoraria or advisory board fees from AbbVie, Bristol Myers Squibb, Eli Lilly, Fzata, Janssen, Magellan Health, Pfizer, Samsung Bioepis, and Takeda.

Multimedia Appendix 1
Supplemental tables.
[DOCX File , 34 KB - resprot_v11i12e40382_app1.docx]

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Abbreviations

BAC: best available care
CD: Crohn disease
HAT: Home Automated Telemanagement
HBI: Harvey-Bradshaw Index
IBD: inflammatory bowel disease
MES: Mayo Endoscopic Score
MPR: medication possession ratio
PRO: patient-reported outcome
PRO-2: patient-reported outcome scale, 2-item version

QoL: quality of life
RTM: remote therapy monitoring
SCCAI: Simple Clinical Colitis Activity Index
TELE-IBD EOW: telemedicine for patients with inflammatory bowel disease every other week
TELE-IBD W: telemedicine for patients with inflammatory bowel disease weekly
TELE-IBD: telemedicine for patients with inflammatory bowel disease
UC: ulcerative colitis

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Protocol

Mobile Health–Supported Virtual Reality and Group Problem Management Plus: Protocol for a Cluster Randomized Trial Among Urban Refugee and Displaced Youth in Kampala, Uganda (Tushirikiane4MH, Supporting Each Other for Mental Health)

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Abstract

Background: Although mental health challenges disproportionately affect people in humanitarian contexts, most refugee youth do not receive the mental health support needed. Uganda is the largest refugee-hosting nation in Africa, hosting over 1.58 million refugees in 2022, with more than 111,000 living in the city of Kampala. There is limited information about effective and feasible interventions to improve mental health outcomes and mental health literacy, and to reduce mental health stigma among urban refugee adolescents and youth in low- and middle-income countries (LMICs). Virtual reality (VR) is a promising approach to reduce stigma and improve mental health and coping, yet such interventions have not yet been tested in LMICs where most

forcibly displaced people reside. Group Problem Management Plus (GPM+) is a scalable brief psychological transdiagnostic intervention for people experiencing a range of adversities, but has not been tested with adolescents and youth to date. Further, mobile health (mHealth) strategies have demonstrated promise in promoting mental health literacy.

Objective: The aim of this study is to evaluate the feasibility and effectiveness of two youth-tailored mental health interventions (VR alone and VR combined with GMP+) in comparison with the standard of care in improving mental health outcomes among refugee and displaced youth aged 16-24 years in Kampala, Uganda.

Methods: A three-arm cluster randomized controlled trial will be implemented across five informal settlements grouped into three sites, based on proximity, and randomized in a 1:1:1 design. Approximately 330 adolescents (110 per cluster) are enrolled and will be followed for approximately 16 weeks. Data will be collected at three time points: baseline enrollment, 8 weeks following enrollment, and 16 weeks after enrollment. Primary (depression) and secondary outcomes (mental health literacy, attitudes toward mental help–seeking, adaptive coping, mental health stigma, mental well-being, level of functioning) will be evaluated.

Results: The study will be conducted in accordance with CONSORT (Consolidated Standards of Reporting Trials) guidelines. The study has received ethical approval from the University of Toronto (#40965; May 12, 2021), Mildmay Uganda Research Ethics Committee (MUREC-2021-41; June 24, 2021), and Uganda National Council for Science & Technology (SS1021ES; January 1, 2022). A qualitative formative phase was conducted using focus groups and in-depth, semistructured key informant interviews to understand contextual factors influencing mental well-being among urban refugee and displaced youth. Qualitative findings will inform the VR intervention, SMS text check-in messages, and the adaptation of GPM+. Intervention development was conducted in collaboration with refugee youth peer navigators. The trial launched in June 2022 and the final follow-up survey will be conducted in November 2022.

Conclusions: This study will contribute to the knowledge of youth-tailored mental health intervention strategies for urban refugee and displaced youth living in informal settlements in LMIC contexts. Findings will be shared in peer-reviewed publications, conference presentations, and with community dissemination.

Trial Registration: ClinicalTrials.gov NCT05187689; https://clinicaltrials.gov/ct2/show/NCT05187689

International Registered Report Identifier (IRRID): DERR1-10.2196/42342

Introduction

At the end of 2021, there were 89.4 million forcibly displaced persons across the globe, 83% of whom were hosted in low- and middle-income countries (LMICs) and 41% were children and youth under 18 years old [1]. Mental health challenges such as depression and anxiety disproportionately affect persons in humanitarian contexts; yet, most forcibly displaced persons do not receive the mental health support needed [2,3]. Myriad stressors contribute to psychological distress among refugee and displaced youth, including trauma, violence, food insecurity, and social marginalization [2,4]. Chronic psychological stress among adolescents can have life-long harmful impacts on neurobiological systems that are connected with emotional and behavioral regulation [5]. It is therefore of particular importance to mitigate psychological distress and to promote mental well-being among refugee and displaced adolescents and youth.

Uganda is the largest refugee-hosting nation in Africa with over 1.5 million refugees in 2022 [6]. There are 118,000 urban refugees in Uganda who live in Kampala, 27% of whom are youth aged 15-24 years [7]. There is a trend of urbanization of refugees globally, with more than 60% of refugees and 80% of internally displaced persons globally living in urban regions [8]. Many urban refugees such as those in Kampala live in informal settlements, including slums [9-11]. Socioenvironmental stressors in slums and informal settlements—such as violence and poverty—may harm mental well-being, yet mental health interventions in these contexts have not centered on the needs and priorities of urban refugee and displaced youth [12]. Most studies on the health of refugee and displaced persons have focused on refugee settlement contexts, leaving knowledge gaps regarding efficacious strategies to improve mental health among urban refugees [11].

A systematic review of mental health and psychosocial support for children (7-18 years old) in humanitarian settings identified knowledge gaps regarding effective strategies to reduce depression and anxiety [3]. Strategies in Uganda included sports for development, which only resulted in positive effects for boys [13], and a creative play group, which only resulted in positive effects for girls [14]. A 2018 cross-sectional survey with urban refugee and displaced youth (N=445) aged 16-24 years in Kampala, Uganda, found that three-quarters (74%) of adolescent girls and young women, and nearly half (49%) of adolescent boys and young men reported depressive symptoms [4]. These alarming statistics highlight the need for concrete solutions developed with and for urban refugee youth to alleviate this distress and risk of depression. In July 2020, Uganda opened its borders to receive more refugees from the Democratic Republic of the Congo (DRC) in the midst of the COVID-19 pandemic [15]. While mental health risks may be heightened during pandemics such as COVID-19 [16], researchers identified a chronically high prevalence of depression among urban

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refugee youth in Kampala both before (27.5%) and after (28.9%) declaration of the pandemic in March 2020 [17], signaling the urgent need to address chronic depression among this population.

Two key mental health needs that are understudied among refugee youth in LMICs such as Uganda include mental health literacy and mental health stigma reduction. Mental health literacy comprises knowledge and understanding of (1) different types of mental health issues and distress, (2) mental health risks and underlying causes of mental health challenges, (3) self-help strategies for mental health, (4) accessible and available professional help, and (5) recognizing when to seek mental health support and how to access it [18]. Interventions to advance mental health literacy may result in help-seeking for depression, anxiety, and psychological distress; however, there is a need for rigorous evaluations of the benefits of mental health literacy programs in LMIC and humanitarian contexts [19]. Researchers have called for more mental health literacy interventions specifically in Africa [20]. Indeed, mental health literacy programs tailored for refugees have largely focused on adults and/or high-income contexts [21,22]. This is also true for mental health stigma reduction, with the only randomized controlled trial (RCT) identified with refugees having been conducted with adult refugee men in the high-income context of Australia [23]. A systematic review reported that no trials have focused on reducing mental health stigma in low-income countries [24]. This review also reported a range of efficacious approaches to reducing mental health stigma, including via advancing mental health literacy [24]. Another systematic review on mental health stigma reduction reported that educational interventions were effective in reducing stigma, and that there were no differences in effectiveness between online and face-to-face mental health stigma reduction [25].

Emerging evidence suggests that tailored virtual reality (VR) scenarios can contribute to improved mental health outcomes. For example, a recent systematic review documented the efficacy of VR in treating posttraumatic stress disorder [26]. Yet, all studies were focused on adults in high-income settings and most were conducted with veterans [26]. To our knowledge, VR has not been piloted with youth in LMIC or humanitarian settings. Another promising mental health intervention approach is Group Problem Management Plus (GPM+), a World Health Organization (WHO) scalable group-based brief psychological transdiagnostic intervention for persons experiencing a range of adversities [27]. Problem Management Plus, delivered to individuals, was associated with reduced psychological distress, anxiety, depression, personally identified problems, and posttraumatic stress in RCTs with Kenyan adults [28] and conflict-affected adults in Pakistan [29]. The group-based delivery format, GPM+, was feasible and acceptable among conflict-affected adults in Nepal [30] and Pakistan [31], and is currently being tested among adult refugees in Turkey [32] and Jordan [33]. The WHO states that this program is likely efficacious among adolescents aged 16 years and older [27]; however, GPM+ has not yet been evaluated with refugee adolescents and youth.

This paper provides the study protocol for the Tushirikiane (roughly translating to "Supporting Each Other" in Swahili) for

Mental Health (Tushirikiane4MH) study that aims to address these knowledge gaps regarding efficacious mental health interventions with and for urban refugee and displaced youth in Kampala, Uganda. Specifically, Tushirikiane4MH will test the effectiveness and feasibility of a VR intervention on its own and the combination of VR and GPM+ compared with standard of care. The findings can be used to inform the implementation and scale-up of mental health interventions with urban refugee and displaced youth across Uganda and other humanitarian contexts.

This study aims to evaluate the feasibility of two youth-tailored mental health interventions: (1) a VR experience focused on mental health literacy and psychological first-aid [34] skills, supplemented with mobile health (mHealth) delivered via SMS-based bidirectional messages and information; and (2) GPM+ in combination with the VR experience. A third arm, the waitlist control arm, will receive the GPM+ intervention on its own after the first two interventions are complete. The primary study objective is to determine the effectiveness of the interventions on reducing depression [35]. Secondary objectives include examining the effectiveness of the interventions on (1) improving mental health literacy [36-38], (2) increasing adaptive coping strategies [39,40], (3) reducing mental health stigma [41], (4) increasing mental health well-being [42], and (5) improving level of functioning [43].

Methods

Study Design

To evaluate intervention effectiveness, we will conduct a cluster randomized controlled trial (cRCT), in which five informal settlements in Kampala will be randomized at a 1:1:1 ratio to one of the three study arms. Peer navigators, refugee youth living in the five informal settlements, are trained in research methods and ethics, and will enroll youth into the study following obtaining written informed consent. Youth will be assigned to the study arm corresponding to the informal settlement they live in. A cluster randomization approach was selected to mitigate challenges of experimental contamination, as youth living in slums and informal settlements have shared sociophysical environments [44], thus addressing internal validity threats, although we will collect individual-level outcome data. We will perform data collection at three time points: baseline enrollment, 8 weeks following implementation, and 16 weeks following implementation.

Study Setting

This trial is being conducted in the Ugandan capital of Kampala in five informal settlements, grouped into three sites based on geographic proximity (1: Kabalagala and Kansanga, 2: Katwe and Nsambya, and 3: Rubaga). These settlements were purposively chosen because: (1) they host many refugee and displaced persons in Kampala [45-48], largely from the DRC, Rwanda, and Burundi [49]; (2) these communities share similarities in socioeconomic status and living conditions, health care access, and languages; and (3) prior research noted a high prevalence of depressive symptoms among urban refugee youth in these communities [4,17]. Full details regarding the trial site geography and population have been described elsewhere [50].

Study Population and Eligibility Criteria

Approximately 330 youth (110 per cluster) aged 16-25 years will be enrolled into this study. Eligibility criteria for inclusion are: (1) currently living in one of the five selected informal settlements in Kampala (Kabalagala, Kansanga, Katwe, Nsambya, or Rubaga); (2) identifying as a refugee or displaced person, or having refugee or displaced parents; (3) aged 16-25 years; (4) owning or have daily access to a mobile phone; and (5) speaking French, English, Luganda, Kirundi, Kinyarwanda, or Swahili. Eligibility screening (via phone, in person, or WhatsApp) with interested participants will be conducted by trained peer navigators.

Participant Recruitment and Retention

The project team includes a refugee youth–focused community-based nongovernmental organization with expertise on youth engagement and programs for refugee youth. The team also includes academics, community-based practitioners, and stakeholders from the Ugandan Ministry of Health. Peer navigators—refugee and displaced youth aged 18-24 years living in these same five informal settlements (Kabalagala, Kansanga, Katwe, Nsambya, or Rubaga)—will work with the study coordinator and implementing partners to facilitate participant recruitment, and will further participate in study design and pilot testing. The 12 peer navigators (6 young women, 6 young men) have experience working in the various study communities as health educators or peer educators. They were identified and recruited by community-based collaborators and are deeply respected and connected in their communities.

Participants will be recruited within each settlement using purposive methods, including word-of-mouth and venue-based sampling at refugee agencies and community events. Recruitment will begin with participants who belong to the Tushirkiane cohort with this same study team and participated in previous completed trials on HIV self-testing [50] and COVID-19 prevention [51]. There will be additional purposive recruitment of 16- and 17-year-old participants to refresh the cohort. To engage and retain participants, peer navigators employed multiple strategies, including SMS and WhatsApp reminders, and local community partners also facilitated maintaining connection with study participants through outreach events.

Patient and Public Involvement in Research

Study collaborators at Young African Refugees for Integral Development (YARID), a well-established youth refugee nongovernmental organization in Kampala, have been involved in the research from the initial stage of developing the research question and focus. The study protocol was developed after a formative qualitative research phase (Phase 1), which included: (1) in-depth semistructured key informant interviews with professionals in various roles supporting the health and well-being of refugee youth in Uganda (n=10); and (2) age- and- gender-segregated focus groups (4 discussions with 6 people in each focus group; n=24 participants in total) with refugee youth in Kampala aged 16-24 years. One focus group discussion each was held with young women aged 16-19 years, young women aged 20-24 years, young men aged 16-19 years, and young men aged 20-24 years, respectively. This formative qualitative work explored refugee youth perspectives on mental health, mental health literacy, and mental health stigma. These qualitative findings were used to identify key themes for development of the VR scenario, SMS content, and to adapt GPM+ to this context and population group. In this way, the study responds to the mental health needs and priorities of urban refugee youth in this context.

Intervention Description

Design

The study was designed as a three-arm cRCT consisting of two treatment arms and one control arm. Clusters will be randomized to one of three arms: (1) VR, (2) VR plus GPM+, or (3) waitlist control, followed by GPM+ after intervention implementation and follow-up. Data will be collected at baseline, after intervention implementation (8 weeks postintervention), and at follow-up (16 weeks postintervention). The third arm (waitlist control) will receive an additional survey 8 weeks following the intervention to evaluate outcome changes. The VR and GPM+ arms receive weekly SMS messages with mental health literacy information and bidirectional check-ins ("how are you?" messages) where they can access any needed peer support. All study members will receive YARID resources and referrals as needed for mental health support from a trained social worker. The trial arms and interventions are described below and summarized in Figure 1.

Figure 1. Study design for Tushirikiane4MH, a cluster randomized controlled trial of mental health literacy and mental health promotion strategies among urban refugee and displaced youth in Kampala, Uganda. GPM+, Group Problem Management Plus; VR: virtual reality.
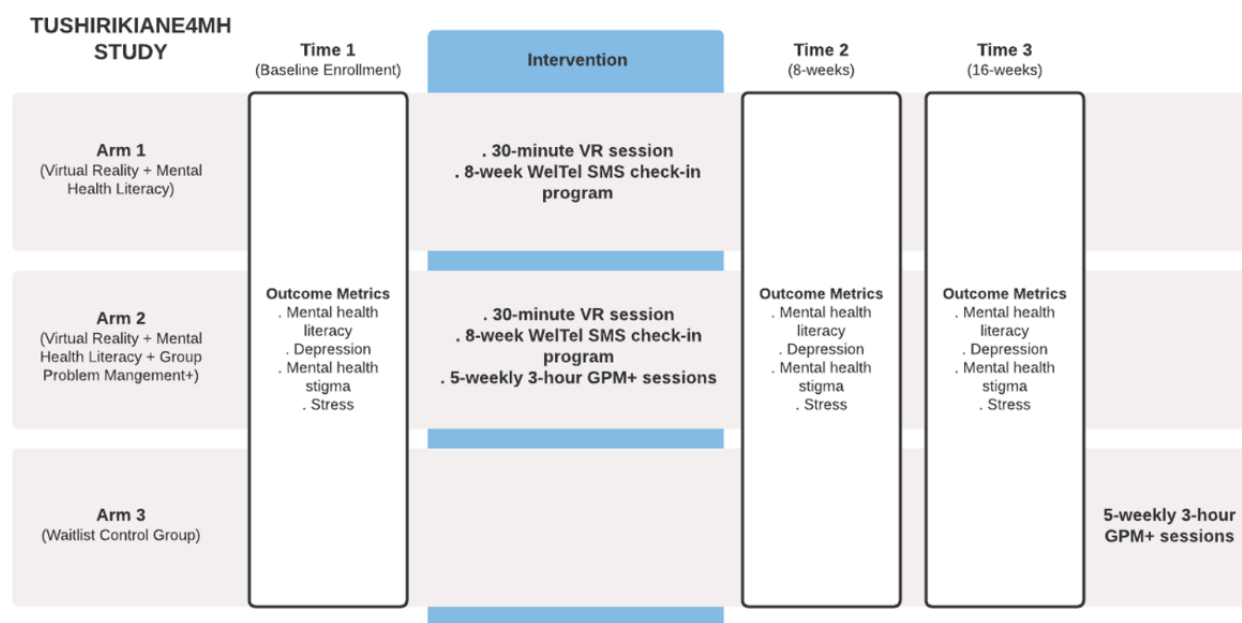
Arm 1: VR Alone

Participants in this arm will be enrolled into an immersive, interactive 15-minute VR session. The VR scenario was designed to address Phase 1 findings, and integrates mental health literacy [18], psychological first aid [34], and mindful self-compassion information and activities [52]. The VR space was designed to be visibly similar to the environment of informal settlements in Kampala, and will be offered in participants' language of choice (French, English, Kirundi, Kinyarwanda, or Swahili). Participants will be invited to participate in the VR scenario in a private room or in an outdoor setting at the partner organization. The VR session will be viewed on low-cost VR headsets and the study equipment will be sanitized and cleaned between uses.

Arm 2: VR and GPM+

Participants in this arm will be enrolled into the VR intervention (as described above) as well as GPM+. GPM+ is a WHO brief psychological transdiagnostic intervention for persons experiencing a range of adversities, including poverty and war, that, over five group sessions, aims to address both practical (eg, housing) and emotional (eg, stress) challenges [27]. Sessions employ evidence-based approaches to stress management, problem-solving, behavioral activation, and social support to reduce a range of mental health concerns. The intervention includes five 3-hour sessions, each with a distinct mechanism of action, which are described in Table 1.

Table 1. Group Problem Management Plus sessions and their mechanisms of action.

Session	Key mechanisms of action
Managing stress	Identifying goals, learning deep breathing and techniques for stress management
Managing problems	Identifying one solvable and practical problem, brainstorming possible solutions together
Get going, keep doing	Learning about depression and inactivity, and identifying and planning small enjoyable activities
Strengthening social support	Discussing a range of social support resources and making plans to increase social support
Staying well	Reviewing all of the mechanisms of action in the prior four sessions

Training materials and content were adapted with peer navigators and based on formative qualitative findings to enhance relevance to urban refugee youth in Kampala. The WHO suggests making small changes to case examples such as relatable problems and social support–seeking examples. Peer navigators will deliver the five group sessions with groups of up to 20 participants.

We will provide participants in Arm 1 and Arm 2 with additional mHealth support, including SMS bidirectional check-ins, SMS mental health literacy messages, and supportive WhatsApp conversations. The aim of this mHealth support is to ensure that any participant in the VR/GMP+ group who needs additional mental health support or information will receive it, and that mHealth will also reinforce the information and access to resources shared in the intervention arms. The SMS program

includes weekly SMS blasts designed to reinforce information provided in the VR on mental health literacy [18], psychological first-aid information and skills [34], and self-compassion activities [52]. There are also weekly bidirectional check-ins asking participants "how are you?" in their preferred language; any participant who responds they are not well or requests help will be referred within 48 hours to a social worker based at YARID as well as their peer navigator. This SMS platform is hosted by WelTel [53,54], a nonprofit agency [55]. The WelTel system will manage this bidirectional SMS intervention on their structured mobile phone platform on which all SMS interactions will be logged. To provide additional group-based support to participants, we will invite Arm 1 and Arm 2 participants to take part in weekly WhatsApp group discussions between peer navigators with ~25 participants assigned to each peer navigator. These discussions will be moderated by peer navigators, a research assistant, and a trained research coordinator, and will address the same content regarding mental health literacy, stigma, and stress-coping strategies covered in the VR intervention.

Arm 3: Waitlist Control

Participants in this arm will be waitlisted and receive the GPM+ intervention after implementation and follow-up. The waitlist control group will complete a fourth survey at 8 weeks to evaluate changes after participating in GPM+. In the meantime, the waitlist control group will have access to YARID resources and referrals as needed for mental health support.

Outcomes

Primary Outcome

The primary outcome measured in this trial is *depression*, which will be measured using the Patient Health Questionnaire-9 [56].

Secondary Outcomes

Secondary outcomes include (1) *mental health literacy*, assessed with a modified depression literacy scale validated in LMICs [36-38]; (2) *attitudes toward mental health help–seeking*, assessed with the Inventory of Attitudes Towards Seeking Mental Health Services [57]; (3) *adaptive coping strategies*, assessed with the Kidcope [39] and Self-Compassion Scale for Youth [40]; (4) *mental health stigma*, measured using the Brief Version of the Internalized Stigma of Mental Illness scale [41]; (5) *mental well-being*, assessed with the WHO-Five Wellbeing Scale [42]; and (6) *level of functioning*, measured using the WHO Disability Assessment Schedule [43].

Sample Size and Power Analysis

The study aims to include 330 participants, with 110 per study arm. Cluster sizes of 90 per group (n=270) are required to have 80% power ($P<.05$) to detect a difference of ~3 points in mean depression score (moderate effect size) at a level of significance of $α=.05$, assuming an intraclass correlation of 0.01 and SD of 7. With 10% attrition, 297 participants (99 per cluster) are required. Computations were performed using RStudio version 3.3.0, based on formulae for multiple comparisons of proportions and adjusted for design effect [58].

Data Collection and Management

Data will be collected using a structured survey on cell phones or tablets in all study languages by trained research assistants using the SurveyCTO app (Dobility), a secure platform that automatically encrypts data, which will be uploaded using a Secure Sockets Layer (SSL) certificate to a password-protected server. SurveyCTO allows for offline data collection, facilitates multilingual data collection, and has branching logic and consistency checks. To enhance confidentiality, all participants will be assigned a unique participant ID and no personal identifying information will be collected. Only study staff will have access to the data set on a need-to-know basis for the purpose of data management and outcome reporting. All data sets will be saved on a password-protected server.

Data Analysis Plan

Analysis and reporting for the cRCT (Phase 2) will be conducted in accordance with CONSORT (Consolidated Standards of Reporting Trials) guidelines [59] (Multimedia Appendix 1). The analyst will be blinded to group allocation. A flow diagram will be used to illustrate patient flow (screening, randomization, allocation, follow-up). Baseline data will be reported for all three groups and summarized as mean (SD) or median (IQR) for continuous variables, and as counts and number (%) for categorical variables. The primary analysis will be intention-to-treat analysis (data from participants will be analyzed according to their allocation, irrespective of whether they actually received that intervention).

We will perform multivariable regression analyses, adjusting for the outcome measure at baseline and stratification variables. For the primary analysis to assess differences among the three intervention conditions on the outcomes, indicator variables will include intervention assignment and a vector of baseline covariates (eg, sociodemographics). Analyses will adjust for multiple comparisons across the three intervention conditions using the Fisher protected least-significant difference test, first assessing differences between intervention groups and, if the Omnibus *F* test is significant, subsequently calculating pairwise comparisons.

Between-group comparisons will be performed using multilevel mixed-effects logistic or linear regression models (to account for clustering) depending on which outcome is being evaluated. For these models, the intervention group will be entered as a fixed effect. The significance level will be set at $α=.05$. The results will be expressed as odds ratios or mean differences, as appropriate, accompanied by 95% CIs and *P* values. We will perform an adjusted analysis for the primary outcomes to investigate the role of various covariates on the relative effect. Covariates (eg, age) will be entered as a block. We will explore gender differences in primary and secondary intervention outcomes. Given that the outcomes of this study are related to behavior change and the trial is of a short duration with minimal risks, a data monitoring committee was not deemed necessary.

Ethical Considerations

The Tushirikiane4MH trial protocol has been approved by the Research Ethics Boards University of Toronto (May 12, 2021), Mildmay Uganda Research Ethics Committee (June 24, 2021),

and Uganda National Council for Science & Technology (January 6, 2022). The trial is registered at ClinicalTrials.gov (NCT05187689).

The protocol for the study was developed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Statement [60,61]. The study population includes young adults (aged 16 years and over) capable of providing informed consent. We received ethics approval to allow youth aged 16-17 years to participate without parental consent; this is a common approach to reduce barriers to youth participation in health research on potentially sensitive topics [62,63].

All participants will receive information about the study before being enrolled to ensure understanding of rights for refusal/withdrawal, study processes, and expectations. To ensure the protection of human subjects, all participants will be provided with sufficient time to give written voluntary consent to participate in the study. All informed written consent processes will occur in a private room at a location provided by YARID. The participant will read the consent form themselves or a peer navigator will read the informed consent text aloud in a language comfortable to the participant (French, English, Luganda, Kirundi, Kinyarwanda, or Swahili) and will ask if the participant has any questions and will answer their questions. A peer navigator will ask the participants to sign the consent form or provide a thumbprint to indicate their consent. The consent form will in no way be connected with data collected and will be destroyed 5 years after data collection is completed.

At any time during the study data collection period, participants can withdraw from the study before completing the interview with no adverse consequences on the care or services they receive. All data will be stored on password-protected computers. To maintain confidentiality, all participants will be given a unique Case ID, and no personal identifying information will be stored with the study data.

The risks associated with the Tushirikiane4MH trial are reasonable. All intervention components have been designed as youth-friendly, based on the principles of psychological first aid and evidence with adult populations. Qualitative findings informed intervention design and the interventions were piloted with youth peer navigators. Although these interventions are not expected to cause psychological distress, this risk will be shared with participants. Peer navigators have been trained in psychological first aid, and trained counselors will be on site throughout the intervention. All participants will also be provided with a list of community resources.

Any adverse event will be reported by the peer navigators to the research assistant, who will fill out an Adverse Event Reporting Form and Adverse Event Narrative Form if appropriate. Adverse events can also be directly reported by study participants to YARID and the study team. Any adverse event requiring a narrative form will be reported to the principal investigators within 24 hours.

Data Sharing

The final data set will be shared between the Uganda-based research team and members of the Toronto-based research team via a secured, encrypted, and password-protected system. The final deidentified data set will be available to users who enter a data-sharing agreement and secure research ethics approval via a research ethics board amendment with the University of Toronto.

Results

The VR scenario, WelTel SMS content, and adaptation of GPM+ were conducted between January and May 2022. Research staff, including peer navigators, were trained in VR use, mental health literacy, and GPM+ in March 2022 and May 2022 in person, and virtually from May to June 2022. Baseline data collection was conducted in April 2022 and the intervention was conducted in June 2022. The first follow-up survey was conducted in August 2022 and the final follow-up survey will be conducted in November 2022. Any important protocol modifications will be included as amendments in Research Ethics Board submissions and updated on ClinicalTrials.gov.

Discussion

Projected Significance

Trial findings will generate novel evidence on promising low-cost mental health interventions delivered by and for refugee and displaced youth. Specifically, we anticipate finding that VR and GPM+ conducted on their own are feasible and will each be associated with improved mental health outcomes in comparison with standard of care. We also anticipate finding that when conducted in tandem, VR and GPM+ will be associated with greater improvements in mental health compared to when they are conducted separately and when compared with the standard of care. Importantly, the findings will enhance understanding of how VR interventions, effective in supporting adult mental health in high-income contexts [26], could be effective among urban refugee youth in LMICs. Study findings will also advance knowledge of how the WHO GPM+, effective with adults [30,31], could potentially benefit adolescents aged 16 years and older [27]. In sum, the findings will build on the limited evidence base of interventions to improve refugee youth mental well-being [3].

By measuring the effectiveness and feasibility of these novel, low-cost mental health innovations, this study has the potential to inform research, policy, and practice in the health, education, and social development sectors. Community partners and knowledge users will be involved in all stages of trial design, conduct, analysis, and dissemination. Findings regarding the effectiveness of GPM+ or VR in supporting mental health outcomes of refugee and displaced youth can inform the scale-up of such mental health interventions for other refugee youth in Uganda—both urban- and refugee settlement–based—as well as other urban forcibly displaced youth in East Africa.

Dissemination

Irrespective of the study findings, trial results will be published in peer-reviewed scientific journals following international authorship guidelines, and will be presented to academics and researchers at key scientific conferences. The findings will be disseminated through a variety of methods, including community reports and policy briefs, to a range of stakeholders, including academics and researchers in mental health, international collaborating organizations such as the United Nations High Commissioner for Refugees, Ugandan Ministries of Health and Education, implementing partners in adolescent health and social work, and refugee community organizations and members. We will also create a short video on how to implement the findings into practice, as well as a graphic novel depicting the intervention and findings.

Strengths and Limitations

Strengths of this study include its focus on identifying effective intervention approaches for improving mental health among urban refugee and displaced youth in Kampala, Uganda, an understudied population in mental health research. Another strength is adapting and evaluating evidence-based approaches for a different context (eg, adapting VR for the LMIC context) and different age groups (eg, adapting GPM+ for refugee youth). Finally, our study will conduct gender- and age-stratified analyses, providing insight into gender or age differences in intervention effectiveness. The primary study limitations are loss to follow-up due to the mobile nature of the population and resulting missing data points.

Authors' Contributions

Study design: CHL, MO, NK, DKM, RH, PK, LM. Data collection: CHL, MO, JLK, LG, NK, RH, DKM, AN, BK, TK. Data management: CHL, MO, JLK, LG, RH, DKM, AN, BK, RL. Manuscript writing: CHL, LG, JLK. Manuscript editing: CHL, MO, JLK, LG, NK, RH, DKM, AN, BK, PK, TK, RL, LM.

Conflicts of Interest

RL is an academic physician-researcher and also has interests in a nonprofit and private company social enterprise, WelTel Inc, that develops and provides digital health software. He is not being paid or otherwise compensated by WelTel for this project. No other authors declare a conflict of interest.

Multimedia Appendix 1
CONSORT-EHEALTH checklist (V.1.6.1).
[PDF File (Adobe PDF File), 664 KB - resprot_v11i12e42342_app1.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
cRCT: cluster randomized controlled trial
DRC: Democratic Republic of Congo
GPM+: group problem management plus
LMIC: low- and- middle-income country
mHealth: mobile health
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SSL: Secure Sockets Layer
VR: virtual reality
WHO: World Health Organization
YARID: Young African Refugees for Integral Development

Protocol

A Text-Based Smoking Cessation Intervention for Sexual and Gender Minority Groups: Protocol for a Feasibility Trial

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Abstract

Background: Smoking among sexual and gender minority (SGM) groups, which include lesbian, gay, bisexual, transgender, and queer individuals, has been reported to be highly prevalent. This is attributed to several factors, including minority-specific stress and targeted tobacco marketing. Therefore, this population is at an increased risk for tobacco-related diseases. SMS text messaging programs have been found to be effective for smoking cessation and appeal to traditionally hard-to-reach populations over other interventions. It has also been suggested that targeted and tailored interventions could be more effective among SGM smokers because they can be designed to assure a safe, validating health care environment that enhances receptivity to cessation.

Objective: The aim of this study is to develop SmokefreeSGM, a text-based smoking cessation program tailored to and tested among SGM smokers.

Methods: The study consists of three phases, culminating in a feasibility trial. In Phase 1, our research team will collaborate with a Community Advisory Board to develop and pretest the design of SmokefreeSGM. In Phase 2, the tailored text messaging program will be beta tested among 16 SGM smokers. Our research team will use a mixed-methods approach to collect and analyze data from participants who will inform the refinement of SmokefreeSGM. In Phase 3, a feasibility trial will be conducted among 80 SGM smokers either enrolled in SmokefreeSGM or SmokefreeTXT, the original text-based program developed by the National Cancer Institute for the general population. Our research team will examine recruitment, retention, and smoking abstinence rates at 1-, 3-, and 6-month follow-up. Additionally, a qualitative interview will be conducted among 32 participants to evaluate the feasibility and acceptability of the programs (SmokefreeSGM and SmokefreeTXT).

Results: This study received approval from The University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects to begin research on August 21, 2020. Recruitment for the beta testing of SmokefreeSGM (Phase 2) began in January 2022. We estimate that the feasibility trial (Phase 3) will begin in September 2022 and that results will be available in December 2023.

Conclusions: Findings from this research effort will help reduce tobacco-related health disparities among SGM smokers by determining the feasibility and acceptability of SmokefreeSGM, an SGM-tailored smoking cessation intervention.

Trial Registration: ClinicalTrials.gov NCT05029362; https://clinicaltrials.gov/ct2/show/NCT05029362

International Registered Report Identifier (IRRID):   DERR1-10.2196/42553

KEYWORDS

smoking cessation; sexual and gender minorities; LGBTQ+; SMS text messaging; mobile health; mHealth

Introduction

Background

Cigarette smoking among sexual and gender minority (SGM) groups in the United States is higher than heterosexual and cisgender individuals. Nearly 1 in 4 SGM adults smoke cigarettes compared with about 1 in 6 heterosexual adults [1]. The National Institutes of Health define SGM as an umbrella term that includes individuals who identify as lesbian, gay, bisexual, asexual, transgender, Two-Spirit, queer, or intersex. It also includes individuals with same-sex or same-gender attractions or sexual behaviors and those with a difference in sex development, as well as those whose sexual orientation, gender identity or expression, or sex development is characterized by nonbinary constructs [2]. The high rate of cigarette smoking among SGM groups is attributed to several factors, including additional stress due to stigmatization and discrimination, as well as targeted tobacco marketing [3]. Therefore, this population is at an increased risk for developing tobacco-related health conditions, including heart disease and stroke. Because smoking accounts for at least 30% of all cancer deaths, SGM individuals are also at an increased risk of suffering from this fatal disease as a result of their smoking behaviors [4].

It has been suggested that targeted and tailored interventions could be more effective among SGM smokers because they assure a safe, validating environment that enhances receptivity to cessation [5,6]. The few reported smoking cessation interventions for SGM smokers are minimally tailored, lack a control group, lack objective verification of self-reported quit rates, or are based on group interventions [7-10]. Mobile health (mHealth) programs that use SMS text messaging have been found effective for smoking cessation and other behavior change interventions [11-13]. These programs are appealing to marginalized groups who experience barriers to smoking cessation interventions and who have high rates of mobile phone and text messaging use because they allow for self-management and discretion [11-14]. Although the number of people enrolled in text messaging programs for smoking cessation is increasing, no study has evaluated their feasibility, specifically among SGM smokers.

SmokefreeTXT is an automated, personalized, and interactive mHealth program for smoking cessation developed by the National Cancer Institute (NCI), which sends supportive text messages 2 weeks before and up to 6 weeks after a quit date. SmokefreeTXT has been successfully tested among the general population [15]. It has also been successfully tailored to special populations such as pregnant women, homeless individuals, and veterans [11,16-19]. However, theoretically-based smoking cessation treatments delivered via text messaging and focused on enhancing treatment engagement and targeting the specific needs of SGM smokers are needed.

This project is guided by a conceptual framework consistent with existing models and health outcomes, models of SGM health disparities, and social cognitive models of smoking cessation [20-24]. We hypothesize that sociodemographic features, particularly sexual orientation and gender identity, will determine level of stress, systematic harassment and discrimination that will thereby influence individuals' access to resources, experience of stressful events, and predisposed vulnerabilities. These factors will serve as immediate precipitants of smoking episodes.

The proposed project provides an advantageous opportunity to test the feasibility of a promising cessation practice for SGM smokers supported by mobile phone text messaging. SGM individuals have been identified as groups at elevated risk for cancer, in part because of their high smoking rates, which are largely reflected by the tobacco industry's long history of targeting SGM communities [4]. Furthermore, factors such as low rates of health insurance coverage, high rates of stress due to systematic harassment and discrimination, and a low level of SGM-related cultural competency in the health care system have negatively affected the health of SGM individuals, as well as their access to smoking cessation treatments, including counseling and medication [25].

The rapid increase in the number of people, including SGM individuals owning a mobile phone, has led to the development of new apps in the self-management of chronic diseases and behavior change interventions [26]. The proposed text-based smoking cessation intervention will include motivational messages or content specifically tailored to SGM participant characteristics to distract from cravings and will be sent based on participants' needs. While there is strong evidence that text-based tobacco cessation interventions help smokers quit smoking, no similar intervention has been conducted specifically among SGM smokers [27-29]. Reducing smoking prevalence among SGM individuals by implementing a cost-effective and tailored text-based smoking cessation intervention is a powerful cancer prevention strategy for this population.

Objective

The objective of the study is to develop SmokefreeSGM, an SGM-tailored version of SmokefreeTXT that will be tested among SGM smokers. This protocol proposes 3 aims, each corresponding to Phases 1, 2, and 3 of this study:

- Aim 1: to develop an SGM-tailored text-based smoking cessation program and assess the readability and acceptability of its text messages
- Aim 2: to beta test the design of SmokefreeSGM through a mixed-methods approach among 16 SGM adult smokers
- Aim 3: to conduct a two-arm (SmokefreeSGM vs SmokefreeTXT) randomized controlled trial for examining recruitment, retention, and smoking abstinence rates at 1-, 3-, and 6-month follow-up among 80 SGM smokers

A qualitative interview will be conducted for 32 participants to evaluate the feasibility (recruitment and retention rates) and acceptability of the programs.

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Methods

Study Design

Phase 1

SmokefreeTXT is a text-based smoking cessation program developed for the general population by the NCI. SmokefreeTXT is a personalized and interactive mHealth program that sends bidirectional text messages timed around a participant's quit date over 2 months. The text messages include pre- and postquit educational messages, peer ex-smoker messages, nicotine replacement therapy medication reminders, and relapse messages. Messages are based on social cognitive theory and are consistent with the US Public Health Service Clinical Practice Guideline [30,31]. Messages are interactive and prompt users to track smoking, report cravings, and provide their smoking status. Participants who report that they have not quit are routed into setting a new quit date. SmokefreeTXT offers both outgoing messages and on-demand help through the use of keywords, including CRAVE (user will receive help with cravings by having a reminder of why they should not smoke), MOOD (user will receive a positive message when having a difficult day), SLIP (user will receive extra encouragement to get back on track), and SMOKEFREE STATUS (indicates if the user has smoked or not by the time they receive the text message).

To develop the SmokefreeSGM, our research team will collaborate with self-identified SGM individuals, tobacco specialists, and scientists and clinicians engaged in SGM research. This will allow us to create encouraging and motivational messages that address unique psychosocial stressors for SGM smokers such as elevated general stress and minority-specific stress (ie, internalized homophobia, sexual orientation concealment, and discrimination events). A new keyword, STRESS, will be created to prompt these additional set of text messages that will be sent from a fictitious peer SGM ex-smoker named Alex who offers evidence-based advice on quitting. The messages sent by Alex will be based on real-life experiences of SGM ex-smokers who understand the user's barriers in order to create a welcoming environment.

Phase 2

Once the SmokefreeSGM program is developed, it will be beta tested among 16 SGM smokers through a mixed-methods approach.

Phase 3

A feasibility trial will be conducted to examine recruitment, retention, and smoking abstinence rates at 1-, 3-, and 6-month follow-up among 80 SGM smokers randomized to either the SmokefreeTXT or SmokefreeSGM program.

Study Population and Recruitment Strategy

Phase 1

Not applicable, as no human subjects will be involved.

Phase 2

The SmokefreeSGM text messaging program will be beta tested among 16 self-identified SGM individuals currently living in Texas. Various efforts on behalf of our research team will be made to identify individuals suitable for enrollment in the study. Flyers offering help to SGM individuals interested in quitting smoking will be distributed at local community organizations and health care facilities working with and for this population in Texas. Information about this part of the study will also be posted in local newspapers and magazines, as well as on web pages and social media sites of local community organizations, health care facilities, and SGM venues (eg, bars and restaurants).

Phase 3

A total of 80 SGM individuals currently living in Texas will be recruited to participate in the feasibility trial through similar efforts to those used by our research team in the beta test (Phase 2). Participants will be randomized into the SmokefreeTXT (n=40, 50%) or SmokefreeSGM (n=40, 50%) text messaging program. Efforts will be made to proportionally balance the study sample with each one of the major SGM subgroups—lesbian, gay, bisexual, and transgender individuals.

Eligibility Criteria

Phase 1

Not applicable.

Phases 2 and 3

The inclusion criteria for participants in the beta test (Phase 2) and feasibility trial (Phase 3) are as follows: (1) self-identifies as an SGM individual, (2) is aged ≥18 years, (3) smokes 5 or more cigarettes per day (smoking status biologically confirmed by saliva cotinine test), (4) has an interest in quitting smoking in the next 15 days, (5) has a cellphone number with an unlimited short messaging service plan, (6) has US mailing and email addresses, and (7) provides positive cotinine saliva test results.

The exclusion criteria for participants in study Phases 2 and 3 are as follows: (1) has a prepaid cell phone, (2) has a cellphone number that does not work or is registered to someone else, (3) is pregnant or breastfeeding, (4) has contraindication for nicotine patches, (5) has current use of tobacco cessation medications, (6) is enrolled in another smoking cessation study, (7) is a non-English speaker, and (8) has inadequate equipment or device (eg, webcam, speakers, and mic) for participating in telehealth sessions. It is important to note that those individuals participating in Phase 2 of the study will be excluded from Phase 3 to reduce the risk of bias.

Data Collection

Phase 1

After completion of the text library for SmokefreeSGM, the Flesch-Kincaid Grade Level and the Dale-Chall scores will be calculated using a web-based tool (datayze.com) to determine the readability of each text message. The Flesch-Kincaid Grade Level assesses the approximate reading grade level of each text message based on sentence length (average number of words in a sentence) and word length (average number of syllables in

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a word) [32]. The Dale-Chall score assesses the readability of text based on a list of 3000 words commonly understood by 4th graders [33]. Both measures will help us determine whether the average adult would be able to comprehend the content of the SmokefreeSGM text messages and allow us to make changes where necessary.

The text library will then be input into a web-based survey to collect suggestions and feedback from our advisory board members (eg, SGM smokers, tobacco specialists, and SGM researchers and clinicians). Experts will rate each text message on a scale of 1 to 5, where 1 indicates *Totally Unacceptable* and 5 indicates *Perfectly Acceptable*. The mean, median, and range of these values will be calculated. Experts will also be able to provide additional feedback in a designated comment box. Data collected from these surveys will help us determine what revisions are needed. The revised text library will be input into a text messaging platform and internally tested by research staff.

Phase 2

Immediately following confirmation of the participant's eligibility and enrollment into the study, a baseline assessment will be completed, and an 8- or 10-week supply of nicotine patches (according to each study participant' smoking status) will be sent to the participant via mail. The baseline web-based questionnaire will include items assessing demographic (eg, age, gender, sexual orientation and gender identity, race or ethnicity, and education) and smoking characteristics of the participants (eg, lives with one or more smokers in the household, cigarettes smoked per day, and past quit attempts). Nicotine dependence will be measured with the Fagerstrom Test for Nicotine Dependence [34].

A follow-up survey at 1 month after the participant's quit date (6 weeks following screening) will include measures of smoking cessation through self-report of 7-day smoking abstinence [35]. A 10-item questionnaire, the System Usability Scale (SUS), will be used to assess the usability of SmokefreeSGM. This will be complemented by a structured interview where qualitative data on the usability will be collected among study participants. For this purpose, the SUS will be used because it is a quick and cost-effective yet accurate approach to assessing usability [36].

Phase 3

Individuals interested in the study will be screened and if eligible, consented. Those individuals enrolled into the study will be randomized into either the SmokefreeTXT (n=40) or SmokefreeSGM (n=40) text messaging program. All participants will receive their 8- or 10-week supply of nicotine patches via mail. The baseline survey will include the same items included in Part 2. Recruitment will be assessed as explained above. Retention and smoking abstinence rates will be examined at 1-, 3-, and 6-month follow-up. Smoking abstinence outcome will be defined as 7-day smoking abstinence along with a negative saliva cotinine test.

Additionally, structured web-based interviews will be conducted with a subsample of 32 study participants completing the feasibility trial. Participant satisfaction with the program will be assessed by a series of questions in which participants will be asked to comment on the text messages (eg, "Could you tell us if the program was helpful or not in getting you to try to quit?" "What ideas on how to quit did you like the most about the program?" and "Would you recommend the program to a friend interested in quitting? Why?"). Participants will be also asked to make suggestions for improving the program and note which features they liked and disliked. Questions will be open-ended to elicit qualitative feedback. Some open-ended probes will be used to learn why a participant responded a certain way to the keywords; for example: "When and why did you text CRAVE?" "How would you improve some of the text messages?" "How do you feel about your ability to remain smoke-free?" and "Can you tell me if there was anything confusing about the texts?" Concepts will be discussed with the study participants until data reach saturation.

Analysis

Phase 1

The Flesch-Kincaid Grade Level test uses a formula that depends on sentence length and word length. The formula is as follows: 0.39 x (words/sentences) + 11.8 x (syllables/words) – 15.59. The resulting score corresponds with the grade level needed to understand the content. A resulting score ≥80 means that the text message is easy or very easy to read [32]. The Dale-Chall score is another readability test that uses a list of 3000 words that groups of 4th grade American students could reliably understand. A score of <7.0 means that the text is easily understood by an average 8th grade student or lower [33]. Our research team will verify that each text message created for the SmokefreeSGM program has a Flesch-Kincaid Grade Level score of ≥80 and a Dale-Chall score of <7.0 to ensure that they will be easily understood by all users.

Phase 2

The recruitment rate will be defined by dividing the number of SGM smokers who consent and complete the baseline assessment by the number of SGM smokers who are approached and invited to participate in the text-based program. Similarly, the retention rate will be defined by dividing the number of SGM smokers who remained in the text-based cessation program and completed the 1-month assessment by the number of SGM smokers recruited. Additionally, 1 month following the quit date, participants will take part in a structured interview to collect both quantitative and qualitative data using the SUS. After each participant assigns points—Strongly Disagree (1) to Strongly Agree (5)—to each of the 10 items of the scale, a score is calculated. SUS is scored on a 0-100 scale. A score of 74 or more will indicate that SmokefreeSGM has high perceived usability [36]. It is important to note that after the participants score each SUS item, the moderator will ask "Why did you assign this many points to this question?" to obtain the corresponding qualitative data. The audio recordings from these responses will be transcribed for qualitative analysis. Qualitative data will be analyzed using a descriptive framework approach. which allows for the exploration of prior concepts and for new themes to emerge [37]. Transcripts will be read and reread to gain familiarity with the subject. Analysis of the transcripts will be based on data grouping, creation of a code guide, and identification of themes from the narrative text. The code guide

will be drawn from the domains shaped by the discussion guide and themes that will emerge during the study. The method of constant comparison (comparing concepts across categories to identify links, patterns, connections, and differences) will be used to identify themes within the data. Themes will be compared with theoretical constructs in the conceptual framework to determine if the model captures the phenomena of interest and to inform the refining of the SmokefreeSGM design.

Phase 3

The recruitment rate will be calculated as explained above. Retention rate will be defined by dividing the number of SGM smokers who remained in the text-based cessation program and completed the 3- and 6-month assessments by the number of SGM smokers recruited. The recruitment and retention rates will be calculated along with CIs for both arms (both arm-specific and combined arms). Targeted recruitment and retention rates are not considered in this protocol paper as they vary considerably in smoking cessation interventions (4% to 95% and retention rates from 36% to 100%) [38]. However, we will use *t* test or Mann-Whitney, on the one hand, or chi-square or Fisher exact test, on the other, to compare baseline demographic variables between SGM smokers and those who refuse to participate or drop out from the study. Additionally, we will assess the predictors of recruitment and attrition rates across study participants.

Smoking abstinence outcome will be defined as 7-day smoking abstinence along with negative saliva cotinine. Because abstinence is a binary variable (yes or no) the primary method of analysis will be a simple posttest analysis among SGM smokers with a generalized logistic mixed model, using a random intercept to incorporate the intrasubject correlation. Important covariates that will be used to adjust for potential baseline differences include age, level of education, biological sex, marital status, gender identity or sexual orientation, race or ethnicity, working status, health insurance, income, years of smoking, smoking initiation, nicotine dependence, use of other tobacco products, and living with other household members who smoke. Odds ratio of smoking abstinence in the SmokefreeSGM group relative to the SmokefreeTXT group will be used to estimate effect size. Using logistic regression, abstinence will be regressed onto a dummy coded SmokefreeTXT versus SmokefreeSGM group indicator, with the exponentiated coefficient of the group indicator yielding the odds ratio.

Once the smoking cessation intervention concludes and in order to quantitatively assess engagement, a series of 32 individual interviews will be conducted with individuals previously enrolled in the feasibility trial. In this sense, the number of text messages a participant sends to the computer system, including replies to the SmokefreeTXT and SmokefreeSGM programs and keywords used, will be totaled, and averages will be calculated across participants. The total will not include use of the keyword STOP, a keyword for unsubscribing from the program. The percentage of participants who use this keyword will serve as an indicator of program disengagement. We will examine means and standard deviations of the number of text messages over the course of the 6-month program in each arm. We will use *t* test or Mann-Whitney to compare the average numbers of text messages from the two arms.

Transcripts from the qualitative interviews will be analyzed following the procedures described for the structured interviews in Part 2.

Quantitative data will be analyzed using computer software (Excel [Microsoft Corporation], SPSS [IBM], R [R Foundation], SAS [SAS Institute], or STATA [StataCorp]). Qualitative data analysis will be performed using computer software (ATLAS.ti), which will significantly reduce the amount of time needed for coding and categorizing qualitative data.

Ethics Approval

This study received Institutional Review Board approval (HSC-SPH-0318) from The University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects.

This study involves no more than minimal risk to subjects.

Results

This study has been designed to develop an SGM-tailored smoking cessation text program (SmokefreeSGM) and test its feasibility among SGM smokers. Study findings will contribute to reducing tobacco-related health disparities among SGM groups.

Principal investigator (IT-M) received approval from UTHealth Committee for the Protection of Human Subjects to begin research on August 21, 2020, and was awarded funding from the NCI on September 1, 2020. The development of the SmokefreeSGM program has been completed, and recruitment for beta testing began in January 2022. We estimate that recruitment for the feasibility trial will begin in September 2022 and that results will be available in December 2023.

Discussion

Overview

We anticipate that the findings of our feasibility trial will support the need for SGM-tailored smoking cessation interventions and mHealth tools. SmokefreeSGM is not only cost-effective and user friendly but allows for personalized care and self-management. Findings from our feasibility trial will be used to design and implement large-scale mHealth-based interventions to address the high prevalence of cigarette smoking and tobacco-related health disparities among SGM individuals. Additionally, our findings will help inform future text-based smoking cessation studies for SGM groups and other marginalized populations and contribute to the body of evidence for mHealth behavior change interventions.

Generalizability and Limitations

While we have limited recruitment to SGM individuals living in Texas, the state's diversity enhances the generalizability of our findings. Texas ranks sixth in the country for highest diversity index, a measure of the probability that 2 people chosen

at random will be of different racial and ethnic groups [39]. Furthermore, a recent analysis found Texas to be the second most diverse state in the country when accounting for the following categories: socioeconomic diversity, cultural diversity, economic diversity, household diversity, religious diversity, and political diversity [40].

We recognize that excluding Spanish speakers limits the potential generalizability and reach of our text-based smoking cessation program, considering that Latinx people represent approximately 40% of the total population in Texas [41]. However, we do believe that developing and delivering an SGM-tailored intervention in 2 languages (English and Spanish) will be the logical next step in our research programs.

We implemented procedures to limit biases that arise from conducting a randomized controlled trial. While the investigators will be aware of the study arm (SmokefreeTXT or SmokefreeSGM) that participants are enrolled in, participants will be masked to that information in order to mitigate performance bias. We will also be randomizing participants to the intervention conditions to help limit the influence of confounders and mitigate selection bias. Our outcome measures will rely on saliva cotinine tests, which will deter social desirability bias from incorrect self-reported cessation status from participants who have not quit smoking. To account for attrition bias due to possible differences in the number of withdrawals between study arms, we will include all participants who were randomized into the study in our data analysis, as opposed to only those who completed the entire intervention.

Regarding our proposed timeline, it should be noted that our study was first delayed because of the COVID-19 pandemic. This required us to revise and resubmit our protocol to account for data collection being moved to a virtual environment. Our efforts were also interrupted by the winter storm that impacted Texas in February 2021.

Data Availability

Data sharing is not applicable for this article as data collection has not been completed, and data sets have not yet been generated for analysis in the current study.

Conflicts of Interest

LCA receives royalties for the sale of Text2Quit from George Washington University.

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Abbreviations

mHealth: mobile health
NCI: National Cancer Institute
SGM: sexual and gender minority
SUS: system usability scale

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<u>Protocol</u>

Comparison of Sun Protection Factor (SPF) 30 Persistence Between Inorganic and Organic Sunscreen in Swimmers: Protocol for a Multicenter, Randomized, Noninferiority, Split-Body, Double-Blind Clinical Trial

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Abstract

Background: Outdoor swimming athletes are often exposed to undesirable environmental conditions such as long-term sun exposure. The risk of sunburn can still occur in this population due to the loss of sunscreen and an increase in the sensitivity of the skin to ultraviolet rays, particularly ultraviolet B, in wet conditions. Some previous trials showed that organic sunscreens had a longer shelf-life than inorganic sunscreens after exercise due to their characteristics to bind better with the skin layer. Meanwhile, inorganic sunscreens tend to form layers on the skin's surface so that they can be more easily removed. To our knowledge, no studies evaluate sunscreens' resistance, either inorganic or organic, after exercising in Indonesia.

Objective: This study aims to evaluate the persistence of inorganic versus organic sunscreens used by swimmers. The primary objective is to assess whether the inorganic sunscreen is as good as the organic sunscreen in the field of the persistence of sunscreens after swimming for 1.5 hours.

Methods: This study is a randomized, split-body, double-blind, noninferiority, and multicenter clinical trial in Cikini, Jakarta, Indonesia. An estimated 22 athletes in each group, who aged 18-40 years and practice in the morning or afternoon, will be randomized using a computer-generated randomization method. We calculated the sample size using the difference in the average decrease in sun protection factor (SPF) levels that is considered significant based on the clinical judgment set by the researchers, which was 5. Neither the research subjects nor the researchers are aware of the type of sunscreen that will be applied. The hypothesis will be tested using paired-sample t test or Wilcoxon to assess the difference of SPF levels in each group between organic and inorganic sunscreens with SPSS (version 20.0; IBM Corp).

Results: This study has been approved by the Ethical Committee Faculty of Medicine Universitas Indonesia and is funded by the International Publication Grant from Universitas Indonesia. The enrollment process was completed in December 2020.

Conclusions: This study will test all procedures in preparation for conducting the main study, including several potential obstacles and challenges from the perspective of participating physicians and eligible swimmers. The study results will be disseminated through publications in a peer-reviewed journal with Open Access format. This study will provide information about SPF 30 persistence in sunscreens and the best type of sunscreen to be used while swimming, particularly for athletes.

Trial Registration: ClinicalTrials.gov NCT04618536; https://clinicaltrials.gov/ct2/show/NCT04618536?term=NCT04618536

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KEYWORDS

inorganic sunscreen; organic sunscreen; persistence; sun protection factor; sunscreen; swimmer; swimming

Introduction

Athletes who train and compete for outdoors such as in swimming pools are often exposed to undesirable environmental conditions, such as excessive humidity, hot and cold weather, windy conditions, and long-term sun exposure. These exposures cause some skin conditions [1]. In Indonesia, the average training time of an athlete is 5 times a week for 1.5-2 hours per day. Exercise is carried out in the morning and evening, when the ultraviolet index (UVI) was in the range of 1-4, meaning that taking shelter, wearing closed clothes such as hats, using sunscreen, and other sun protection manners should be done [2].

When swimmers train in an outdoor swimming pool, apart from being exposed to the pool water, they are also exposed to sun's radiation. Water could wash away the applied sunscreen, increasing the risk of photosensitivity [3]. In addition, there will be an increase in humidity in the stratum corneum, which functions to protect the skin from ultraviolet (UV) radiation [4,5].

In order to prevent sunburn, sun protection is needed, which can be achieved in several ways, such as using a sunscreen [4]. There are 2 types of sunscreens used based on the filter component, specifically organic and inorganic sunscreens. Organic sunscreen absorbs and prevents UV light to enter the epidermis; meanwhile, inorganic sunscreen works by reflecting and scattering radiation [6-8].

Some previous trials showed that organic sunscreens had a longer shelf-life than inorganic after exercise due to its characteristics to bind better with the skin layer. Meanwhile, inorganic sunscreens tend to form a layer on the skin's surface, so that it can be more easily removed. Until this time, there have been no previous studies regarding the resistance of sunscreens, either organic or inorganic, after exercising in Indonesia. Therefore, this study aimed to evaluate the persistence of sunscreen with a sun protection factor (SPF) 30 used by swimmers after 1.5 hours.

Methods

Study Aims and Objectives

First, this study aims to assess whether inorganic sunscreen is as good as organic sunscreen in the field of the persistence of sunscreens after swimming for 1.5 hours. SPF of inorganic and organic sunscreens will be calculated before and after swimming training. The difference between those times will be measured and compared. SPF will be quantified using the minimal erythema dose (MED) test that will be conducted in 2 days. Irradiation will be carried out on the first day, and MED results will be collected 24 hours after irradiation.

Second, we assess the SPF value resulting from in vivo method conducted before swimming. The SPF of either organic or inorganic sunscreens will be compared in the manner of MED. This trial also aims to know the decreasing level of SPF after swimming for 1.5 hours and which type of sunscreen provides higher persistence.

Study Design and Setting

This is a randomized, split-body, double-blind, noninferiority, multicenter clinical trial. The recruiting center is Cikini swimming pool, located in Jakarta, Indonesia. Recruitment began in August 2020 and ended in December 2020.

Research subjects were selected from Cikini swimming center in Jakarta, Indonesia. Data collection will be carried out on the same person using the split-body method. Each research subject will receive 2 treatments in the form of inorganic and organic sunscreens. The sunscreen application will be executed on the back area on the right and left for each treatment simultaneously.

Eligibility Criteria

Inclusion criteria are as follows: female or male swimming athletes aged 18-40 years, practicing swimming at least 3 times a week with a duration of 1.5-2 hours per practice in the morning or afternoon, willing to be the subject of research by signing the consent form, do not have skin diseases or a history of allergies to sunscreens.

Exclusion criteria were as follows: existence of skin lesions in the test area; undergoing phototherapy; using drugs with photosensitivity side effects; history of skin malignancy, photosensitivity reactions, or disease affected by UV rays; exposure to direct sunlight to the test area 24 hours before the study and during the study period; absence of an erythema response 24 hours after the radiation test; and erythema occurs in the entire test area box 24 hours after the radiation test.

Interventions

This study used a sunscreen made by PT Paragon Technology and Innovation. Both sunscreens are made in the form of an oil-in-water emulsion with the addition of a film-forming layer to maintain their resistance to water. Both organic and inorganic sunscreens have been tested using a simulator to determine their SPF levels.

Interventions will be conducted according to research manual of operations (Multimedia Appendix 1). First, we will mark the area on the back. In each area, we will draw 6 circles as locations for the irradiation test. We will apply as much as 2 mg/cm^2 sunscreen on each area within 2 stages, particularly at the first and second sessions. The sunscreen will be applied using a 1-cc syringe to cover all areas. After that, the sunscreen is spread using gloves, starting with circular and then followed by horizontal and vertical movements with light pressure. During

the smearing process, the smearing finger remains in contact with the skin for 35 seconds ±5 seconds. Gloves are changed at each smearing of a different test area.

At the first meeting, the back is marked with 3 areas (Figure 1). Sunscreens are applied to 2 areas; meanwhile, 1 area is left

without any sunscreen applied. After 20 minutes, the irradiation test is performed. The MED values were calculated 24 hours after irradiation to determine the SPF of each sunscreen. This procedure is carried out to take note of the basic data and the suitability of the SPF with data that are listed on the packaging.

Figure 1. Study procedure at the first meeting.
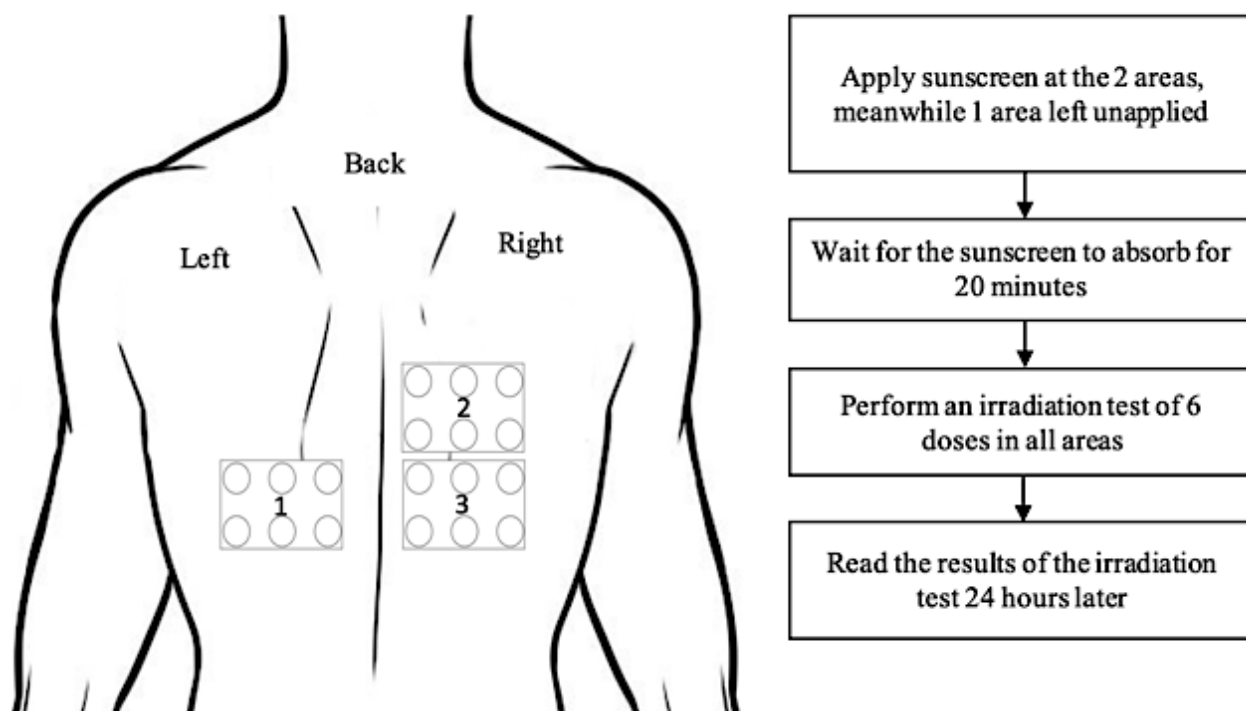
The second meeting will be conducted 1 week after the first one. At the second session, the back is marked with 4 areas (Figure 2). Both types of sunscreens are applied to all areas, where 2 areas are for the test before swimming and the other 2 areas are for the test after swimming. After 20 minutes, an irradiation test is performed. Athletes were then asked to carry out the exercise for 2 hours. After completion, the athletes were asked to dry their body without using a towel. The MED values were calculated 24 hours after irradiation to determine and compare the SPF of each sunscreen before and after the

swimming period. Swimming activities are carried out in the morning or evening when the UVI is in the range of 0-2.

The SPF measurement of pre- and postswimming was obtained using an in vivo method adapted with modifications from ISO 24444 in 2019 and COLIPA 2006 by bringing the instrument to the study site and in a room with a temperature of 18-26 °C. The back area will be marked into 3 sections measuring 8 cm×5 cm each. Each area will be marked with a 6×3 cm^2 perforated sticker according to The Daavlin Lumera probe.

Figure 2. Study procedure at the second meeting.
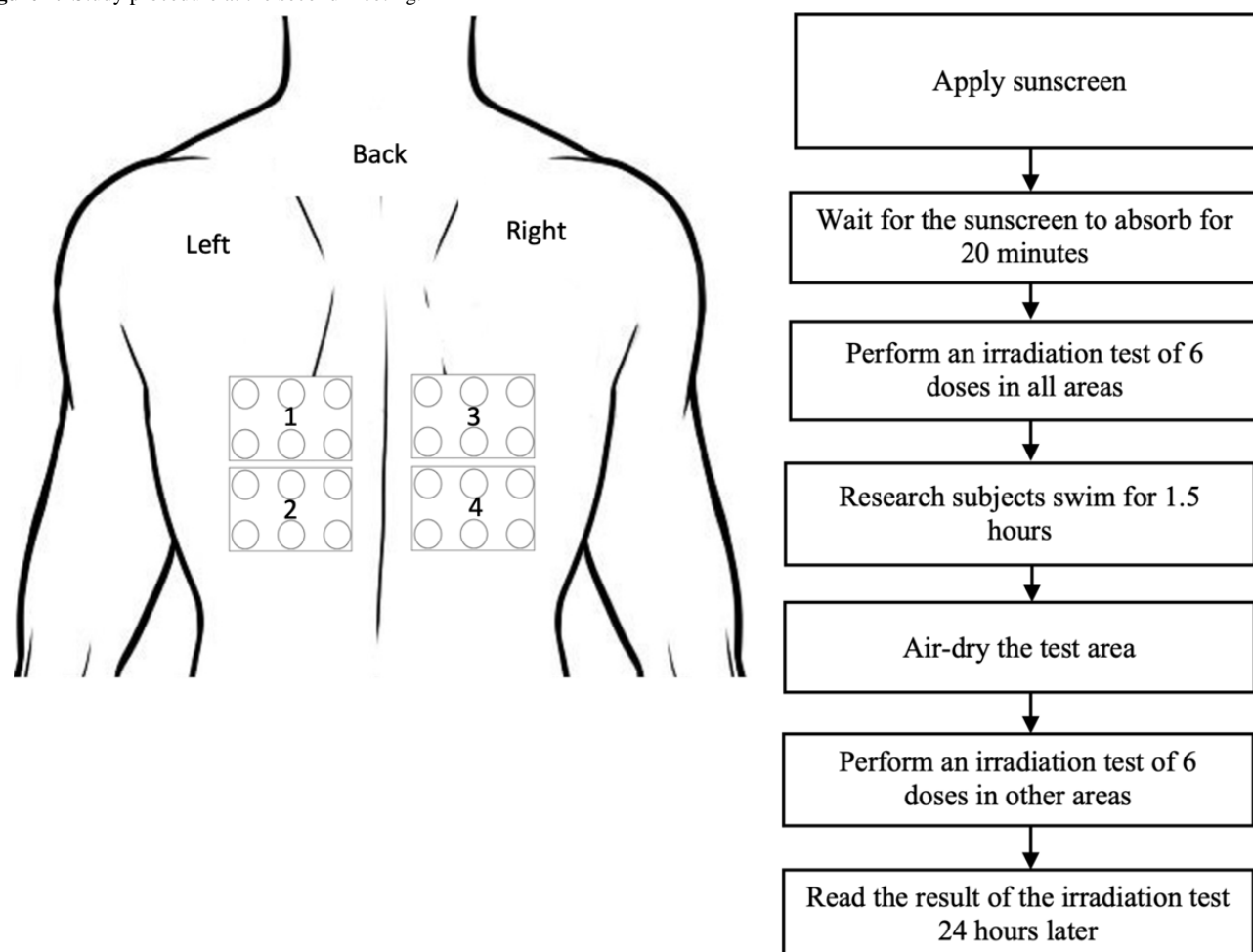
Discontinuation of Study Medication

The study medication must be discontinued if a suspected anaphylactic reaction or there are serious adverse events on the MED test square such as pain and formation of blisters during its administration or if the patient participation consent is withdrawn.

Standard Treatment for the Management of Adverse Events

If side effects occur in the form of blisters, pain, edema, or bright red erythema after irradiation, the research subjects will be treated with normal saline compresses for 15 minutes twice a day. The compresses can be continued with topical corticosteroids twice a day after bathing. Research subjects who experienced side effects will be excluded from the study, but their development will continue to be followed until they recover.

Outcomes

This study will provide mean differences in SPF by 4 to establish noninferiority with a 95% lower confidence limit. The hypothesis will be tested using paired samples *t* test or Wilcoxon test to assess the difference of SPF levels in each group between organic and inorganic sunscreens. The difference in SPF level will be declared to be no different if the *P* value for the paired *t* test or Wilcoxon test is >.05, and the upper limit of the CI does not exceed 4 SPF level. The persistence of organic and inorganic sunscreens is assessed using the following parameters: (1) the MED is defined as the dose of UV radiation that induces just perceptible erythema on exposed skin 24 hours after irradiation. This MED result will be stated in mJ/cm^2. (2) SPF is defined as the ratio of MED between protected and unprotected skin areas. The average SPF value from each type of sunscreen will be computed. The SPF value will be rounded up to one decimal in the index unit. (3) Persistence of SPF is defined as the lowest differences of SPF value before and after 1.5 hours swimming, stated in index unit.

Participant Timeline

Participants will be directed according to the timeline in Figure 3. The enrollment of study participants will take 7 days from the eligibility screen until the allocation. There will be 2 measurement sessions in this study with a time interval of 7 days. The SPF measurement for each session will be carried out 24 hours after the session.

Figure 3. The schedule of enrollment, interventions, and assessments. SPF: sun protection factor.

	Study period				
	Enrollment	Allocation	Postallocation		Closeout
Timepoint	$-t_1$ (D7)	0 (D0)	t_1 (D1)	t_2 (D8)	t_3 (D9)
Enrollment					
Eligibility screen	✓				
Informed consent	✓				
Allocation		✓			
Interventions:					
[Intervention A] Inorganic sunscreen			•———————————•		
[Intervention B] Organic sunscreen			•———————————•		
Assessments:					
Baseline data (Minimal Erythema Dose, Suitability of the SPF with the packing)	✓	✓			
SPF measurement before swimming				✓	
SPF measurement after swimming					✓
Adverse effects					✓

Sample Size Estimates

The calculation of the sample size was carried out using the continuous variable noninferiority test formula and the comparison of the mean of the 2 groups in pairs. From the 2 formulas, the largest number of samples was taken for further use in research. Based on the previous clinical trial and risk of dropout, we estimated a minimum sample size of 22 participants in each group. We calculated the sample size using the difference in the average decrease in SPF levels that is considered significant, based on the clinical judgement set by the researchers (ie, 5). In total, 22 experimental subjects and 22 control subjects will be adequate to reject the null hypothesis that the population means of the experimental and control groups are equal with a probability (power) of 0.9. The type I error probability associated with this test of this null hypothesis is 0.05.

Recruitment

Researchers will conduct COVID-19–related health protocols when collecting data in the context of preventing the pandemic spread. The body temperature and oxygen saturation of the research subjects will be checked before the examination. Each subject will be given a mask and face shield and asked to wash their hands. Researchers will provide the instructions to maintain a distance of at least 1 m during data collection. We will limit the number of subjects, only 4 athletes per day, to attend each sampling session. Before and after the test of each research subject, the tools will be cleaned using an alcohol swab.

Allocation of Sequence Generation and Concealment Mechanism

Treatment allocation is applied by computer-based randomization [9] to determine the back area and type of sunscreen provided [10]. The allocation data for each subject will be placed in a nontransparent, sealed envelope along with sunscreen. At the time of data collection, the envelope will be

opened, and sunscreen will be applied by the research assistant. Both randomization and treatment allocation will be carried out by statisticians who were not known by the researchers or the research subjects. The data will not be accessed until data collection for all subjects is completed.

Blinding

Treatment will be allocated by numbering the research subjects and including the right-back area as number 1 and the left-back area as number 2. We will use computer-generated randomization method [9] to determine the back area and the type of sunscreen to be given [10]. Neither the research subjects nor the researchers will be aware of the type of sunscreen that will be applied. The allocation data for each subject will be placed in a sealed opaque envelope. At the time of data collection, the envelope will be opened, and the sunscreen will be applied by the research assistant. Both randomization and treatment allocation will be carried out by statisticians. The data will not be accessed until data collection for all subjects is completed. The irradiation test and the assessment of results will be carried out by researchers.

Data Collection Methods

Before data collection begins, a preliminary study will be conducted to determine the value of broadband ultraviolet B (BB-UVB) MED on various skin types as well as to conduct inter-reviewer reliability tests. The data will be obtained from the literature and the tool guide and used as a source of information on the differences in the test doses upon irradiation. Therefore, a preliminary study will be conducted to equalize the dose of the irradiation test. Reliability testing will be performed to achieve same perception to assess erythema to ensure the quality of the data produced during the research. The test will be carried out by showing 11 skin photos to 3 assessors to determine the MED of each photo [11]. After that, the readings of the 3 assessors will be compared based on the intraclass correlation (ICC). An ICC value close to one, in this

study set at 0.9, indicates that the reviewer has the same understanding of the MED reading so that, in the study, the MED reading can be carried out by the researcher.

We will use inclusion and exclusion criteria to select the research subjects. We will provide explanations about the purpose and research method before research subjects sign a consent form. There will be 2 sessions in the study: the first one for basic data collection and research sample selection and the second one for providing treatment and executing the randomization process.

After the consent form is signed, we will conduct history taking, physical examination, and documentation. History of systemic disease, skin disease, daily activities, malignancies, and family history will be recorded. We will assess the skin type and identify any skin lesion on physical examination.

This study will use metal halide UV enhanced lamp BB-UVB in the active spectrum of 290-320 nm (The Daavlin Lumera) for UVB radiation test. The device will be calibrated before every data collection.

Data Management and Statistical Methods

All data obtained on the research status will be recorded for further coding. The collected data will be analyzed using SPSS (version 20.0; IBM Corp). The analysis will be carried out in 2 stages: descriptive and inferential analyses. In descriptive analysis, each variable is explained according to the type of data. The distribution of numerical data is assessed by looking at the normality value. The distribution of normal data is displayed with the mean and SD values. Categorical data are displayed in the form of frequency and percentage tables. In the inferential stage, the hypothesis will be tested using paired t test or Wilcoxon test to assess the differences in the decrease in SPF levels in each group of inorganic and organic sunscreens, and between the 2 groups. We used a 1-sided CI approach in the statistical analysis. The mean difference in SPF will be no different if the P value for the paired t test is >.05, and the upper limit of the CI does not exceed 4 SPF.

Data Monitoring

Since this is a short study, it does not require a data monitoring committee. The process and quality of patient recruitment, data entry, and a compilation of research data in the main database will be supervised by an independent assessor from the Clinical Epidemiology and Evidence-Based Medicine unit of Dr. Cipto Mangunkusumo Hospital (CMH), Faculty of Medicine Universitas Indonesia (FMUI), who is not involved in this study. Physicians will identify, evaluate, and handle any cases of major adverse events. These cases will be recorded and reported to, as well as be reviewed by, the Medical Ethics Committee Faculty of Medicine University of Indonesia.

Harms

Contrary to adverse effects or adverse drug reactions, which are all unpleasant and unintended responses to a study drug related to any dose, an adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the study

medication. After the eligible participants sign the written agreement and enroll themselves in the study, adverse events and adverse drug reactions will be gathered. All negative events that take place after study enrollment, throughout additional treatment, or during hospitalization owing to negative occurrences or negative reactions will be documented.

Any untoward medical occurrence at any dose that may result in inpatient or prolonged hospitalization, persistent or significant disability, medically significant events, life-threatening events, or death is considered a serious adverse event, and the subject will receive adequate treatment in addition to being recorded and reported to the Medical Ethics Committee of the FMUI. Unless there is a temporal relationship between the study medications or another protocol procedure and the events, or if the event is unexpected or unexplained given the subjects' clinical course, previous medical conditions, and concomitant medications, we will not report serious adverse events that occur after the study is discontinued. The serious adverse event form will contain a record of every serious adverse incident.

Auditing

We will create an audit committee from the Clinical Epidemiology and Evidence-Based Medicine unit of the Dr. Cipto Mangunkusumo Hospital, Faculty of Medicine Universitas Indonesia, which is separate from the research investigators of the main study. The International Conference Harmonization-Good Clinical Practice standards and the protocol will always be followed when observing and evaluating the study's quality.

Access to Data

The cleansed data sets will be accessible to the primary investigator. The primary investigator will also be able to request and have direct access to each site's data sets. Passwords will be used to safeguard the project data sets. Data will be distributed to project team members blinded of any participant identifying information in order to ensure confidentiality.

Ethics Approval

This clinical trial has been registered into ClinicalTrials.gov with identifier NCT04618536 and approved by the Clinical Research Ethics Committee of Faculty of Medicine Universitas Indonesia ID numbers 20-09-1037. Study results will be disseminated through peer-reviewed publications in the Open Access format.

Results

This study is funded by International Publication Grant from Universitas Indonesia. The enrollment process was completed in December 2020 and data analysis was conducted in January-March 2021. The study result is expected to be completed in January 2022 and submitted for publication in February 2022.

Discussion

We developed a protocol for a randomized, split-body, double-blind, noninferiority clinical trial to evaluate the

persistence of the inorganic versus organic sunscreens in the outdoor swimmers with estimated 22 participants in each group. This study aims to assess whether inorganic sunscreen is as good as organic sunscreen in the field of the resistance of sunscreens after swimming for 1.5 hours of training. The secondary objectives are SPF value resulting from in vivo method, which types of sunscreens provide higher persistence.

COVID-19 health protocol during the pandemic will be conducted. Before data collection begins, we will conduct a preliminary and inter-reviewer reliability testing. The instrument will be calibrated first before use at each session of data collection. All subjects had to sign the consent form if they are willing to participate. Irradiation test will be done and then followed by SPF measurement of the sunscreens developed by

PT Paragon Technology and Innovation in the form of an oil-in-water emulsion. The study medication must be discontinued if suspected adverse events occur or if patient consent for participation is withdrawn. Research subjects will be excluded from the study, but their recovery will be followed by researchers.

The collected data will be analyzed using SPSS (version 20.0; IBM Corp). This clinical trial has been approved by the ethic committee and registered to ClinicalTrials.gov. Study results will be disseminated through publications in the Open Access format. This study will provide information about SPF 30 persistence in sunscreens and the best type of sunscreen to be used while swimming, particularly to athletes.

Acknowledgments

Data Availability

The data sets analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Manual of operation as a summary of the study procedures for the research team.
[DOCX File , 422 KB - resprot_v11i12e42504_app1.docx]

Multimedia Appendix 2
Peer reviewed by University of Indonesia Q3 PUTI Grant / Hibah PUTI Q3 Universitas Indonesia Tahun 2020 (Jakarta, Indonesia).
[PDF File (Adobe PDF File), 68 KB - resprot_v11i12e42504_app2.pdf]

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Abbreviations

BB-UVB: broadband ultraviolet B
ICC: intraclass correlation
MED: minimal erythemal dose
SPF: sun protection factor
UV: ultraviolet
UVI: ultraviolet index

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Protocol

MIRA Rehab Exergames for Older Male Residents in a Care Home Center in Saudi Arabia: Protocol for a Feasibility Randomized Controlled Trial

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Abstract

Background: Physical activity leads to improvements in morbidity, mortality, and quality of life, especially when it is progressive, challenging, and regular. There is strong evidence that strength and balance exercises decrease the risk of falling. However, traditional exercises may be tedious and not very motivating for participants. Exergames have been found to increase engagement and enjoyment for older users.

Objective: This study will conduct a feasibility randomized controlled trial (RCT) on the use of MIRA Rehab Exergames among older male residents in a care home setting in Saudi Arabia. A sample of 30 eligible participants will be recruited to meet feasibility study requirements.

Methods: We will recruit 38 residents in the care home who will be randomly allocated to either an intervention or a control group. The intervention participants will perform gamified exercises using the MIRA telerehabilitation platform (30 minutes 3 times per week for 6 weeks). The control group will receive educational advice based on booklets of the Otago exercise program and be encouraged to exercise (30 minutes 3 times per week for 6 weeks). Participants will be assessed at weeks 0, 6, and 12. Assessments will include feasibility measures (eligibility, recruitment and attrition rates, and practicalities of data collection methods) and participant outcome measures (balance, strength, mobility, adherence, quality of life, fear of falling, depression, acceptability, and usability).

Results: Data collection started in November 2021 and ended in March 2022. The study is currently in the data analysis stage, which commenced in May 2022. The findings from this feasibility RCT will be used to design a definitive RCT to test whether the MIRA Rehab Exergame program benefits older people in Saudi Arabia who may not like participating in traditional exercise programs and may be unwilling or unable to leave their homes.

Conclusions: This study will contribute to our understanding of how to recruit in this specific population and provide information to inform the design of a future RCT.

International Registered Report Identifier (IRRID): DERR1-10.2196/39148

Introduction

Background

A fall is defined by the Prevention of Falls Network Europe group as "an unexpected event in which the participants come to rest on the ground, floor, or lower-level" [1]. Approximately 27% of older people who fall 3 or more times per year are transferred to emergency departments, while 20%-30% of older fallers sustain injuries that cause movement difficulties [2]. In addition to negative consequences such as higher morbidity levels, decreased activity, poor quality of life, and early nursing home admission, falls have been associated with increased death rates [3]. Many older adults who fall also experience notable fear of falling, and their activity levels can be reduced by up to 40% [4]. Almegbel et al [5] reported in a cross-sectional study (with a sample size of 1182 individuals) that 49.9% of the older population (aged 65 years and older) of Saudi Arabia experiences a fall every year. Moreover, the United Nations has reported that nearly 5.5% of the population of Saudi Arabia were aged 60 years or older by 2017, and that by 2050, the proportion of people aged over 65 years in the population will rise to 23% [6]. The average life expectancy in Saudi Arabia is 73.5 years for males and 76.5 years for females, with an overall life expectancy of 74 years, and increasing healthy longevity is of importance [7]. To prevent falls and their negative consequences, evidence-based physical activity such as strength and balance training needs to be implemented and adhered to [8,9]. However, physical activity engagement among older people remains low, particularly among those living in relatively lower-income neighborhoods. Older adults may be encouraged to expand their activities if others influence them, expenses are kept low, and enjoyment is high, which can increase self-efficacy for exercise [10].

Physical Activities

Previous studies have found that physical inactivity leads to higher morbidity and mortality rates, while physical activity improves quality of life [11]. Furthermore, systematic reviews have concluded that exercise is the best single intervention for fall prevention, especially when it is progressive, challenging, and regular [8,12]. Balance training requires both strength and balance components, which increase stability [13]. Successful exercise plans are differentiated by various features, including whether multiple static and dynamic stability tasks are adapted to the risk level of older adults, whether balance training increases in challenge over time, and whether it is carried out with minimal assistance. In addition, resistance exercise training that progresses over time needs to be included. Appropriate programs should include strategies to encourage long-term behavior change in older adults as well as fall prevention components [14].

According to Al-Hazzaa and Al-Marzooqi [15], while the benefits of exercise are well recognized, it remains a great challenge to encourage inactive people to start participating in exercise programs. Brumels et al [16] suggested that traditional exercises may be tedious and not very motivating for the participants. A lack of interest in workouts may contribute to lower-than-expected adherence [16]. Furthermore, rapid urbanization, extreme weather, cultural hurdles, a lack of social support, the absence of an efficient physical activity program, and a lack of time and resources can all make physical activities a difficult decision for Saudis [17]. Therefore, Saudis need to develop ways to make exercise practice more engaging, available, and accessible in educational institutions, clinics, workplaces, and communities.

Novel Technology

Exergames are video games that blend gaming and physical activity with animation. When Exergames include therapy-based exercises, they can be a form of telerehabilitation [18]. They can also include virtual reality simulations [19]. Exergames are considered to be a feasible way of enhancing engagement and removing barriers to training, leading to improvements for older people [19]. Exergames can be designed to cover a wide variety of conditions. Furthermore, in the case of some systems, the types of exercises and the difficulty level of the program can be prescribed by qualified physiotherapy professionals. The MIRA Rehab Exergames system has been codeveloped with older adults. The gamified exercises are based on the Falls Management Exercise (FaME) and Otago exercise programs [20,21], which have been shown to reduce falls in older people [18]. MIRA is an exergaming software product designed for medical use, and it has been Conformité Européenne–certified as a class I medical device [22]. It complies with UK National Health Service safety standards for patient data protection and privacy [22]. To date, this technology has not been used in Saudi Arabia.

Aims and Objectives

The main aim of this study was to conduct a feasibility randomized controlled trial (RCT) using MIRA Rehab Exergames among older adults in Saudi Arabia. Feasibility was assessed in terms of participant recruitment rates, intervention delivery, intervention acceptability (barriers and facilitators), 6-week follow-up attrition rates, and data collection and evaluation processes. Feasibility was also assessed in terms of the suitability of the outcome measures (balance, physical function, lower limb strength, depression, fear of falling, quality of life, and adherence among older adults). Intervention acceptability included factors relating to the acceptability, viability, and usability of MIRA Rehab among older adults, either positively or negatively (ie, barriers and facilitators to use). This study did not assess the effectiveness of the intervention. However, such information is required before conducting a definitive future RCT. As this is a feasibility study, it was underpowered to assess the effectiveness of the intervention. However, preliminary results in relation to outcomes are presented.

Methods

Study Design

The study was conducted in Saudi Arabia and was a single-center, 2-arm, single-blind, parallel-group feasibility RCT. The reporting of this feasibility RCT followed the Consolidated Standards of Reporting Trials extension for

feasibility trials in order to offer a clear report and appraisal [23] (see Multimedia Appendix 1).

The Study Setting: A Care Home Center

The trial was undertaken at the Social Care Home for the Elderly (the Dar Al-rieayat Al-aijtimaeia social care home) in Makkah, Saudi Arabia, which is a care home center for older male adults. This is the only center in Makkah providing specialist services for older males, and it is funded by the government. The residential home center provides care for any male citizen who is aged 60 years or older and is unable to conduct his own affairs. It offers care for patients referred from hospital and for those who have no families. The aim of this center is to provide care for citizens who are aged 60 years and older and are unable to live independently. Residents are required to be registered as free from infectious and mental health conditions [24]. Such governmental homes and residential care facilities for older people provide social, medical, and psychological care. Their services vary, but they generally facilitate cultural, professional, recreational, and sports activities [24]. For cultural reasons, as the researcher is male, we were unable to recruit females. Women receive residential care in separate facilities away from the main center (the Dar Al-rieayat Al-aijtimaeia center).

Participant Recruitment

To enable participant identification and recruitment in this residential care setting, the involvement of professional staff was required in the care setting.

Meeting With Professionals

The aim of the meeting with professionals was to confirm the arrangements for identifying potential participants (older adults) on the basis of the professionals' knowledge, expertise, and records. The researcher needed to interact with health care providers, including physiotherapists, rehabilitation specialists, nurses, social workers, physicians, and other health workers responsible for caring for older people at the center. These professionals provide basic medical services and ensure the physical and psychological well-being of the residents. Seeking assistance from the staff was crucial for the feasibility of the study. During the meeting, the researcher described the study (but not the specific hypotheses), focusing on the study's eligibility criteria (see below). The researcher then asked the professionals to use the eligibility criteria to screen for eligible participants.

Participants

Potential participants (male residents at the care home center who meet the eligibility requirements) were contacted by the health care professionals to assess their ability and willingness to take part in the study. The health care professionals then provided each potential participant an invitation letter, a participant information sheet, and a consent form. As some residents may be illiterate or have difficulty reading, verbal descriptions were provided as necessary. After a period of 2-3 days, potential participants were contacted in person by the health care professionals to confirm that they are willing to take part in the study and to obtain their consent. Only after obtaining consent, they were approached by the researcher.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for this feasibility study are outlined in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Older adults aged 60 years and older (60 years is the retirement age in Saudi Arabia)

- Resident at the participating care home center for older adults

- Ability to communicate in Arabic

- Ability to provide informed consent

- Ability to walk 9.1 m (30 ft) with or without a supportive aid

- Ability to participate physically

- Medically stable (based on patient medical notes)

Exclusion criteria

- Deaf, registered blind, or severe visual or auditory problems identified from medical records

- Use of medications that induce sleep, fatigue, dizziness, or drowsiness (eg, antihistamines, antidepressants, anxiety medications, cancer treatments, and some antihypertensive medications)

- History of severe mental health problems

- Uncontrolled movements owing to neurological disorders (eg, Parkinson disease, ataxia, and cerebral palsy)

- Severe middle ear problems, vestibular problems, or severe vertigo or dizziness

- Fracture within 6 months

- Severe cardiovascular problems (eg, deep vein thrombosis) or unstable diastolic blood pressure

- Recent surgery within 6 months

- Unwilling to participate

Sample Size

As this is a feasibility study that does not intend to assess effectiveness, demonstration of differences between groups is not a key objective. We are interested in the parameters of the outcome measurements in order to assess the utility of each outcome measure and enable sample size estimation for a future definitive trial. Thus, the focus is on the acceptability and usability of the MIRA Rehab program, and we shall use the results to guide the design of a potential definitive RCT [25]. As recommended by Hooper [26], the total number of participants was approximately 30. Anticipating an attrition rate of 20% for feasibility study, we recruited 19 persons in each arm to recruit approximately 15 older participants in each group [26].

Randomization

Randomization to the intervention or control group was undertaken by a separate member of the research team after baseline measurements were taken. We used an equal allocation ratio of 1:1. Taking into account the allocation ratio for 2 groups, the block size can be 2, 4, or 6. Randomization was undertaken by permuted blocks of size 2-6, using the Sealed Envelope randomization service [27].

Intervention

Consistency of measurement for the MIRA Rehab intervention is based on the trajectories of human skeletal joints [28] (Figure 1). This system has been developed to provide a way of performing physiotherapy activities using avatars, live motion tracking, direct feedback, and an intelligent environment. The MIRA Rehab Exergames keep track of the clients' achievements (eg, speed, score, and number of games played). They have been developed with and for older people with support from the University of Manchester and fall prevention therapists [22].

MIRA Rehab Exergames provides feedback on correct movements and tracking features (eg, range of movement) to a wide number of patients and health professionals who interact with them. They can create patient files and assign them to clinicians who can remotely monitor progress if required (Figure 2). The choice of Exergame can be made and adapted on the basis of clinical recommendations and patient preferences (Figure 3). However, certain exercises can be adapted to improve balance, strength, and mobility, such as sitting to standing, squatting, forward leaning from the standing position, leg extension from the seating position, and reaching the upper extremities in multiple directions. The choice of Exergames in the study was based on the participants' preference for colors, game play, and music. For patients who are not familiar with MIRA Rehab Exergames, video tutorials are provided. Furthermore, it is possible to personalize the Exergame software and set practical personal objectives to facilitate improvement [29].

Figure 1. A participant in the United Kingdom performing single-leg support using MIRA Rehab Exergame (reproduced with permission of author ES).

Figure 2. Example of an individual account and patient assignment screen view (MIRA Rehab website).
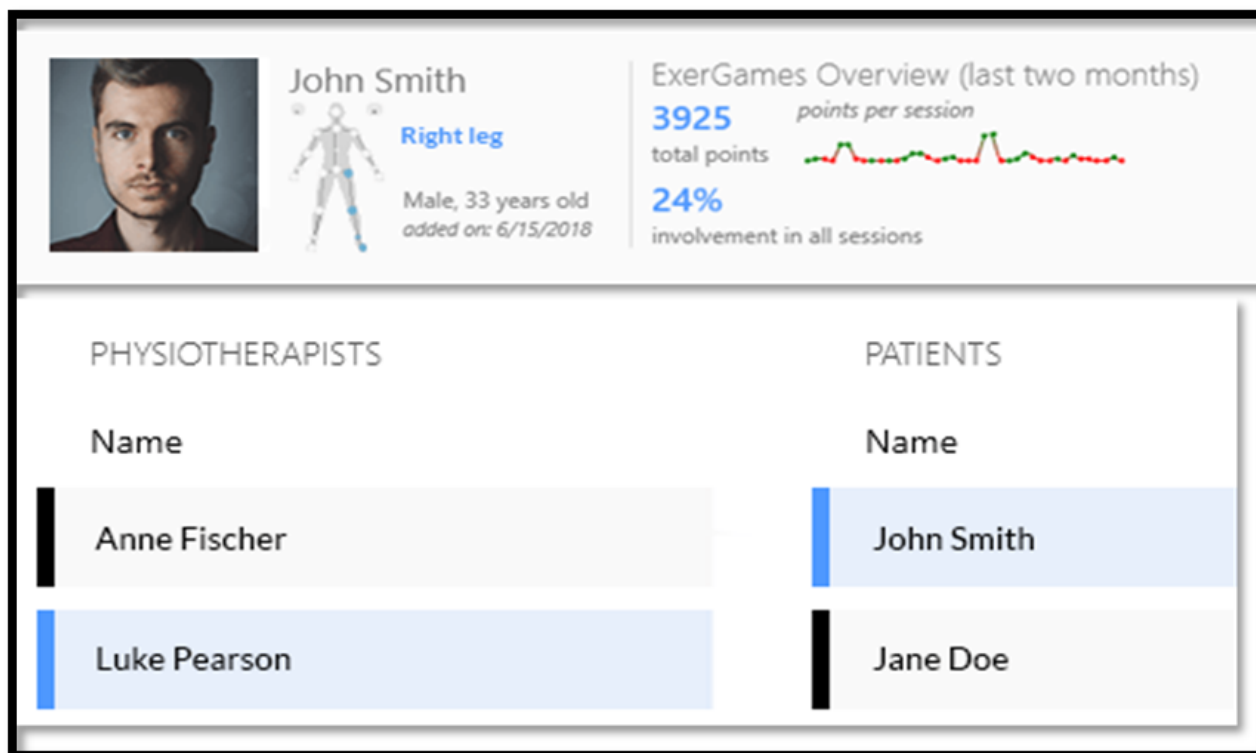
Figure 3. Example of a variety of games and exercises, which can be personalized on the basis of patients' needs and game preferences (MIRA Rehab Exergame).

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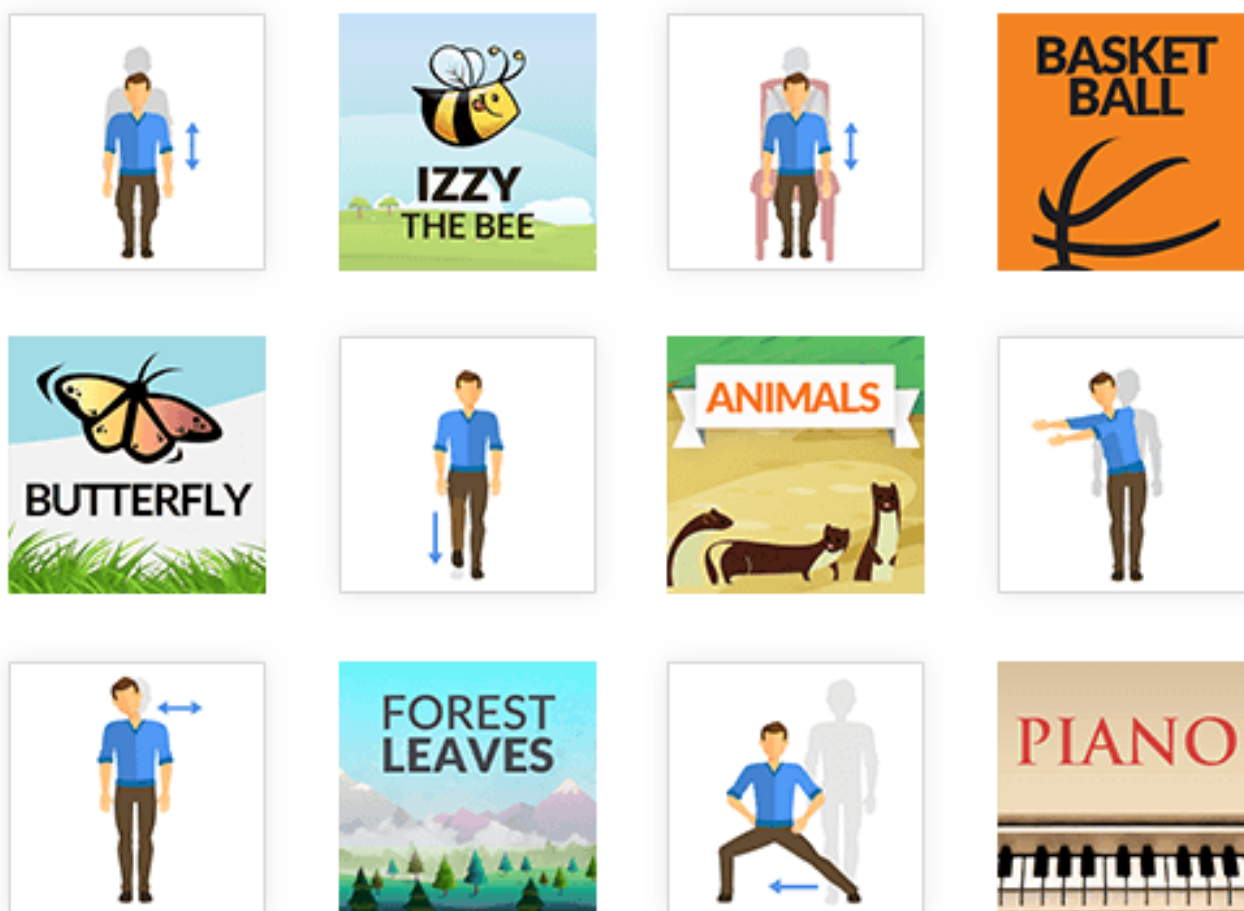
Preparation and Setup

For preparing the MIRA Rehab Exergame, the room must be at least 2×2 m to accommodate the equipment and space needed to exercise. The training room that was used is a part of the indoor physiotherapy clinic located at the care home center that is only available during daytime. The MIRA Rehab software (installed on a laptop computer) and a transportable Microsoft Kinect sensor with a 3D motion-sensor camera (version 2; Microsoft Corp) were connected to a TV screen. Each session started with calibration so that the users could correctly position themselves for optimal performance and efficient motion tracking. The lead investigator (MZ) and assistants explained to the participants how to perform the exercises [18].

Participants' Files

A participant file could be created for each individual using the MIRA Rehab software. Participant files record all the data from MIRA Rehab regarding each participant's activities and status (ie, selected Exergames, completed games, uncompleted games, game modifications, and game scores). Each file stores this information together for each individual for ease of reference during the treatment plan. To create individual accounts and establish files for the participants, certain information is needed (eg, name or identifier, age, date of birth, weight, and height). All the physical activities conducted by participants were saved on the MIRA Rehab platform drive, which is protected by a username and password and accessed only by the main researcher. The participants' involvement in the sessions was represented as a percentage indicating adherence to the exercises. Adherence was presented as the number of attended classes or sessions.

Duration

The participants participated in 30-minute sessions that were repeated 3 times a week for 6 weeks. Participants did not perform the required physical activities for the study during the next 6 weeks' follow-up. However, they continued their regular physical therapy sessions.

Safety and Support

The Exergame program was conducted and directed under the supervision of a physiotherapist to ensure participants' safety. For additional participant support and safety reasons, a shock absorber mat, 2 supportive chairs, and a parallel bar facing the TV screen at a distance of 2 m was required in the Exergame room (training room). Additionally, the physiotherapists observed the participants during the exercise session. The nurses also continuously checked the participants for any changes in health during the exercise sessions. Warming up exercises were provided to avoid possible muscle soreness and pain. It was explained to the participants that muscle soreness, pain, and fatigue are a natural physiological responses to exercise.

Tailoring the Fall Prevention Strategy of MIRA Rehab Exergames

The participants were initially assessed by the physiotherapist, who then adapted the program in accordance with individual participants' needs and abilities. Next, the physiotherapists selected the most suitable Exergames from a list based on Otago/FaME traditional exercises. The duration of each Exergame, the duration of the rest periods, and the number of exercises were tailored to the individual's level and rehabilitation needs. Since the aim of the study is to assess the feasibility of the intervention for improving physical abilities, selected games were used on the basis of specific movements.

Control Group

In this study, all the participants received an educational package provided by physiotherapists (30 minutes 3 times per week for 6 weeks) to the control group in addition to their usual care. They continued their usual activities. These included their normal exercise, recreation, and television watching as well as other aspects of their everyday routine at the care home center. The researcher explained and demonstrated the educational materials to staff in one of the meeting rooms at the center, making sure that the staff agreed that the educational materials were suitable for the older adults at the center. The materials are available in English and Arabic, and the physiotherapists provided these materials to the participants as verbal instructions based on the FaME and Otago exercise programs [20,21]. The participants performed these exercises at the physiotherapy department or at their rooms if they could do it independently. The educational material involved chair-based exercises, and it was available at the Later Life Training website [30] (see Multimedia Appendices 2 and 3).

Outcome Measures

This feasibility study included all the quantitative and qualitative outcome measures we anticipate, including in the future RCT, to inform the design of the main study. The outcome measures were assessed for their suitability for the main trial. These were assessed in terms of practicality (ie, recruitment rates, attrition rates, and eligibility criteria), data collection methods, required resources, and adherence (see Textbox 2).

Other variables of interest for this trial were as follows: (1) balance (measured by the Berg Balance Scale) [31]; (2) functional ability (balance, functional ability, and mobility measured by the Timed Up and Go test) [32]; (3) outcomes on the Functional Reach Test [33,34]; (4) the Short Physical Performance Battery [35]; (5) fear of falling (measured with the Fall Efficacy Scale–International) [36]; (6) depression (measured using the Geriatric Depression Scale) [37]; (7) quality of life (measured using the EQ-5D-5L) [38]; (8) exercise adherence (measured through the MIRA Rehab platform); and (9) usability and acceptability (measured using the System Usability Scale and the Technology Assessment Model) [39]. We also collected qualitative structured interview data from the participants who were asked to describe their experiences, including what they liked (facilitators) and disliked (barriers), to help us understand the success (or otherwise) of the intervention (Multimedia Appendix 4 and Table 1).

Textbox 2. Feasibility outcomes.

Recruitment and eligibility (no criteria set):

- Participants were identified through medical records. The participants were screened on the basis of the eligibility criteria.

- Participants who do not meet the eligibility criteria.

- Participants who do not participate and their reasons for not participating.

Data collection (no criteria set):

- Participants who completed the 6-week sessions (intervention group).

- Participants who completed the assessments.

Attrition (no criteria set):

- The number of participants who did not complete the 6-week sessions (intervention group).

- Participants who did not complete the assessments.

Resources (no criteria set):

- The time required to complete the questionnaires.

- The time required to perform the physical assessments.

- The time required to complete the intervention.

Adherence (no criteria set):

- The participants who attended each Exergame session in accordance with the MIRA Rehab system (based on the participants' logging in or logging off).

Table 1. Schedule of outcome measurements.

Outcome measure	Week 0 (baseline)	Week 6 (follow-up 1)	Week 12 (follow-up 2)
Balance (Berg Balance Scale)[a]	✓	✓	✓
Functional ability (Timed Up and Go)[a]	✓	✓	✓
Functional Reach Test[a]	✓	✓	✓
Short Physical Performance Battery[a]	✓	✓	✓
Fear of falling (Fall Efficacy Scale–International)[a]	✓	✓	✓
Depression (Geriatric Depression Scale)[a]	✓	✓	✓
Quality of life (EQ-5D-5L)[a]	✓	✓	✓
Exercise adherence (through the MIRA Rehab platform)[a]	Daily	Daily	Daily
Usability (intervention group)[a]			✓
Acceptability (intervention group)[a]			✓
Structured interview[b]	✓	✓	

[a] Quantitative outcome measures.

[b] Qualitative outcome measures.

Blinding

A physiotherapist (independent from the investigator) performed the baseline assessments for all the older participants (before allocation) during the first week. Then, an independent member of the team allocated the participants to different groups using a random number generator and informed the main investigator. The second assessment in week 6 was performed by another physiotherapist or physician (different from the initial one who performed the baseline measurements). The third and final assessment at week 12 was performed by another physiotherapist or physician who was not familiar with the previous assessments. While we attempted to maintain blinding at follow-up, this was not possible. Double blinding was not possible, as the participants knew whether they were exercising using the MIRA Rehab system. It was not possible to blind the

medical team and the participants because the participants received rehabilitation sessions as part of their daily routines.

Statistical Analysis

Statistical analysis is currently underway. The baseline characteristics of the participants will be reported using mean and SD values for normally distributed variables and median and IQR values ranges for nonnormally distributed variables. Analysis is being conducted using SPSS (version 27.0; IBM Corp) [40]. Continuous data, such as retention and recruitment rates, will be identified as percentages. Both groups will be compared at baseline with respect to their continuous and categorical variables using independent samples *t* tests and the Fisher exact test, respectively. Changes in balance and function will be compared between the intervention group and the control group from baseline (week 0) to follow-up (weeks 6 and 12). Inferential findings will be interpreted cautiously, as the feasibility analysis is underpowered for detecting significant effects. Distribution of data will be explored as normal or skewed. For normal distributions, mean and SDs will be used. For skewed distributions, minima, maxima, medians, and quartiles will also be used. We will report 95% CIs for unadjusted differences in mean outcome scores between the groups. Changes in mean scores over 3 time points (weeks 0, 6, and 12) as well as changes in average scores for each result will be recorded using repeated measures ANOVA. The effect size for the differences between the intervention and control groups and the variations within the intervention group will be estimated. Other relevant models will be used in the case of nonnormally distributed data. The findings will be used to calculate the optimum sample size (number of participants) for determining a statistically significant true effect in preparation of a future definitive RCT. Both intention-to-treat and per-protocol analyses will be undertaken. This feasibility RCT is a hypothesis-generating study for preparing and conducting additional analyses not identified in this protocol paper.

Ethics Approval and Research Governance

This study has been approved by the University of Manchester Research Ethics Committee (reference number 2021-11191-20154). To enable access to participants at the social care home for older individuals, permission has also been obtained from the local institution in Saudi Arabia that is responsible for the investigator's research and training. This study adheres to the tenets of the Helsinki Declaration. Prior to participation in the study, all participants were given a written informed consent form.

Results

This study is funded by Saudi Arabian cultural mission as part of a PhD project. Data collection started in November 2021 and ended in March 2022. The study is currently in the feasibility data collection stage, which commenced in May 2022. Additional qualitative data collection and analysis are ongoing and will be completed in January 2023.

Discussion

Expected Findings

This is the first feasibility RCT of MIRA Rehab Exergames in a residential care center for older adults (aged 60 years and older) in Saudi Arabia. While other researchers have studied various Exergame technologies, they have not examined purposely designed Exergame technology for older adults. Exergames for fall prevention were administered for over 6 weeks with a 6-week follow-up and compared to a control group receiving an exercise educational package. The study tested the feasibility of conducting an RCT of this novel technology in a new cultural context. This feasibility study protocol is intended to provide as much information as possible for a future randomized controlled trial. The study investigates the delivery of MIRA Rehab Exergames in the context of Saudi Arabia and included a small sample, with one site researcher. The findings may also inform whether Arabic and Saudi adaptations should be added to provide an adapted Exergame system that reflects cultural considerations. It will be critical for future research to examine how Exergames affect larger populations. Researchers should also carry out longitudinal investigations to assess changes in fall rates. Additionally, researchers should evaluate optimal exercise doses to inform potential future implementation.

Conclusions

This study will contribute to our understanding of how to recruit in this specific population and provide information to inform the design of a future RCT. MIRA Rehab Exergames may be a feasible and practical exercise intervention for enhancing the functional performance of older adults and to improve physical activity levels. Health care providers, such as physiotherapists and rehabilitation teams, may include Exergames such as the MIRA Rehab programs as part of a comprehensive physical therapy intervention for older adults living in care homes or similar settings.

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Data Availability

All data generated during this study and included in this published article and its supplementary information files are available upon request. For further details, pleases contact MZ (mohammad.zougar@postgrad.manchester.ac.uk).

Authors' Contributions

All the authors contributed to the conception and design of this protocol. MZ wrote the protocol, while ES, CT, and LM edited, revised, and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT 2010 checklist for reporting pilot or feasibility trials.
[[PDF File (Adobe PDF File), 325 KB](#) - [resprot_v11i12e39148_app1.pdf](#)]

Multimedia Appendix 2
The Arabic version of chair based training (CBT) provided by Later Life Training.
[[PDF File (Adobe PDF File), 1519 KB](#) - [resprot_v11i12e39148_app2.pdf](#)]

Multimedia Appendix 3
The English version of chair based training (CBT) provided by Later Life Training.
[[PDF File (Adobe PDF File), 1150 KB](#) - [resprot_v11i12e39148_app3.pdf](#)]

Multimedia Appendix 4
Participants' observations during data collection.
[[DOCX File , 23 KB](#) - [resprot_v11i12e39148_app4.docx](#)]

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Abbreviations

FaME: Falls Management Exercise
RCT: randomized controlled trial

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Protocol

Integration of Artificial Intelligence Into Sociotechnical Work Systems—Effects of Artificial Intelligence Solutions in Medical Imaging on Clinical Efficiency: Protocol for a Systematic Literature Review

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Abstract

Background: When introducing artificial intelligence (AI) into clinical care, one of the main objectives is to improve workflow efficiency because AI-based solutions are expected to take over or support routine tasks.

Objective: This study sought to synthesize the current knowledge base on how the use of AI technologies for medical imaging affects efficiency and what facilitators or barriers moderating the impact of AI implementation have been reported.

Methods: In this systematic literature review, comprehensive literature searches will be performed in relevant electronic databases, including PubMed/MEDLINE, Embase, PsycINFO, Web of Science, IEEE Xplore, and CENTRAL. Studies in English and German published from 2000 onwards will be included. The following inclusion criteria will be applied: empirical studies targeting the workflow integration or adoption of AI-based software in medical imaging used for diagnostic purposes in a health care setting. The efficiency outcomes of interest include workflow adaptation, time to complete tasks, and workload. Two reviewers will independently screen all retrieved records, full-text articles, and extract data. The study's methodological quality will be appraised using suitable tools. The findings will be described qualitatively, and a meta-analysis will be performed, if possible. Furthermore, a narrative synthesis approach that focuses on work system factors affecting the integration of AI technologies reported in eligible studies will be adopted.

Results: This review is anticipated to begin in September 2022 and will be completed in April 2023.

Conclusions: This systematic review and synthesis aims to summarize the existing knowledge on efficiency improvements in medical imaging through the integration of AI into clinical workflows. Moreover, it will extract the facilitators and barriers of the AI implementation process in clinical care settings. Therefore, our findings have implications for future clinical implementation processes of AI-based solutions, with a particular focus on diagnostic procedures. This review is additionally expected to identify research gaps regarding the focus on seamless workflow integration of novel technologies in clinical settings.

Trial Registration: PROSPERO CRD42022303439; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=303439

International Registered Report Identifier (IRRID): PRR1-10.2196/40485

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Introduction

In medicine, vast changes in patient care because the development of artificial intelligence (AI) is foreseen and ongoing. AI is broadly defined as "the ability of computers to perform tasks that normally require human intelligence" [1]. The introduction of these technologies in medicine promises to improve the quality and safety in health care and accessibility of medical expertise [1]. In the future, AI-human collaboration can augment the ability of clinicians in health care delivery by extracting relevant information from big data sets or performing tasks with higher precision [2,3]. The areas where AI technologies can assist the health care professionals are manifold, for example, clinical diagnostics, decision-making, or health care administration [2,4,5]. These technologies "can be used as powerful tools and partners to enhance, extend, and expand human capabilities, delivering the types of care patients need, at the time and place they need them" [4].

When integrating AI applications into clinical practice, these technologies will become part of highly complex sociotechnical work systems. A model that considers the complexity and scope of the clinical care work environment is the systems engineering initiative for patient safety (SEIPS) 2.0 model [6]. On the basis of SEIPS 2.0, the conceptual model of workflow integration was developed to investigate the integration of a new technology into clinical work processes, which has also been applied to the integration of AI [7,8]. The model uses a sociotechnical system approach and proposes that the whole work system and workflow must be considered to evaluate the success of an AI technology implementation [8].

Some work systems in medicine are faster or more suitable in adopting AI-facilitated technologies. Especially, in specialties that are largely image-based or process big amounts of data, AI is expected to support physicians and improve patient care by leading to more effective and efficient diagnostics [9,10]. Health care providers in image-based medical disciplines handle a growing amount of imaging data that require thorough interpretation [11]. Moreover, the shortage of physicians in radiology and a limited time available per image to meet the current workload are common challenges [12]. The introduction of AI into clinical practice holds a significant potential for changes in clinicians' duties and improvements such as advancing routine tasks and freeing clinicians' time for other important tasks [1,2].

One of the main objectives in introducing AI into health care is efficiency improvement because AI is expected to take over not exceedingly complex but time-consuming tasks [1,13,14]. This goal can only be achieved if these technologies are seamlessly integrated into the existing clinical workflow [15]. Therefore, a correlation between workflow integration and usability outcomes, which include efficiency, effectiveness, and satisfaction, has been proposed [7,16]. Efficiency is defined as "resources used in relation to the results achieved. […] Typical resources include time, human effort, costs and materials" [16]. Drawing upon the conceptual model of workflow integration, efficiency-related clinician outcomes include the adaptation of workflow, time to complete tasks, and workload [7,13].

To our knowledge, there is currently no systematic literature review or structured synthesis available on whether the integration of AI into the clinical workflow is associated with improved efficiency. Therefore, comprehensive evidence is necessary, concerning the major promise of freeing physician time for other care activities, for example, direct patient care. As the potential fields of application for AI technologies in health care are diverse, we focus on AI used for medical imaging to enable comparability. In this review, efficiency-related clinician outcomes such as workflow adaptation, time to complete tasks, and workload will be considered. Moreover, reported facilitators or barriers for the successful integration of AI into the workflow will be reviewed as "workflow integration is crucial for making this kind of software [computer-aided detection based on AI] a success" [13].

Our systematic review addresses the following question: how do AI technologies influence the efficiency of workflows in medical imaging?

Specifically, it aims to synthesize the literature base concerning two specific objectives: (1) Identification and overall aggregation of the effects of AI technology implementation on efficiency-related clinician outcomes such as workflow adaptation, time to complete tasks, and clinicians' workload; and (2) Description of the facilitators and barriers for the integration of AI into the workflow of medical imaging.

Methods

Protocol Registration and Reporting Information

A systematic literature review will be performed to assess the existing literature base and findings. The review's protocol is registered in the PROSPERO database (registration: CRD42022303439). The protocol and subsequent systematic review follow the reporting guidelines of preferred reporting items for systematic review and meta-analysis protocols statement. The checklist is included in Multimedia Appendix 1.

Eligibility Criteria and Study Design

Only original studies retrieved in full-text and published in peer-reviewed journals will be included. The review will include prospective observational and interventional studies such as randomized controlled trials and nonrandomized studies of interventions, for example, before–after studies and those with an interrupted time series design.

Population

We will include studies conducted in health care facilities such as hospitals, clinics, or outpatient settings using medical imaging. All types of health care professionals, including all age groups, sexes, professions, and qualifications, will be included from the hospital and clinical care settings.

Exposure and Intervention

Studies targeting AI used for medical imaging and its effects on health care professionals interacting with the technology will be eligible for inclusion in this review, including a broad range of AI solutions and clinical work settings. Regarding clinical

medical imaging and diagnostics, AI can be defined as "any computer system that can correctly interpret health data, especially in its native form as observed by humans" [17]. AI is often used in this context to identify or forecast a disease state [17]. This review will exclusively focus on AI used for image data interpretation for diagnostic purposes as well as medical imaging [2]. Therefore, our working definition for AI used for medical imaging activities as well as clinical diagnostics in this study will be as follows: any computer system used to interpret imaging data to make a diagnosis, support an image-based clinical (intervention) task, or screen for a disease, a task previously reserved for specialists.

Comparators

Studies comparing the use of AI in clinical diagnostics and medical imaging with only human specialists will be the comparison of interest; however, it is not a necessary condition for studies to be included in this review.

Outcomes

Overview

Our central study objective is to investigate the impact of AI solutions for clinical diagnostics on the workflow efficiency in clinical care settings. On the basis of our theoretical background, we will focus on three associated outcomes, namely, (1) workflow adaptation, (2) workload, and (3) time-to-complete tasks. In addition, we will systematically assess any facilitators and barriers of AI integration into practice that are mentioned in eligible studies (Figure 1).

Figure 1. Outcomes and measures of effect in this review. AI: artificial intelligence.
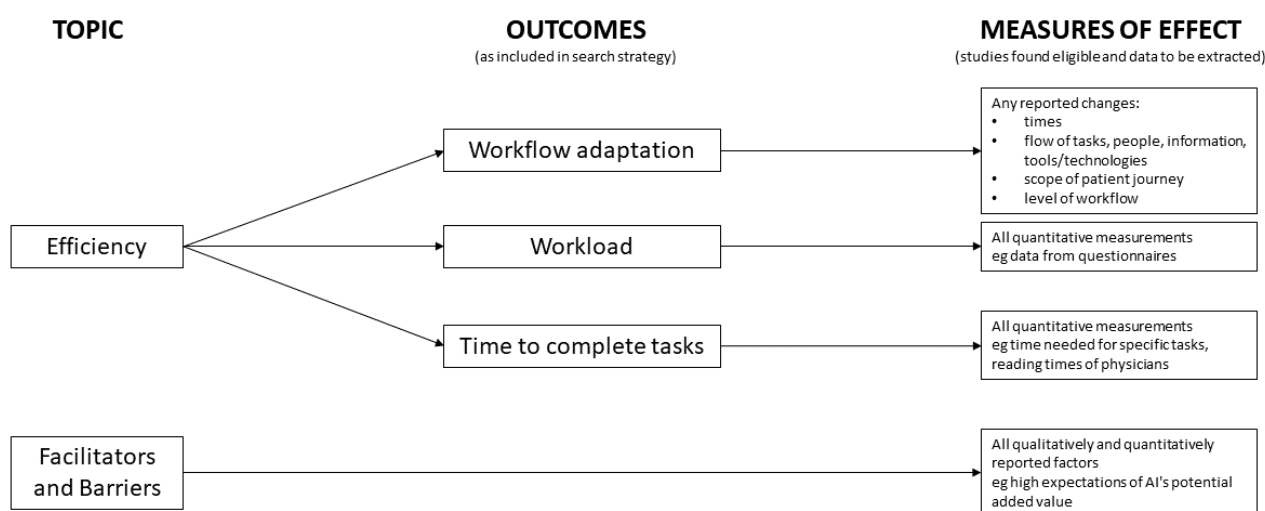
Workflow Adaptation

Workflow is defined as "the automation of a business process, in whole or part, during which documents, information or tasks are passed from one participant to another for action, according to a set of procedural rules" [18]. This definition was given by the workflow management coalition for business processes but can be also used for clinical contexts [18]. Thus, we will systematically evaluate the adaptation of the workflow in form of any reported changes to the existing processes due to the introduction of an AI technology.

Workload

Workload is defined as "the task demand of accomplishing mission requirements for the human operator" [19,20]. Measuring and analyzing clinical workload is "dependent on the tasks performed, the total time needed to complete the tasks and other care delivery needs of patients" [20,21]. Workload can be measured using objective measures, for example, cases seen or physiological data, and subjective measures such as questionnaires [22]. We will include all forms of quantitative workload measurements that compare the use of an AI software to traditional or previous methods such as pre-existing IT solutions, tools, and technologies in the workplace.

Time to Complete Tasks

New technologies provide opportunities to reduce the time needed to complete tasks, such as the time needed to examine magnetic resonance (MR) or computed tomography images [7,13]. Therefore, we will consider all reported measures on the time-to-task completion or duration. Time to complete tasks will be included if time changes on tasks of interest, such as diagnostic reading of MR images or writing of patient reports, are reported quantitatively with a comparison between the use of AI and traditional methods.

Facilitators and Barriers

A facilitator is defined as any factor that promotes or expands the integration or use of the AI system in the workflow. A barrier is defined as any factor that limits or restricts the integration or use of the AI system. The definitions were developed based on a systematic review by Niezen and Mathijssen [23], and the reported results will be classified according to these definitions. We will extract and synthesize facilitators and barriers in a narrative form using the Nonadoption, Abandonment, Scale-Up, Spread, and Sustainability framework for novel medical technologies in health care organizations [24].

Publication Types

We will include studies published from January 2000 onward because deep learning was developed in the early 2000s, which is thus marked as the beginning of a new area of AI use in medicine [25]. The article must be in English or German to be eligible for this review.

Owing to our rigorous scope, we limit our review to peer-reviewed journal articles and exclude dissertations, theses, and conference proceedings; as for the latter, the peer-review standards differ across conferences or disciplines. Furthermore, research on AI in medicine not used for medical imaging or diagnostics or research excluding the effects on the work system, such as studies on human interaction with the technology, will not be considered in this review.

Search Strategy

Literature will be retrieved through a structured literature search in several electronic databases: MEDLINE (PubMed), Embase, PsycINFO, Web of Science, IEEE Xplore, and Cochrane Central Register of Controlled Trials. We will use further the snowball method to identify literature not detected through electronic databases, thus screening through the references of identified studies and using Google Scholar. Table 1 outlines the search strategy, following the PICO framework. Because we have decided that comparator is not a necessary condition to be included in this review, we did not list it in the search strategy (see eligibility criteria above). To expand the list of search terms, a preliminary search will be performed before the main search.

Table 1. Search strategy according to the PICO framework.

Classification	Connector	Search term
Population	__a	"hospital" OR "clinic" OR "healthcare" OR "health care delivery" OR "clinical care" OR "medical" OR physician* OR clinician* OR doctor* OR nurse* OR "health care professional" OR "patient care" OR patient* OR surg* OR "oncology" OR "radiology" OR "health information"
Intervention	AND	"artificial intelligence" OR "machine intelligence" OR "machine learning" OR "deep learning" OR "neural network" OR "natural language processing" OR "AI " OR "automated image recognition" OR "decision-support" OR "AI application*"
Intervention	AND	"adoption" OR "deploy*" OR "implementation" OR "integration"
Intervention	AND	diagnos* OR "Magnetic Resonance Imaging" OR MRI OR "computer tomography" OR imag* OR detect* OR "data interpretation" OR "information system*" OR "health information technology*" OR "health IT*" OR "medical informatics" OR "electronic health record*" OR "medical record*" OR "patient data"
Outcomes	AND	"workload" OR "work reduction" OR load* OR "cognitive load" OR demand* OR time* OR stress* OR "satisfaction" OR "usability" OR "workflow" OR efficienc* OR "work system" OR "work adaptation" OR "turnaround" OR "clinician outcome" OR "performance"

aNone.

Screening and Selection Procedure

All retrieved articles will be imported into the software *Zotero*, an open-source reference management software [26]. For title and abstract screening, *Rayyan*, a web application for an initial title and abstract screening, will be used [27,28]. In the first step, the titles and abstracts will be independently screened by 2 reviewers who will undergo training to increase interrater agreement. In case of disagreement, a third researcher from the team will be consulted to solve the conflict in a discussion. If the disagreement cannot be solved through obtaining consensus, the 3 researchers will solve the conflict democratically, that is, majority vote. In the second step, full texts of all eligible publications will be retrieved. These will also be screened by 2 reviewers, and potential conflicts on whether the articles should be included will be resolved in a discussion moderated by a third member of the study team. Studies that are excluded in the process will be recorded. A flow diagram presenting the study selection process will be prepared, following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 flow diagram for new systematic reviews, which included searches of databases, registers, and other sources [29].

Data Collection Procedure

The study data will be extracted by 1 author and imported into MS Excel (Microsoft Corp). The study data contain details on study characteristics, sample, setting, type of intervention, type and assessment of outcomes, statistical analyses, reported results, moderators or control of confounders, and further information of interest (Textbox 1). The studies and extracted data will be checked at random by another reviewer from the study team. To obtain an agreement on relevant data to be extracted, data from the first 5 studies will be extracted by both reviewers, and a guideline for data extraction will be developed. The extracted data will be divided into several main categories. If any information is missing, the authors of that particular study will be contacted for further details. In case of multiple publications on 1 study, only the key publication will be included.

Textbox 1. Main categories for data to be extracted.

1. Study characteristics

- Authors

- Year of publication

- Location

- Study design

2. Sample

- Sample size

- Participants: demographics and professional characteristics

3. Setting

- Type of clinic

- Medical specialty

- Task

4. Type of intervention

- Artificial intelligence technology (category, reliability, and source)

5. Type and assessment of outcomes

- Workflow adaptation, workload, and times other reported outcome variables

- Facilitators and barriers (if reported)

- Sources of outcomes

- Assessment method (eg, interview, questionnaire, and observation)

6. Statistical analyses

- Types of statistical methods and analyses

- Means and variance metrics of outcomes (eg, standard deviations and confidence intervals)

7. Reported results

- Quantitative results

  - Coefficients (β, γ) and measures of strength of association between artificial intelligence and changes in outcome variables

  - Effect sizes (if reported or calculable)

  - *P* values

- Qualitative results

  - Named facilitators and barriers

  - Any reported analysis

8. Moderators or control of confounders

- Potential moderators or confounding variables (if reported)

9. Further information of potential interest

- Further information, for example, on limitations

Study Appraisal and Risk of Bias (Quality) Assessment

To assess the methodological quality of the included studies, a standardized risk of bias assessment will be performed. Three established tools to assess the risk of bias, applied by two independent reviewers, will be used. Cochrane Risk of Bias Tool (Rob2) [30] will be used for randomized controlled trials. For nonrandomized studies, the risk of bias in nonrandomized studies of interventions tool [31] will be used. These tools address different sources of bias, including the steps from selection to reporting. For observational studies, a checklist of

quality of reporting of observational longitudinal research [32] will be used. In case of disagreement, a third reviewer will be consulted until consensus is achieved.

Strategy for Data Synthesis

First, we will qualitatively describe the overall sample and summarize the information extracted from each study. We will then provide an overview concerning the classification in our main categories (Textbox 1). The results of the risk of bias assessment will be provided in a narrative and tabular format. If an adequate set of studies of 5 or more studies is found eligible and the homogeneity level allows, we will perform a meta-analysis that reviews the effects of the introduction of AI on efficiency-associated outcomes. We will quantitatively synthesize data from the retrieved studies using the metafor package in R (R Core Team, R Foundation for Statistical Computing), which contains a set of functions for calculating meta-analyses such as effect-size calculation or model fitting to the data [33]. As we expect a level of heterogeneity of effects in the included studies, a random effects model will be used to estimate the average effect across studies. The heterogeneity across the included studies will be assessed using the Cochran Q test [34] and I^2 statistic [35]. If the number of studies (at least 5 studies per group) and heterogeneity among them allow, subgroup analyses concerning specific characteristics within our eligibility criteria (ie, participants' demographics, particular work settings, outcomes, study designs, and quality) will be performed.

If a meta-analysis is not possible, the results will be summarized in a narrative form and will also be presented in a tabular format. Regardless of the possibility of a meta-analysis, the results will be presented graphically to summarize the retrieved information in a user-friendly manner. We will also adopt a narrative synthesis approach for our additional outcomes, namely, facilitators and barriers. The narrative synthesis will be consistent with that of Strohm et al [36] who conducted an interview study on the factors facilitating and hindering the implementation of AI in radiology. They used the nonadoption, abandonment, scale-up, spread, and sustainability framework for new medical technologies in health care organizations, which will be also used in our data analysis [24,36].

Meta-biases

Regarding the potential sources of meta-bias (eg, publication bias across studies and selective reporting) in the results of the review and meta-analysis, we plan to create a funnel plot, which plots study size against the reported effect size. If a publication bias occurs, the resulting scatterplot is asymmetric with more studies showing a positive than a negative result [37]. We will include at least 10 studies (if possible) to check for small-study effects [38-40]. Additionally, we will use the critical appraisal tool for systematic reviews on randomized or nonrandomized studies of health care interventions AMSTAR-2, which consists of 16 items assessing the quality of conduct of our systematic review [41].

Confidence in Cumulative Evidence

The strength of the body of evidence will be assessed by using the Grading of Recommendations Assessment, Development and Evaluation, a system for rating the quality of evidence and strength of recommendations [42,43]. This rating system has been successfully used in clinical medicine, public health, and policy making, and more recently, in occupational and environmental health [44]. It supports the authors in rating their confidence whether the estimate of an effect is correct. In systematic reviews, the quality of evidence is rated separately for each outcome on a scale from high to very low [45].

Results

The search and screening for the systematic literature review are anticipated to be finished in October 2022. Data extraction, quality appraisal, and subsequent data synthesis will begin in November 2022. The review is expected to be completed by April 2023, and the study results will be published in 2023.

Discussion

Principal Findings

We propose a protocol for a systematic review on the influence of AI technologies on workflow efficiency in clinical care settings. Our review will summarize the existing literature and provide a comprehensive overview on the work system effects of AI technologies in clinical care. This will focus on efficiency outcomes as these are promising factors in the integration of AI into clinical practice. To our knowledge, no systematic overview has been yet conducted on this subject.

The focus in our review will be on workflow and clinician outcomes in imaged-based disciplines as in these fields AI technologies are predominantly and continuously integrated into clinical care practice. Presumably, in the future, almost every medical specialty will interact with AI-based technologies because of a broad range of potential AI application fields in this domain [46]. Contrary to the popular belief that AI will replace radiologists or other health care staff, the future of medicine will rather depend on optimized interactions between AI and humans, enabling AI systems to augment the physician's performance [12,47]. AI is foreseen to change clinicians' work environments and affect their work processes such as task flow and workload [3,46]. Notwithstanding the various promises being proposed with the introduction of AI in real-world care environments, current evidence concerning its effects on clinicians' workflow and practices is missing. Our review will therefore provide valuable insights into the existing evidence base on the immediate effects of AI implementation on work systems and clinician outcomes. Thus, our research synthesis will facilitate understanding if the current AI technologies live up to the expectation of significantly supporting clinicians in their work [48].

Comparison to Previous Research

Notably, in light of the current gap between the broad utilization of AI for research purposes and few AI applications being applied in routine patient care, facilitating AI implementation and adoption into clinical care has become essential. Although academic publications on AI solutions for medical imaging, diagnostic, and therapeutic contexts are numerous, only a few real-world solutions have been yet officially approved and

implemented in the health care sector [49]. Furthermore, we expect that only a fraction of these solutions has been systematically evaluated regarding their impact on clinician outcomes or workflow integration. This expectation is supported by the review of Asan and Choudhury [3] who demanded systematic research that addresses AI's impact on clinical workflow and usability with emphasis on the importance of human factor research.

Because the seamless integration of AI is crucial for unfolding its potential in clinical practice, our review will specifically address the facilitators and barriers of implementation practices elicited from the retrieved studies [13]. The consideration of facilitating and hindering factors of AI adoption is an essential step in gaining a more detailed understanding of how AI implementation can be optimized in hospital and other clinical care settings. A study suggests that various process factors affect seamless AI adoption into hospital practices, such as a perceived high added value or hospital-wide innovation strategies, technical performance, and well-structured implementation processes [36]. We acknowledge that we will only extract the process characteristics from studies found eligible regarding clinician outcomes. Nevertheless, our synthesis approach, which draws upon a previously established framework, allows for a comprehensive understanding of AI implementation experiences and will expand the existing preliminary findings [36].

Limitations

Our review will focus on AI used for medical imaging used for diagnostic purposes. AI applications offer a great potential for image-based specialties and address a pressing issue, namely, the vastly growing amount of imaging data that need thorough interpretation [15,47]. Significant technological advancements have been made recently through the development of AI solutions and their application into clinical practice [1,50,51]. We solely focus on this clinical domain and a specific clinical task (eg, image-based tasks and diagnostics) to strengthen internal and external validity as well as to allow comparability across the work settings included. Nonetheless, we capture a medical field with the most extensive availability of AI technologies already integrated into clinical routine practices.

The algorithms or features used in the AI technologies included in this review might be different; however, this is not of central interest for answering our research question. We will not assess the quality or clinical effectiveness of the AI systems because this is covered by numerous systematic reviews with regard to the specific task for which comparable AI solutions were developed, such as in the reviews by Kunze et al [52] or Chidambaram et al [53]. Therefore, no specific conclusions regarding the technologies or characteristics of AI will be drawn as we will focus solely on the work system effects.

To achieve our goal of summarizing the existing literature on the impact of AI implementation on clinician outcomes, we will establish a rigorous list of exclusion criteria regarding study design, setting, and population. Therefore, conclusions will only be drawn for the specific setting of work environments where

AI is used for image-based and diagnostic purposes. We acknowledge that this may result in limited generalizability of our results. In future research, it would be valuable to compare the workflow integration of AI across different health care settings such as ambulant care settings or nursing facilities. Our review approach may be an exemplary approach on how to systematically aggregate research findings on AI workflow integration, which can be transferred to other health care sectors and clinical domains.

Our outcome variables of interest draw upon the conceptual model of workflow integration [7]. Our key focus will be on clinician outcomes, workflow, and efficiency—the key issues for AI introduction. Notably, we will only address clinician outcomes named in the model, namely, those related to workload and efficiency. For future research, it would be valuable to include further outcomes such as perceived use and acceptance. Furthermore, it would be interesting to augment research with concepts such as trust and technology characteristics as these are important determinants of AI adoption [36,54,55].

Regarding our key concepts extracted from the conceptual model of workflow integration [7], there is substantial heterogeneity of applicable terms in the literature; for example, time to complete tasks is a collective term for measures such as physician's reading times [13] or time undertaken to review an image [56]. Moreover, some concepts used in this literature review, such as the use of AI in clinical diagnostics or facilitators and barriers for AI implementation, do not have a consistent definition in the literature. Therefore, we propose working definitions on the background of existing research [2,19,23]. Nonetheless, we acknowledge that key terms might be conceived differently in other contexts or publications. Thus, we limited the deviation from previous studies by conducting a pilot search and expanding our search terms to include common variants of key concepts.

Conclusions

Our review and meta-analysis or systematic narrative data analysis will allow first systematic conclusions on how AI for medical and diagnostic imaging affects clinician efficiency outcomes. We expect to provide a structured overview and systematic synthesis of the current literature. Thus, the findings of our review are expected to expand the existing knowledge on how AI affects clinical efficiency in medical imaging. Particularly, by providing a quality appraisal of the included studies, we will identify shortcomings of the current research. Moreover, our review will help to recognize research gaps regarding the seamless workflow integration of novel technologies into clinical settings. Our findings will eventually also provide guidance on provider-centered design and application of AI-based solutions in clinical settings, with potential improvements in clinical safety and performance. Furthermore, our consideration of the facilitators and barriers of AI implementation will provide an evidence-based foundation for hospital leadership and practitioners to successfully manage AI implementation in patient care.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P Checklist.
[PDF File (Adobe PDF File), 411 KB - resprot_v11i12e40485_app1.pdf]

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Abbreviations

AI: artificial intelligence
SEIPS: systems engineering initiative for patient safety
MR: magnetic resonance
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Protocol

Identifying Challenges, Enabling Practices, and Reviewing Existing Policies Regarding Digital Equity and Digital Divide Toward Smart and Healthy Cities: Protocol for an Integrative Review

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Abstract

Background: Digital equity denotes that all individuals and communities have equitable access to the information technology required to participate in digital life and can fully capitalize on this technology for their individual and community gain and benefits. Recent research highlighted that COVID-19 heightened the existing structural inequities and further exacerbated the technology-related social divide, especially for racialized communities, including new immigrants, refugees, and ethnic minorities. The intersection of challenges associated with racial identity (eg, racial discrimination and cultural differences), socioeconomic marginalization, and age- and gender-related barriers affects their access to health and social services, education, economic activity, and social life owing to digital inequity.

Objective: Our aim is to understand the current state of knowledge on digital equity and the digital divide (which is often considered a complex social-political challenge) among racialized communities in urban cities of high-income countries and how they impact the social interactions, economic activities, and mental well-being of racialized city dwellers.

Methods: We will conduct an integrative review adapting the Whittemore and Knafl methodology to summarize past empirical or theoretical literature describing digital equity issues pertaining to urban racialized communities. The context will be limited to studies on multicultural cities in high-income countries (eg, Calgary, Alberta) in the last 10 years. We will use a comprehensive search of 8 major databases across multiple disciplines and gray literature (eg, Google Scholar), using appropriate search terms related to digital "in/equity" and "divide." A 2-stage screening will be conducted, including single citation tracking and a hand search of reference lists. Results will be synthesized using thematic analysis guidelines.

Results: As of August 25, 2022, we have completed a systematic search of 8 major academic databases from multiple disciplines, gray literature, and citation or hand searching. After duplicate removal, we identified 8647 articles from all sources. Two independent reviewers are expected to complete the 2-step screening (title, abstract, and full-text screening) using Covidence

followed by data extraction and analysis in 4 months (by December 2022). Data will be extracted regarding digital equity–related initiatives, programs, activities, research findings, issues, barriers, policies, recommendations, etc. Thematic analysis will reveal how barriers and facilitators of digital equity affect or benefit racialized population groups and what social, material, and systemic issues need to be addressed to establish digital equity for racialized communities in the context of a multicultural city.

Conclusions: This project will inform public policy about digital inequity alongside conventional systemic inequities (eg, education and income levels); promote digital equity by exploring and examining the pattern, extent, and determinants and barriers of digital inequity across sociodemographic variables and groups; and analyze its interconnectedness with spatial dimensions and variations of the urban sphere (geographic differences).

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Introduction

Background

Access to digital technologies and ensuring digital equity have gained traction in recent policy debates and become priority concerns for transforming smart cities across the world. According to the National Digital Inclusion Alliance, digital equity is defined as "a condition in which all individuals and communities have the information technology capacity needed for full participation in our society, democracy, and economy" [1]. When the state fails to ensure the capacity of accessing and using information and communications technology and services among different segments of its people, it is denoted as digital inequity or digital divide [2]. Access to critical services, jobs, lifelong learning, and civic and cultural involvement depend on digital equity [1]. This notion has gained further momentum during the COVID-19 pandemic and emerged as a dominant agenda in urban planning [3]. However, despite continued efforts to bridge the digital divide, numerous studies have reported issues of growing digital inequity concerning access to the internet, software, and hardware; level of digital literacy (the ability and skills to use); and adoption of digital technology [4-8]. Nevertheless, this underlying phenomenon of the digital divide is not an isolated thing but is, in fact, embedded in pre-existing structural and systemic inequities [6], often resulting from socioeconomic marginalization and socio-spatial disparities. Therefore, critical calls are increasing for a more careful analysis of the intersectionality of digital inequity with a special focus on the interplay between varying sociodemographic backgrounds or factors and urban socio-spatial factors [6].

Pandemic-induced restrictions and subsequent lockdowns, which had already placed disproportionate burdens on marginalized groups, have diminished (in-person) social interactions and resulted in increased dependency on digital technologies. Previous research highlighted that the COVID-19 pandemic has heightened the existing structural inequities [9] and further exacerbated the technology-related social divide, especially for older adults [10], the economically marginalized, and members of racialized communities (ie, immigrants, refugees, and ethnic minorities) [8,11], by limiting their access to health services [12], economic activity, and social life. Moreover, this crisis

has also exposed the multifaceted nature of digital inequities, which are compounded by the ongoing equity challenges, and how they disproportionately impact those vulnerable groups who are already affected by socio-spatial inequities [13]. Emerging research on the pandemic has demonstrated that digital equity is not only a social determinant of health [12] but also a precondition for gaining access to economic activity, social life or sphere, and other urban services. Therefore, given the complexity, multidimensionality, and severity of the crisis for disadvantaged groups resulting from digital inequities, scholars and practitioners have emphasized developing robust mitigation and adaptation strategies by considering the broader socioeconomic [11] and socio-spatial context [13] of urban areas. Since access to digital technology has become fundamental to everyday life, if equity is not ensured, it may reinforce systemic inequity for digitally disadvantaged groups, who may fall behind during the postpandemic recovery phase.

Many studies reported that access to the internet for racialized communities is much lower than the national average [14,15]. Ethnic minorities were found to be significantly more worried (40%-53%) regarding the ability to pay for the internet than their counterparts (29%), according to a report on the digital divide in Toronto, Ontario [16]. Some members of this category are also at risk of the digital divide because of a lack of content accessibility [17], in addition to the barriers to access to devices and subscription vulnerabilities [18]. The capacity and ability of those in racial and ethnic minorities to navigate the digital sphere and space are constrained, which may shape or limit their ability to engage in a variety of complex web-based activities including accessing health [18,19] and social support services [20]. Immigrants and refugees are made up of varied groups with a range of skills and socioeconomic circumstances [21]. For example, economic migrants tend to be highly educated and have digital-literacy skills, whereas family migrants or refugees may have low digital-literacy skills [21]. However, regardless of the subtypes, immigrants and refugees usually undergo resettlement challenges including language, employment, and financial barriers, which may affect the accessibility and affordability of digital devices and services [22].

Previous research has mainly focused on digital inequity in limited-income countries when considering the global context

[2,23]. In the context of Canada, most studies specifically have explored the rural-urban divide [15,24]. Previous literature reviews related to digital equities in racialized communities generally focused on motivation for internet adoption and information practices [25,26], the eHealth literacy aspect [27,28], older immigrants [29,30], and social media use [31]. What remains understudied is how systemic inequities and various social determinants affect the racialized population in multicultural urban centers, where people from diverse backgrounds and socioeconomic capacities thrive under the same jurisdiction, governing bodies, and supposedly same facilities of internet and digital services, yet live on the extreme ends of the digital equity spectrum [32]. There is a need for understanding how the intersection of various systemic inequities (racism, discrimination, ableism, etc) and characteristics of racialized communities (eg, culture and language) lead to and exacerbate existing digital inequities among racialized communities [33]. This study, therefore, aims to understand this complex issue by drawing on previously published studies and inform public policy on treating digital inequity by illustrating the interconnectedness of digital equity with systemic inequities and its spatial variations in the urban sphere.

Study Objectives

We intend to capture the current understanding of digital equity through an integrative review of academic and gray literature to achieve the following two specific objectives:

- Objective 1: we plan to explore the current level of research regarding digital inequity and synthesize the knowledge of the barriers and facilitators and potential outcomes of digital inequity. This understanding will help us determine and

undertake the next steps in working on this important but overlooked issue.

- Objective 2: we plan to identify the reported initiatives for overcoming digital inequity in racialized communities. Having this information will allow different levels of stakeholders in this area to access the preliminary knowledge to undertake solution-oriented research and program initiatives.

Methods

A Community-Engaged Research Approach

As a part of a community-engaged program of research, we strive to engage with various communities through knowledge cocreation, knowledge comobilization, and equitable partnership strategies where the partners have decision-making capacities across the steps of the research process [34,35]. Community members, community champions, citizen researchers, nonprofit organizations, and policy makers such as municipalities, local government bodies, and others are involved in our research program at various levels of capacity [36]. Through our outreach activities, we have the opportunity to engage with the City of Calgary, which identified a research need regarding digital inequity, to explore why and how digital equity affects racialized communities in Calgary. Therefore, together with the city team, we developed the study protocol, which seeks to synthesize knowledge from existing research, policies, programs, and initiatives on this issue in the urban context in high-income countries. Textbox 1 presents the guiding questions of this research. The knowledge obtained through this study will allow us to understand the current extent of the research regarding digital equity and will inform policy makers and community partners to develop strategies to effectively address existing inequity.

Textbox 1. Guiding questions.

1. To map the publications about digital inequity and the digital divide focusing on racialized communities

2. To summarize the existing policy, strategy, interventions, regulatory frameworks, and recommendations against digital inequity in racialized communities

3. To identify the key determinants of digital inequity in racialized communities

4. To explore the key constructs and dynamicity of the digital divide in racialized communities

5. To inspect the partnership approaches across actors and stakeholders used in digital equity initiatives and programs

Systematic Integrative Review

Overview

We will be conducting a systematic integrative review using Whittemore and Knafl's [37] methodological approach. Integrative reviews gather comprehensive knowledge from both empirical and theoretical literature and allow a better understanding of a particular issue [38]. This review approach does not place restrictions on a certain methodology, thus allowing evidence on a particular topic to be illustrated from a broader perspective, which helps in developing theories and practices [37]. To ensure rigor, we will adapt the guidelines from the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) for this integrative review

to enhance methodological and reporting quality [39] (Multimedia Appendix 1).

Identifying the Problem

Based on previous studies and our community engagement activities, we observed inequities across various population groups and areas in terms of accessibility, availability, and affordability of internet connection; internet-enabled devices; digital literacy and skills; and useful materials, resources, and outcomes [15,40]. Through our discussions with the City of Calgary and community partners, we coidentified the questions that will guide our study (Textbox 1).

Literature Search

Using the PCC (Population, Concept, Context) framework [6], we developed the following inclusion and exclusion criteria.

Population

For this integrative review, we will include studies conducted among the urban racialized population including immigrants, refugees, and ethnic minorities. Our focus is on various groups of the racialized populations in urban contexts, as in comparison to rural dwellers, who are more likely to be able to avail themselves of the infrastructure necessary to access high-speed internet if they were not affected by various systemic inequities [41]. We define high-speed internet as 50 Mbps download/10 Mbps upload in accordance with the Canadian Radio-television and Telecommunications Commission's service objective [42].

Concept

Our search parameters will include any type of research project, as well as pilot, temporary, and experimental studies addressing digital equity and sustainable and failed initiatives, programs, or activities aimed at establishing digital equity. In this review, we will interpret digital equity, equality, or inclusion similarly, a concept we define as having access to and the capacity to utilize information technology with positive outcomes by all individuals and communities [1]. Any disruption to this concept, such as certain individuals or communities being unable to access the internet or utilize available digital technology, is denoted as digital inequity, inequality, divide, exclusion, or gap in this study. All types of studies, including, but not limited to, exploring barriers, facilitators, outcomes, policies, reforms, and so on, will be considered in this review.

Context

Based on discussions with our partners, we want to focus on studies conducted in multicultural and high-income cities similar to the City of Calgary, which is a cosmopolitan city of approximately 1.4 million people in Alberta, Canada. Therefore, we will include studies in urban areas of high-income countries. High-income countries will be selected using the United Nations' list of countries with high-income economies [43]. We will include studies that address structural, technological, legal, business, and other aspects of internet access and quality,

increased accessibility, availability, and affordability of internet-enabled devices, and improvement of digital skills and literacy that connect their findings or discuss them in relation to digital equity. We will include studies about digital equity in any context (eg, digital equity in health care access, law and order, social support, employment and economy-related aspects, etc).

Search Strategy

We will keep our inclusion criteria broad in terms of types of study design. We plan to capture the maximum possible work undertaken on this topic, so we will include original and review studies, qualitative, quantitative, and mixed method studies, theses and dissertations, editorials, commentaries, and case studies. We will not, however, include books or book chapters in this review. We will only include English-language studies and studies published since January 2010.

We have developed a search strategy in consultation with a librarian and following the evidence-based Peer Review of Electronic Search Strategies (PRESS) guideline [7]. The strategy is designed to capture both peer-reviewed journal-published articles and gray literature from sources from multiple disciplines, including social sciences and humanities, computer science and technology, and health sciences. A list of keywords, index terms, and search algorithms is presented in Textbox 2. We have also provided a detailed search strategy for 1 database—MEDLINE (Multimedia Appendix 2). It is important to note that different databases have different search mechanisms, and we will adapt search strategies accordingly. For example, the search keywords and combinations used in MEDLINE will need to be modified for Scopus to yield optimal search outcomes. To further ensure our search is extensive, we will review the reference lists of the initially selected studies to elicit additional articles we may have missed during our initial search. The academic and gray literature databases we will search for this review are provided in Textbox 3. As gray literature will contain a wide variety of non–peer-reviewed publications, we will apply the AACODS (authority, accuracy, coverage, objectivity, date, and significance) checklist to ensure the credibility and validity of the information from each data source [44].

Textbox 2. Search terms and search strategy.

Keywords for digital (in)equity

(Digital* OR "digital literacy" OR "information technology" OR "digital technology" OR technology OR internet OR "information and communications technology" OR ICT OR computer OR mobile OR phone OR smartphone OR "smart devices" OR cyber OR web OR "data literacy" OR "information literacy") AND

Keywords for high-income countries

("OECD countr*" OR "developed countr*" OR "Western countr*" OR "Organisation for Economic Co-operation and Development" OR "developed nation*" OR "advanced countr*" OR "advanced nation*" OR "industrialized nation*" OR "industrialized countr*" OR "high-income countr*" OR "first world count*" OR "MEDC countr*" OR "More economically developed countr*") AND

Keywords for (in)equity

(Equity OR inequity OR divide OR inclusion OR exclusion OR gap OR inequality OR apartheid OR equality OR disadvantage* OR inconvenien* OR access* OR unfair OR fair OR justice OR injustice OR discrimination OR bias OR unjust OR need* OR barrier* OR obstacle* OR limitation* OR deficit OR shortage OR inadequate OR poverty OR scarcity OR insufficient OR scant)

Textbox 3. Academic and gray literature databases.

Academic articles

- Web of Science

- Scopus

- Academic Search Complete

- Canadian Research Index

- MEDLINE

- SocINDEX with Full Text

- Communication & Mass Media Complete

- IEEE Xplore digital library: Standards

Gray literature

- Google Scholar

- ProQuest (theses and dissertations)

- OAISter (WorldCat)

- National Digital Inclusion Alliance

- Canadian Radio-television and Telecommunications Commission

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Evaluating Data

All identified records following the search will be uploaded into Covidence, a systematic review tool, and duplicates will be removed. Initially, the title and abstract will be screened by 2 independent reviewers to identify potential studies for full-text review according to the inclusion criteria stated above. Potentially eligible articles during title/abstract screening will be thoroughly screened by the same reviewers for final eligibility. Articles fulfilling all inclusion criteria will be selected for this review. The agreement between the 2 reviewers is expected to be 80% or greater. Any conflicts between the 2 reviewers will be resolved by a discussion including a third reviewer. Each step of the study-selection process will be documented and reported using an adapted version of the PRISMA-P flow diagram (Figure 1) [5].

Figure 1. Flow diagram of the search, screening, and selection process for the review.
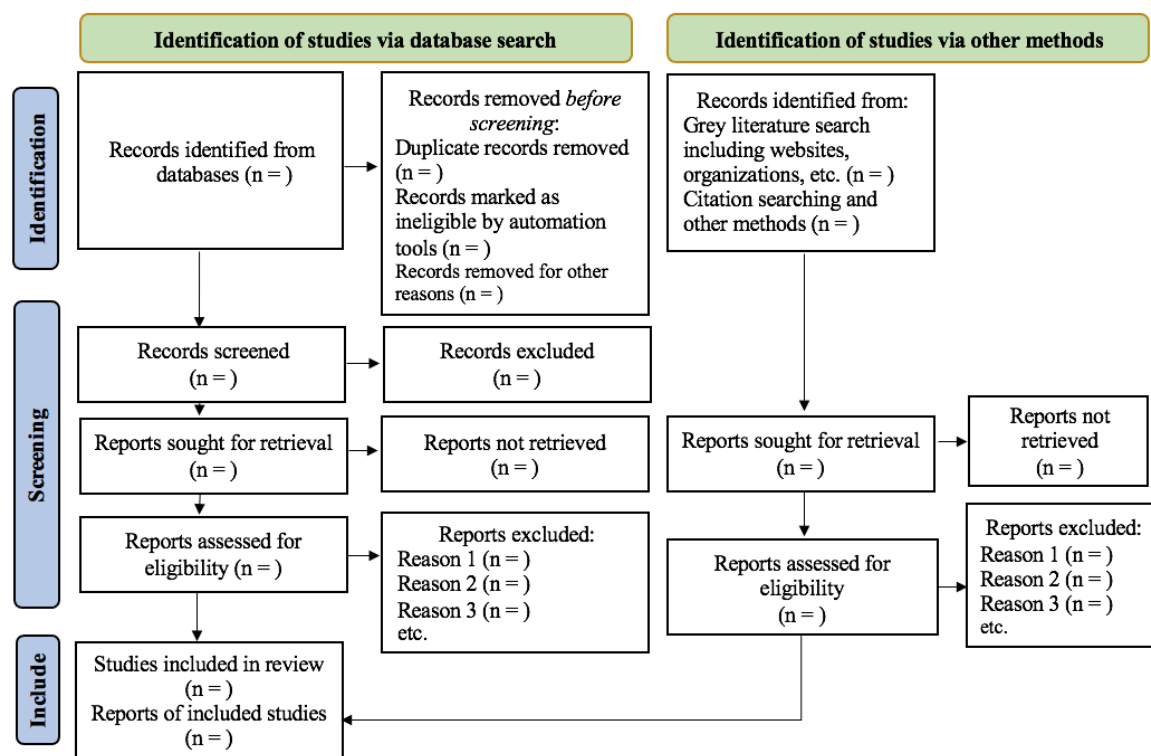
Data Analysis

The data from the eligible articles will be charted and collated by 2 independent reviewers. We have developed a preliminary data extraction instrument (Textbox 4). Nevertheless, as the reviewers go through the studies, they may find new themes and interesting information to extract, and those will be added to the extraction tool. The study characteristics (author, year of publication, methodology and methods, location and context of the studies, objectives and research questions, and population demographics) will be extracted from each study. In addition, we will extract information related to digital equity, such as the barriers, facilitators, outcomes, details of a project and how they were conducted, key findings from the research, recommendations, and future research directions. In case of any disagreements between the reviewers, a third reviewer will mediate to arrive at a consensus. If there is any missing data in the eligible articles, the authors of those papers will be contacted.

We will go through the following phases during the analysis based on the thematic analysis framework by Braun and Clarke [45]:

- Data familiarization: includes an iterative reading of the articles and highlighting interesting points related to the research questions.
- Generating initial code: double-checking the initial highlighted points and identifying new codes or modifying them as initial codes if they represent a specific idea relevant to the research questions.
- Searching for themes across the data: compare and contrast to identify themes and subthemes from the coded data.
- Reviewing themes: through discussion among the research team, the themes will be reviewed to ensure they align with the different perspectives of the team members, including the researchers, city, and community stakeholders of this topic.
- Producing the report: a scholarly report will be produced for peer-reviewed publications.

Textbox 4. Data extraction scheme.

Citation details

- Title

- Authors

- Publication date

- Country of publication

- Journal

- Type of publication

Study demographics

- Participant demographics

- Sample size

- Population subgroups

- City or cities where the project was undertaken

- Stakeholders involved (researchers, policy makers, etc)

- Constructs of the digital divide

Digital equity characteristics

- Primary aim of the study or initiative

- Aspects of digital equity (ie, access, availability, skills, etc)

- Explorative or solution-oriented

- Study focus level (ie, community, city administration, etc)

- Duration or frequency

- Sustained, temporary, pilot, or failed

Initiative/program details

- Description

- Justification

- Recruitment

- Challenges described

- Facilitators described

- Key steps or process description

Study findings

- Outcomes

- Recommendations

- Future research directions

- Future implementation direction

- Applicability

- Limitations, gaps, or concerns

Presenting the Results

Following step 4 above, the extracted data will be iteratively compared, scrutinized, and discussed between the research team to generate key themes and subthemes. In the manuscript, the extracted data will be presented in tabular or diagrammatic form, while a summary and lessons learned will be presented in a narrative format.

The results will be organized based on the key themes and subthemes, and a summary will be generated for meaningful interpretation. The knowledge gained from the studies will be interpreted in light of our research questions and will be presented so that potential knowledge users, such as the City

of Calgary and other stakeholders, can utilize it. Any research gaps will also be pointed out to provide future research directions.

Results

As of August 25, 2022, we have searched 8 academic databases from multiple disciplines (Web of Science, Scopus, Academic Search Complete, Canadian Research Index, MEDLINE, SocINDEX with Full Text, Communication & Mass Media Complete, and IEEE Xplore digital library: Standards). We identified 9776 articles from the search results initially and uploaded them into Covidence. Covidence removed 1312 duplicates, resulting in 8464 articles to be screened. In addition, a gray literature search including Google Scholar, ProQuest (Theses and Dissertations), OAISter (WorldCat), Google, Bing, Yahoo!, and several organizational websites (National Digital Inclusion Alliance and Canadian Radio-television and Telecommunications Commission) were searched. Initially, we identified 178 articles from the search results, and 5 more articles have been sourced by our partner, the City of Calgary's connection in other municipalities and provinces. Two independent reviewers will complete the 2-step screening (title, abstract, and full-text screening) of a total of 8647 articles followed by data extraction and analysis in 4 months (expected by December 2022).

Discussion

Anticipated Outcomes

We intend to identify and summarize key findings from existing digital equity–related initiatives, programs, activities, research findings, issues, barriers, policies, recommendations, etc from the peer-reviewed literature. This will give us an understanding of the landscape of research and initiatives that have been systematically reported. We expect to learn what barriers and facilitators of digital equity exist, which population groups are being affected the most and why, and what social, material, and political issues need to be addressed to establish equity in the context of a high-income and multicultural city. We will learn the findings and recommendations from research projects on digital equity and descriptions of which approaches may or may not work and why and the thoughts and behaviors of community members and private, nonprofit, and government stakeholders. From the gray literature, that is, non–peer-reviewed organization reports and reflections on digital equity–related programs and policies, we will learn about practical experiences from the implementation perspective. The integrative review will also allow us to understand the available and necessary resources in respect of digital equity and how to acquire more resources and apply them in an appropriate way.

This study has a narrow focus on digital equity in racialized communities in the urban areas of high-income countries. In an earlier period, ensuring internet connection and accessibility of internet-enabled devices were the key issues against digital equity in urban areas, which is often termed in the literature as the first level of the digital divide [46,47]. However, having an internet connection and internet-enabled devices accessible and available has shifted the focus of concern toward the second

and third levels of the digital divide. The second level refers to the improvement of digital literacy of the urban population, while the third level focuses on enabling them to gain the maximum output (eg, gaining employment or health services using the internet) [48]. Improving individual digital skills or literacy, including using the internet and understanding and ensuring one's digital privacy, contributes to a gain in digital capital that may contribute to human, economic, and social capital [49]. However, despite having the same level of digital skills, the same 2 people may not benefit at the same level. For example, one may want to learn more about a certain physical condition, but the information on the website is only available in medical terms and not in plain language. Therefore, with the same digital skills, a medically savvy person would gain more from the internet than one who is less so. Further, information may be available in one language but not in another, which also creates a discrepancy between the outcome levels for different users. Digital equity also improves trust in web-based activities and persons on the other side of the digital communication, thus increasing social interaction and harmony [49].

Strengths and Limitations

A key strength of this study protocol is its comprehensiveness in including both a traditional academic literature review and an internet scan. It also ensures rigor by following methodological frameworks for both types of activities. The research team is also a profound strength of this study, as partners represent several stakeholders, including the city, community, and multidisciplinary researchers. We have ensured that each of the research team members provides input in developing the search, screening, and analysis strategies and that all perspectives are addressed. In the same fashion, we also have generated a data extraction tool that ensures we extract the maximum relevant data and are able to generate meaningful themes and subthemes.

We also acknowledge certain limitations in this protocol. Digital equity is a very vague and multisectoral topic and can be viewed from numerous perspectives and contexts. For example, digital equity may mean one thing in medicine while certain issues may not apply in education. While we will attempt to capture studies from all disciplines, it might prove overwhelming to attempt to gather all elements of the topic most salient to every discipline and sector in this proposed study. In addition, while there may be certain similarities between cities, each city is unique and has its own strengths and limitations in relation to the topic. While it is crucial to know what activities have been undertaken in cities similar to Calgary to promote digital equity among racialized communities, their approaches and implementation may not be applicable to other cities.

Community-University Partnership and Dissemination Plan

We are taking a community-engaged research approach in this study [50] following the principles of integrated knowledge translation [51,52] where the research partner is involved in each step of the research process from research design to dissemination. Such involvement of the partner accelerates the research uptake and implementation. As our research questions originated from the knowledge user, our partner organization,

the City of Calgary, and as they will be involved in each following step of the study, the knowledge generated here will be directly transferred to the actively involved knowledge users. In addition, we will create a report or policy brief for the City of Calgary stakeholders, which will be distributed by the partners. In addition to a peer-reviewed manuscript conveying the findings of this study to the academics, we will also create an infographic in plain language and a video doodle summarizing the findings in lay terms. We will disseminate these through our social and ethnic media networks to reach the extended group of stakeholders and the racialized communities in Calgary and beyond. The City of Calgary's digital equity team also has established a cross-sectorial Digital Equity Advisory Panel, and the panel members will be important

knowledge users for this review report as well as important knowledge mobilizers of this review's findings.

Conclusions

Digital equity is complex to achieve, as it intersects with a variety of systemic inequities. Learning from previous studies and other high-income cities through an integrative review and internet scan will provide valuable insights into future research, development, and policy directions. The urban population is generally extremely diverse, and each population group within an urban area may have unique advantages and disadvantages in terms of digital equity. Being informed about those unique aspects will help develop workable and acceptable strategies to improve digital equity for all.

Authors' Contributions

TCT, KK, RW, ER, and MN conceptualized the study. NC, SS, and MMHR were involved in the methodological planning and will be involved in the data curation and formal analysis. TCT, KK, ER, and MN are involved in acquiring resources. TCT is responsible for research supervision. TCT, NC, SS, and MMHR undertook the writing of the original draft, and all authors contributed intellectually with critical appraisal of the draft. All authors agree to take public responsibility for the paper's contents and have approved the final paper prior to submission. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist adapted for a systematic integrative review.
[DOCX File , 33 KB - resprot_v11i12e40068_app1.docx]

Multimedia Appendix 2
Search string (MEDLINE).
[DOCX File , 31 KB - resprot_v11i12e40068_app2.docx]

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Abbreviations

AACODS: authority, accuracy, coverage, objectivity, date, and significance
PCC: Population, Concept, Context
PRESS: Peer Review of Electronic Search Strategies
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

Protocol

Contemporary Databases in Real-world Studies Regarding the Diverse Health Care Systems of India, Thailand, and Taiwan: Protocol for a Scoping Review

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Abstract

Background: Real-world data (RWD) related to patient health status or health care delivery can be broadly defined as data collected outside of conventional clinical trials, including those from databases, treatment and disease registries, electronic medical records, insurance claims, and information directly contributed by health care professionals or patients. RWD are used to generate real-world evidence (RWE), which is increasingly relevant to policy makers in Asia, who use RWE to support decision-making in several areas, including public health policy, regulatory health technology assessment, and reimbursement; set priorities; or inform clinical practice.

Objective: To support the achievement of the benefits of RWE in Asian health care strategies and policies, we sought to identify the linked contemporary databases used in real-world studies from three representative countries—India, Thailand, and Taiwan—and explore variations in results based on these countries' economies and health care reimbursement systems by performing a systematic scoping review. Herein, we describe the protocol and preliminary findings of our scoping review.

Methods: The PubMed search strategy covered 3 concepts. Concept 1 was designed to identify potential RWE and RWD studies by applying various Medical Subject Headings (MeSH) terms ("Treatment Outcome," "Evidence-Based Medicine," "Retrospective Studies," and "Time Factors") and related keywords (eg, "real-world," "actual life," and "actual practice"). Concept 2 introduced the three countries—India, Taiwan, and Thailand. Concept 3 focused on data types, using a combination of MeSH terms ("Electronic Health Records," "Insurance, Health," "Registries," "Databases, Pharmaceutical," and "Pharmaceutical Services") and related keywords (eg, "electronic medical record," "electronic healthcare record," "EMR," "EHR," "administrative database," and "registry"). These searches were conducted with filters for language (English) and publication date (publications in the last 5 years before the search). The retrieved articles will undergo 2 screening phases (phase 1: review of titles and abstracts; phase 2: review of full texts) to identify relevant and eligible articles for data extraction. The data to be extracted from eligible studies will include the characteristics of databases, the regions covered, and the patient populations.

Results: The literature search was conducted on September 27, 2022. We retrieved 3,172,434, 1,094,125, and 672,794 articles for concepts 1, 2, and 3, respectively. After applying all 3 concepts and the language and publication date filters, 2277 articles were identified. These will be further screened to identify eligible studies. Based on phase 1 screening and our progress to date, approximately 44% (1003/2277) of articles have undergone phase 2 screening to judge their eligibility. Around 800 studies will be used for data extraction.

Conclusions: Our research will be crucial for nurturing advancement in RWD generation within Asia by identifying linked clinical RWD databases and new avenues for public-private partnerships and multiple collaborations for expanding the scope and spectrum of high-quality, robust RWE generation in Asia.

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Introduction

Background

Real-world data (RWD) related to patient health status or the delivery of health care can be broadly defined as data collected outside of conventional clinical trials. RWD are derived from a wide range of sources, including databases, treatment and disease registries, electronic medical records (EMRs), insurance claims, and information directly contributed by health care professionals or patients themselves [1].

High-quality, real-world evidence (RWE) relies on the appropriate analysis of RWD collected in ways that maximize their completeness, accuracy, standardization, and timeliness and reduce bias [2]. Yet, effective RWD utilization also requires disparate data sources to be turned into high-quality data sets [3].

Policy drivers have increased RWE adoption, particularly in the Western hemisphere where, for example, the US 21st Century Cures Act required the Food and Drug Administration to develop guidelines for the role of RWD in drug approvals [4]. In the United Kingdom, the Academy of Medical Sciences and the Association of the British Pharmaceutical Industry have recently prioritized supporting the inclusion of RWD in regulatory and health technology assessment processes, as well as the inclusion of electronic health records (EHRs), via the US Health Information Technology for Economic and Clinical Health Act and EHR incentive programs under the Affordable Care Act [3].

The collection of RWE is increasingly crucial in Asia. Only around 17% of clinical trials are conducted in Asia, and Asian populations are often underrepresented in pivotal clinical trials [5,6]. RWE provides certainty about the safety and effectiveness of medications, health interventions, and technologies in local settings for Asian patients [5]. Therefore, there is a need to increase the adoption of RWE by policy makers in Asia to support decision-making in several areas, including public health policy, regulatory health technology assessment, and reimbursement; set priorities; or inform clinical practice [7].

To support the purpose of achieving the benefits of RWE in Asian health care strategies and policies, we sought to identify the linked contemporary databases used in real-world studies from three representative countries—India, Thailand, and Taiwan—and reflect the diversity in Asia by performing a systematic scoping review.

The databases identified in our review will serve as a basis for further guiding approaches and initiatives that aim to drive collaboration and improvements in the generation and utilization of RWE in health care decision-making within Asia.

Rationale for Selecting 3 Diverse Countries (India, Thailand, and Taiwan)

Asia is a very diverse region. For the planned scoping review, we chose a representative country for the following three economy types in Asia: high-income economy (Taiwan), upper-middle–income economy (Thailand), and lower-middle–income economy (India). These economies were defined according to the World Bank analysis for the 2023 fiscal year [8]; low-income economies are those with a gross national income (GNI) per capita (calculated using the World Bank Atlas method) of US $1085 or less in 2021, lower-middle–income economies are those with a GNI per capita of between US $1086 and US $4255; upper-middle–income economies are those with a GNI per capita of between US $4256 and US $13,205, and high-income economies are those with a GNI per capita of US $13,205 or more.

Another factor that contributed to our decision to focus on these three countries was the fact that market approval processes, including reimbursement, and price control mechanisms for medicines and medical devices are very distinct in Thailand, India, and Taiwan. India has a largely self-pay health care system through which patient payments are made to private sector providers [9]. Thailand and Taiwan provide health insurance for universal coverage. Thailand provides differential decentralized benefit packages to those who can contribute the premium, while a single social health insurance scheme exists in Taiwan. Additionally, Taiwan adopts more comprehensive payment system reforms, such as global budgeting, which contributes to cost containment [10]. Further, listing in the National Health Insurance formulary for Taiwan requires evidence of effectiveness, whereas cost-effectiveness is not mandatory in Thailand [11].

Rationale for Our Study

Linked or integrated contemporary databases are like clinical data warehouses or repositories that could serve as excellent resources for the generation of RWD for disease surveillance, monitoring, and treatment outcomes and the timely detection of infection outbreaks [12,13]. However, little is known about the scope and competency of these databases, which are expected to vary based on the economies and health care reimbursement systems in different countries. Hence, the identification and thorough analyses of these databases are the first step in understanding their capabilities, trends, and variations in different countries within Asia and may enable future private-public research partnerships.

Methods

The study protocol and methodology for our scoping review will adhere to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping

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Reviews) guidelines [14]. Herein, we discuss the approaches for the concept and research strategy, data extraction, and data mining.

Concept Strategy and Filters

Articles will be retrieved by searching the National Institutes of Health's PubMed database, using appropriate Medical Subject Headings (MeSH) terms and keywords together with appropriate filters, as described below. The following concepts were used to generate the search strategy for our scoping review.

Concept 1 (RWE and RWD Citations)

Since there are no MeSH terms for RWE and RWD, the MeSH terms and keywords in the following query were adapted from our own research and prior studies [15,16]: *("Treatment Outcome"[MeSH] OR "Evidence-Based Medicine"[MeSH] OR "Retrospective Studies"[MeSH] OR "Time Factors"[MeSH] OR "real world" OR "real-world" OR "RWD" OR "RWE" OR "real life" OR "real patient" OR "real practice" OR "real clinical" OR "real population" OR "actual world" OR "actual life" OR "actual patient" OR "actual practice" OR "actual clinical" OR "actual population").*

Concept 2 (Pilot Countries):

The following query introduced the three countries: *("India"[MeSH] OR "Taiwan"[MeSH] OR "Thailand"[MeSH] OR "India" OR "Taiwan" OR "Thailand").*

Concept 3 (Real-world Research Databases):

The MeSH terms and keywords in the following query were adapted from our own research and prior studies [16]: *("Electronic Health Records"[MeSH] OR "Insurance, Health"[MeSH] OR "Registries"[MeSH] OR "Databases, Pharmaceutical"[MeSH] OR "Pharmaceutical Services"[MeSH] OR "registry" OR "registries" OR "electronic health record*" OR "electronic healthcare record*" OR "electronic medical record*" OR "EHR" OR "EHRs" OR "EMR" OR "EMRs" OR "claims database*" OR "administrative database*" OR "hospital data" OR "claims data" OR "electronic health data" OR "clinical database*" OR "electronic healthcare data" OR "informatics").*

PubMed Filters

In addition to the three concepts outlined above, we also applied the following two filters in PubMed: a filter for English-language publications and a filter for publications within the last 5 years of the date of the search. We focused on English publications to help with identifying studies and RWD and RWE databases that would be of interest to an international audience. We also limited the search to articles published within the last 5 years to help with identifying databases that are currently being used or have recently been used.

Research Strategy for Phases 1 and 2 of the Screening Process

Textbox 1 provides the inclusion and exclusion criteria for the extraction of data from the citations that were retrieved from PubMed by using the above search strategy. The eligibility criteria established for our scoping review were carefully chosen after the consideration of prior systematic reviews and scoping reviews and were selected to help with identifying studies reporting RWD and RWE. Of particular note, we will limit the studies to those involving data that were collected across more than 1 institution, similar to a previous report [17]. We made this decision because single-center databases may be less representative of a country or may include a highly specific patient population. We also decided to exclude pragmatic clinical trials (PCTs). Although such studies may fall within the scope of RWD, as reviewed in the *Discussion* section, these studies are subject to some limitations, and they are sometimes difficult to differentiate from randomized controlled trials (RCTs) [18,19], raising the complexity of the screening process.

A single reviewer performed phase 1 screening (titles and abstracts of publications) and phase 2 screening (full texts) to determine the eligibility of the publications for data extraction. Articles for which full texts were unavailable were also reassessed, and those that clearly satisfied the eligibility criteria were included in the next phase. Phase 1 and phase 2 screening were carried out by using Covidence software (Veritas Health Innovation Ltd), which is recommended by Cochrane. The software screens for duplicates automatically, although duplicates were considered unlikely due to the use of 1 database. The results will be further verified by a second reviewer. Any contradictions or discrepancies that arise between the reviewers will be discussed until a consensus is reached. If there is no consensus, a third reviewer will be consulted.

The hand searching of reviews, other publication types, or the reference lists of eligible articles is not planned. It was considered that any articles that would normally be identified via hand searching were more likely to predate the search filters or would be unlikely to satisfy the eligibility criteria.

Textbox 1. Inclusion and exclusion criteria for the extraction of data from the citations retrieved from PubMed.

Inclusion criteria

- Database types
    - Studies involving electronic health records, health insurance claims, administrative claims, clinical registries, or pharmacy databases
    - Databases with research data involving >1 hospital or clinic

- Publication types
    - Original research, including brief reports, short communications, and research letters

- Study types
    - All types of real-world studies (or their protocols) using the following databases: electronic health records, health insurance claims, administrative claims, clinical registries, or pharmacy databases

- Scope of publication
    - Studies with databases involving Taiwan, India, or Thailand
    - Eligible international, regional, or multicountry studies will be included, provided that any of the target countries are included

Exclusion criteria

- Database types
    - A data source involving electronic health records, health insurance claims, administrative claims, clinical registries, or pharmacy databases is not mentioned
    - Databases with research data involving 1 hospital or clinic

- Publication types
    - Correspondence and letters to the editor; editorials; commentaries; guidelines; case reports; case series (publications with prospective descriptions of a handful of patient cases; retrospective case series with a real-world data study design [20] will be eligible for inclusion); and narrative, systematic, or scoping reviews

- Study types
    - Randomized controlled trials, pragmatic clinical trials, preclinical studies, and nonhuman studies

- Scope of publication
    - Studies with a scope outside of Taiwan, India, or Thailand

Data Extraction

After phase 2 screening, we plan to extract the following data from eligible studies:

1. Article characteristics, including the manuscript type (clinical study vs protocol), year of publication, and contact details of the corresponding author or database manager.
2. Database characteristics, including the region(s) covered, number of participating centers and institutions, and source of data (eg, medical records, health care insurance, clinical registries, pharmacy records, or mixed databases involving more than 1 type of data).
3. Study participant characteristics, including the number of subjects included in the primary analyses and the disease or medical condition studied.
4. Study types, including comparative effectiveness studies (involving clinical benefit, safety, quality of life or cost comparison of at least 2 treatments), single-population studies (eg, the burden of disease, epidemiology, disease

nature course, or treatment pattern), and others. Studies will be further categorized based on the studied outcome(s).

5. Study duration (start and end year).

Eligible abstracts for which full texts are unavailable or cannot be sourced will be included for data extraction to maximize the availability of data from the largest number of published articles as much as possible. This was considered feasible because abstracts often contain the information that we wish to collect for data extraction.

A single reviewer will extract the data from all eligible full texts and abstracts by using a template on Covidence that was standardized based on the data extraction requirements. A second reviewer will review and perform a quality check of the extracted data.

Data Mining

The key databases from each country will be analyzed based on the frequency of the use of each research database to generate published RWD studies that are written in English and indexed

in PubMed. The number and characteristics of key databases from each country will be analyzed further for web-based research, and the frequency with which each major research database is used to generate published, English, PubMed-indexed RWD studies will be analyzed for each country.

Results

We have finalized the search strategy, and Table 1 provides the final number of citations that were retrieved from PubMed via the search conducted on September 27, 2022. After applying the three concepts and the filters for language (English) and publication date (publications in the last 5 years before the search), the search yielded a total of 2277 citations. No duplicates were identified. Further citations may be identified during the screening and data extraction steps.

We have now started phase 1 screening (titles and abstracts) for the retrieved citations. Based on our progress to date, approximately 44% (1003/2277) of the articles were included in phase 2 screening. Of these, we anticipate that around 800 studies will be eligible for data extraction, based on the trend for the proportion of eligible studies in phase 2 screening (full texts) [17]. This accounts for approximately 35% (800/2277) of the articles retrieved via the literature search.

We hope to complete the pilot research and submit the results for publication in early 2023. Although our preliminary research involves 3 selected countries in Asia, we hope to expand our search to include studies from other countries based on the results of the scoping review for the three pilot countries.

Table 1. Final number of citations that were retrieved from PubMed via the search strategy.

Query number	Query	Results, n
1	Concept 1: *("Treatment Outcome"[MeSH] OR "Evidence-Based Medicine"[MeSH] OR "Retrospective Studies"[MeSH] OR "Time Factors"[MeSH]OR "real world" OR "real-world" OR "RWD" OR "RWE" OR "real life" OR "real patient" OR "real practice" OR "real clinical" OR "real population" OR "actual world" OR "actual life" OR "actual patient" OR "actual practice" OR "actual clinical" OR "actual population")*	3,172,434
2	Concept 2: *("India"[MeSH] OR "Taiwan"[MeSH] OR "Thailand"[MeSH] OR "India" OR "Taiwan" OR "Thailand")*	1,094,125
3	Concept 3: *("Electronic Health Records"[MeSH] OR "Insurance, Health"[MeSH] OR "Registries"[MeSH] OR "Databases, Pharmaceutical"[MeSH] OR "Pharmaceutical Services"[MeSH] OR "registry" OR "registries" OR "electronic health record*" OR "electronic healthcare record*" OR "electronic medical record*" OR "EHR" OR "EHRs" OR "EMR" OR "EMRs" OR "claims database*" OR "administrative database*" OR "hospital data" OR "claims data" OR "electronic health data" OR "clinical database*" OR "electronic healthcare data" OR "informatics")*	672,794
4	Query 1 *AND* query 2 *AND* query 3[a]	4168
5	Query 4 with filter for English-language articles	4163
6	Query 5 with filter for articles published in last 5 years[b]	2277

[a]((("Electronic Health Records"[MeSH] OR "Insurance, Health"[MeSH] OR "Registries"[MeSH] OR "Databases, Pharmaceutical"[MeSH] OR "Pharmaceutical Services"[MeSH] OR "registry" OR "registries" OR "electronic health record*" OR "electronic healthcare record*" OR "electronic medical record*" OR "EHR" OR "EHRs" OR "EMR" OR "EMRs" OR "claims database*" OR "administrative database*" OR "hospital data" OR "claims data" OR "electronic health data" OR "clinical database*" OR "electronic healthcare data" OR "informatics")) AND (("India"[MeSH] OR "Taiwan"[MeSH] OR "Thailand"[MeSH] OR "India" OR "Taiwan" OR "Thailand"))) AND (("Treatment Outcome"[MeSH Terms] OR "Evidence-Based Medicine"[MeSH] OR "Retrospective Studies"[MeSH] OR "Time Factors"[MeSH] OR "real world" OR "real-world" OR "RWD" OR "RWE" OR "real life" OR "real patient" OR "real practice" OR "real clinical" OR "real population" OR "actual world" OR "actual life" OR "actual patient" OR "actual practice" OR "actual clinical" OR "actual population")).

[b]The search was conducted on September 27, 2022.

Discussion

We aim to identify the medical and health-related databases used in 3 representative countries within Asia by applying a defined search strategy with a set of inclusion and exclusion criteria, as detailed in this protocol. By using this search strategy, we have already identified a large number of eligible studies from the three countries; our recent estimates suggest that around 35% (800/2277) of the studies that were retrieved via the literature search will be used for data extraction to identify and characterize the relevant databases used in India, Taiwan, and China. This rate is higher than that of a global review of articles published between 2010 and 2015, in which 10,069 articles were screened and 2635 unique data sources were identified (approximately 23%) [17]. This also indicates that our search strategy is focused and vigorous in identifying relevant citations for our research question.

We have excluded databases with research data involving a single hospital or clinic from the scope of our research to identify relevant linked clinical databases with the potential for adopting big data to generate robust, fit-for-purpose RWE in Asia. Our rationale for including databases with research data involving more than 1 hospital or clinic in the search strategy was to gather details on current databases that are linked across clinical centers, which enable holistic RWD generation with good external validity. A similar criterion was also applied in another recent study [17]. Single-center clinical data and study outcomes are known to have limitations, such as limited

generalizability; small study effects; a higher risk of bias, including reporting bias; or limitations related to the selection of participants, treatment administration, and care providers' expertise [21].

Asia is a highly diverse region, and our systematic scoping review will focus on 3 different countries that are deemed representative to reflect that diversity. We understand that the findings from the pilot research countries may not apply throughout Asia because the health care systems and database standards vary across the region. Hence, we hope to expand our research to include other countries in Asia after completing the preliminary research on the selected three countries. We are also mindful of the limitation that our findings will be limited to citations that are retrieved from PubMed only. Searching too few literature databases may yield a biased sample of primary studies, which may influence the accuracy of the summary effects and subsequently reduce the validity and generalizability of the systematic review results. Nevertheless, limiting the search to PubMed is in line with our strategy for identifying research databases that generate and yield robust RWD that are fully published in indexed, peer-reviewed journals and reducing duplicate search results.

We also excluded the PCT design, although it falls within the scope of RWD. PCTs are randomized studies in which the study participants should be similar to patients who would receive the intervention if it became usual care, which is information that may be unknown for new interventions. There are several limitations with the PCT design [18], and a recent review indicated that PCTs have a high degree of diversity in their designs and scopes, PCTs have deficiencies in reporting and trial registry data, and many studies with a pragmatic intent do not use the term *pragmatic* in the title or abstract [19]. Hence, including PCTs would have risked the methodology and complicated the retrieval of eligible studies. Therefore, we decided to exclude them in our search strategy. Likewise, RCTs were excluded because RWD are collected outside of highly controlled RCTs; thus, such studies would not serve the purpose of our review. The lack of randomization is a key criterion for identifying RWD studies and is well reflected in the definitions provided by reputable bodies, including the Association of the British Pharmaceutical Industry and the International Society for Pharmacoeconomics and Outcome Research [22]. Currently, the National Institutes of Health's MeSH database lacks specific terms for RWE and RWD. Therefore, we relied on our own research and on strategies suggested in published studies, as explained in the *Methods* section, to identify relevant articles.

Overall, we believe that our research will be crucial for determining and understanding the scope, spectrum, and competence of linked, clinical, real-world databases in diverse countries with different economies and health care reimbursement systems. We anticipate that this crucial step will nurture advancement in RWD generation by shaping new avenues for public-private partnerships and multiple collaborations for high-quality, robust RWE generation in Asia.

Data Availability

All available data are included within this article.

Authors' Contributions

All authors were involved in the conception of the idea, the design, and the interpretation of the facts and data. SS and DF were involved in manuscript writing, and all authors were engaged in revising the manuscript for scientific content and provided final approval before its submission for publication.

Conflicts of Interest

WYS, SPS, and HS are employees of Pfizer.

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Abbreviations

EHR: electronic health record
EMR: electronic medical record
GNI: gross national income
MeSH: Medical Subject Headings
PCT: pragmatic clinical trial
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

RCT: randomized controlled trial
RWD: real-world data
RWE: real-world evidence

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<u>Protocol</u>

The Use of Passive Smartphone Data to Monitor Anxiety and Depression Among College Students in Real-World Settings: Protocol for a Systematic Review

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Abstract

Background: College students are particularly at risk of depression and anxiety. These disorders have a serious impact on public health and affect patients' daily lives. The potential for using smartphones to monitor these mental conditions, providing passively collected physiological and behavioral data, has been reported among the general population. However, research on the use of passive smartphone data to monitor anxiety and depression among specific populations of college students has never been reviewed.

Objective: This review's objectives are (1) to provide an overview of the use of passive smartphone data to monitor depression and anxiety among college students, given their specific type of smartphone use and living setting, and (2) to evaluate the different methods used to assess those smartphone data, including their strengths and limitations.

Methods: This review will follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Two independent investigators will review English-language, full-text, peer-reviewed papers extracted from PubMed and Web of Science that measure passive smartphone data and levels of depression or anxiety among college students. A preliminary search was conducted in February 2022 as a proof of concept.

Results: Our preliminary search identified 115 original articles, 8 of which met our eligibility criteria. Our planned full study will include an article selection flowchart, tables, and figures representing the main information extracted on the use of passive smartphone data to monitor anxiety and depression among college students.

Conclusions: The planned review will summarize the published research on using passive smartphone data to monitor anxiety and depression among college students. The review aims to better understand whether and how passive smartphone data are associated with indicators of depression and anxiety among college students. This could be valuable in order to provide a digital solution for monitoring mental health issues in this specific population by enabling easier identification and follow-up of the patients.

Trial Registration: PROSPERO CRD42022316263; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=316263

International Registered Report Identifier (IRRID): DERR1-10.2196/38785

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Introduction

Background

Depression is recognized as a leading cause of poor health globally [1]. It is defined as a succession of characteristic depressive episodes, with symptoms including pathological sadness, loss of pleasure, and cognitive symptoms. Depression can lead to an increased risk of death, with suicide rates among clinically depressed patients ranging from 5% to 20% [2]. Anxiety disorders are also common in the general population, with 20% of adults having anxiety at one point in their lives. People affected by anxiety disorders feel intense and persistent anxiety without any tangible danger but in a way that affects their daily life [3]. Anxiety disorders are often correlated with depression and precede it in most cases, even if the inverse has also been observed [3]. Both mental disorders should be treated as early as possible to prevent the risk of relapse and aggravation [2,3].

College students experience substantially higher rates of depression than the general population [4], and several studies have shown that anxiety is prevalent among them [5-10]. One study identified several risk factors for anxiety and depression that were directly linked to college, such as tuition fees and the college's location [6]. Another study noted that regular alcohol consumption—a common behavior among college students—is also a risk factor for anxiety [10]. Mental disorders among college students are a growing concern, and this was especially true during the COVID-19 pandemic. It has been shown that the COVID-19 pandemic led to increases in several psychological disorders among the general population [11], and this result has been confirmed among college students: the prevalence of depression and anxiety greatly increased during the COVID-19 pandemic, rising from 21% and 19%, respectively, before March 1, 2020, to 54% and 37% afterward [12].

The smartphone's potential to help address the critical and challenging issues of depression and anxiety among college students deserves a careful analysis. Smartphones are now ubiquitous in modern societies, with 6.37 billion smartphone users worldwide in 2021, and the average smartphone user checks their smartphone 63 times a day, according to Bankmycell [13,14]. Smartphones are even more present in the lives of young Europeans aged 16-29 years [15].

This omnipresence of smartphones among college students makes them important features in young people's mental health. Indeed, smartphones have been studied as both a potential cause of disorders [16] and a tool for interventional treatment [17]. They also enable data collection through passive sensing, which is the collection of environmental and personal data about a user, with minimal interaction and effort on their part. These passive smartphone data are therefore collected continuously with minimal burden on the user, making it suitable for analyzing the user's mental health. Hence, passive smartphone data collection may provide a clinical opportunity to detect and monitor mental health disorders in the specific population of college students.

The use of passive smartphone data to monitor health and well-being has been reported previously, highlighting the benefits of passive sensing for monitoring mental health, sleep, and sociability, or for fall detection [18,19]. More precisely, passive data from smartphones and wearable devices have been reported as useful in monitoring clinical populations with specific mental health conditions, such as bipolar disorders, schizophrenia, autism, or psychosis [20-23]. Specifically, the use of passive smartphone data for monitoring depressive mood symptoms in people with bipolar disorders has been widely studied [24-32]. Faurholt-Jepsen et al [24,25] found that several features correlate with depressive symptoms, including the number of SMS text messages, the daily average duration of calls, and the amount of screen time. Previous studies also reported the use of machine learning approaches to establish a link between the geolocation of smartphone data [26] or acoustic features from the smartphone's microphone [27], and depressive mood symptoms in people with bipolar disorders [26,27]. Additionally, the use of passive smartphone data for monitoring depression has been studied both in the nonclinical population and in the clinical population with a diagnosis of depression [33-35]. Concerning this clinical population, these studies interestingly showed significant correlations between depressive symptoms and phone call features [33,34]. While one study involving adolescents (n=13, mean age: 14.93 years) showed a significant negative correlation between depression scores and daily average call duration [34], another study involving adults (n=74, mean age: 44.4 years) showed a significant positive correlation [33]. In the nonclinical population, passive smartphone data has been used to monitor anxiety and depression [21,36-42], as well as mental health–related issues, such as stress, well-being, and loneliness [43-49]. These studies reported a large range of possible features derived from passive smartphone data. Alongside the features cited above for clinical populations, we notably reported the time spent in natural outdoor environments [44], sleep disturbance features [40], and daily time spent running [42].

Using passive smartphone data to monitor mental health encounters several challenges that have been previously pointed out by Trifan et al [18] and Harari et al [50]. First, when passive data is collected through an app, battery use and app design are major challenges. Users expect that the battery will not drop out due to the app running in the background continuously and that the app will be easy to use [18]. Providing health-related feedback may help to ensure user interest and adherence [18]. To conduct ethical research, researchers must ensure transparency toward participants. This transparency can be achieved with an informed consent process, including a starting session explaining what and how data will be collected, and a debriefing interview at the end of the study [50]. Authors also raise the fact that studies involving smartphone data demand attention to privacy and security [18,50].

To the best of our knowledge, no prior work has systematically reviewed the use of passive smartphone data to monitor depression and anxiety among college students. Yet, college students are a specific population, both in the way they use their smartphones and in how they experience anxiety and depression. Because they are more at risk from these mental disorders, we

should not miss this potential clinical opportunity to help them use a tool that is in every student's pocket. By identifying and analyzing relevant studies on the topic, we can improve our understanding of the potential to use passive smartphone data to monitor depression and anxiety among college students. This protocol describes the design and methods for a systematic review of published studies analyzing the use of passive smartphone data to monitor depression and anxiety among college students.

Objectives

The review aims to better understand whether and how passive smartphone data is associated with indicators of depression and anxiety among college students. To do so, we will identify and synthesize available literature on methods and main findings regarding the use of passive smartphone data to monitor anxiety and depression among college students.

Methods

Overview

We will initiate the systematic review by following the Population, Intervention, Comparison, and Outcome worksheet guidelines [51]. We will select, analyze, and report on the relevant studies by following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist and guidelines [52]. We recently registered this protocol for our systematic review on the International Prospective Register of Systematic Reviews (CRD42022316263).

Eligibility Criteria

We did not restrict the search to a specific time frame of publication.

The inclusion criteria are as follows:

1. The study participants were college students (in this study, "college students" refer to those who are enrolled in a higher education program, as previously done by Li et al [12] and Lattie et al [53]).
2. The study involved features derived from passive smartphone data. Passive smartphone data refers to data gathered through passive sensing, that is, smartphone-based collection of environmental and personal data about a user, with minimal interaction and effort on their part [18,19,54]. Minimal interaction and effort mean that the user does not need and should not do any input to produce data. For instance, passive smartphone data can be geolocation logs, call logs, text logs, the amount of screen time, and so on.
3. Participants were assessed on a clinically validated rating scale, either self-reported scales or clinical diagnosis scales, used within psychiatry and psychology to screen for depression and anxiety.
4. The study reported measurements quantifying the use of passive smartphone data to monitor anxiety or depression.
5. The study was either a cohort study or a cross-sectional study.

The third criterion is designed to ensure a broad inclusion of studies reporting anxiety and depression symptoms and has been chosen to include both clinical and nonclinical populations.

This is not restricted to a specific rating scale in order to reflect the variety of tools used to assess anxiety and depression symptoms in the literature. However, the inclusion of clinically validated rating scales only, such as Generalized Anxiety Disorder-7 [55], Patient Health Questionnaire-9 [56], or Hamilton Depression Rating Scale [57], was chosen to restrict the analysis to commonly used and validated scales, which enables comparison and generalization.

The exclusion criteria are as follows:

1. The study was not published in English.
2. The study was not published following a thorough peer-review process.
3. No full text was available.
4. The study was one of the following publication types: trial protocols, editorials, letters, opinions, case reports, case studies, reviews, or meta-analyses. Books, book chapters, and other gray literature materials (eg, government reports and theses) will not be included.
5. The study involved only data from smartphone-connected wearables.

This last exclusion criterion is designed to avoid including data from tools that are not as ubiquitous as smartphones, either for financial, cultural, or other reasons. Including data gathered by such tools may lead to a selection bias we want to avoid in the first place, in order to get the most representative sample of college students possible. However, the use of smartphone-connected wearables to monitor mental health conditions has previously been studied in clinical and nonclinical populations [20,23,36].

Data Sources and Search Strategy

Two independent reviewers will search the PubMed and Web of Science electronic databases for published studies meeting the search criteria. No limit to publication dates will be applied. Database-specific search strings will be designed using the Boolean operators "AND" and "OR" in combination with MESH descriptors that might be found in titles or abstracts. The search string will include a combination of terms relating to (1) passive smartphone data and (2) anxiety and depression. The search strings for PubMed and Web of Science were as follows: ("mobile phone location data" OR "mobile phone call data" OR "mobile phone data" OR "cell phone data" OR "cell phone call data" OR "cell phone location data" OR "smartphone location data" OR "smartphone call data" OR " smartphone data" OR "call detail records") AND ("depression" OR "affective disorder*" OR "anxiety" OR "anxiety disorder*" OR "mental health" OR "mood disorder*" OR "unipolar" OR "mental disorder*").

Study Selection

After the removal of duplicates, 2 independent reviewers will screen the articles for eligibility. The 2 reviewers will go through each article's title, abstract, and keywords to make a first selection based on our eligibility criteria. If eligible, the full text will be retrieved, and the same reviewers will screen these for eligibility. In cases of disagreement, the 2 reviewers will find a consensus through discussion, and a third reviewer will be consulted should this prove impossible. As a proof of

concept, a preliminary search and study selection were conducted in February 2022.

Data Extraction

The following 5 data sets will be extracted from each article and compared for coherence by the same 2 reviewers: (1) study characteristics, (2) participant characteristics, (3) methods of passive smartphone data collection and measurement, (4) methods of assessment of anxiety and depression, and (5) main findings on the association between passive smartphone data and levels of anxiety or depression among college students. The authors of the study will be contacted in cases of missing or incoherent data. In cases of disagreement between the 2 reviewers, they will attempt to find a consensus through discussion but will consult a third reviewer should this fail.

Data Synthesis and Analysis

We aim to investigate the use of passive smartphone data to monitor depression and anxiety among college students. We will thus systematically review publications that report any measurements of passive smartphone data and levels of depression or anxiety among college students and that provide any means of using these data to monitor this specific situation. We will report these measurements according to the method used (eg, correlations or regression-based machine learning) and the type of study (cross-sectional or cohort study), with specific attention to the cross-sectional studies, where the causation may be bidirectional. We will compare the results for clinical and nonclinical samples and, notably, verify if the directionality of the association between smartphone features and indicators of depression and anxiety is the same among these two populations. Given that the study will include cross-sectional and cohort studies, no single quality assessment tool is suitable. Hence, the methodological quality of the studies included will be evaluated using a tool created by De Angel and colleagues [36] for a review with a similar scope. The tool combines the Appraisal Tool for Cross-Sectional Studies [58]

and the Newcastle–Ottawa Scale for longitudinal studies [59]. Two independent reviewers will analyze the articles for information about the publication of a protocol, the definition of outcomes, evidence of selective reporting, sample descriptions and definitions of eligibility, statistical controls for confounding and multiple comparisons, missing data, representativeness, and justification of the sample size. The publication of a protocol will be scored as 1 if mentioned and 0 if not mentioned. Each question on the quality assessment tool will be scored 0, 1, or 2. A score of 2 will indicate that the study fulfills the assessment criterion, while a score of 0 will indicate that the assessment criterion is not satisfied. A score of 1 will indicate missing information or a lack of precision in the corresponding items. In cases of disagreement between the 2 reviewers, they will attempt to find a consensus through a discussion but will consult a third reviewer should this fail.

Ethical Considerations

The proposed review will be limited to publicly available materials and information and, therefore, does not require ethical approval. All results will be made available to the public and the scientific community.

Results

As a proof of concept, a preliminary search and study selection were conducted in February 2022 and are schematized in Figure 1. We identified 153 records, of which 115 remained after the removal of duplicates. Of these potentially eligible studies, only 8 fully satisfied our inclusion criteria. We are currently going through the process of data extraction and analysis. We will provide a flowchart that summarizes the search strategy, as well as tables and figures presenting the extracted data and the results of the study quality assessment. We intend to make our results available to an international audience through publication in a peer-reviewed journal.

Figure 1. Study selection flowchart. Electronic databases were searched to retrieve relevant studies. This flowchart represents the review's eligibility criteria.
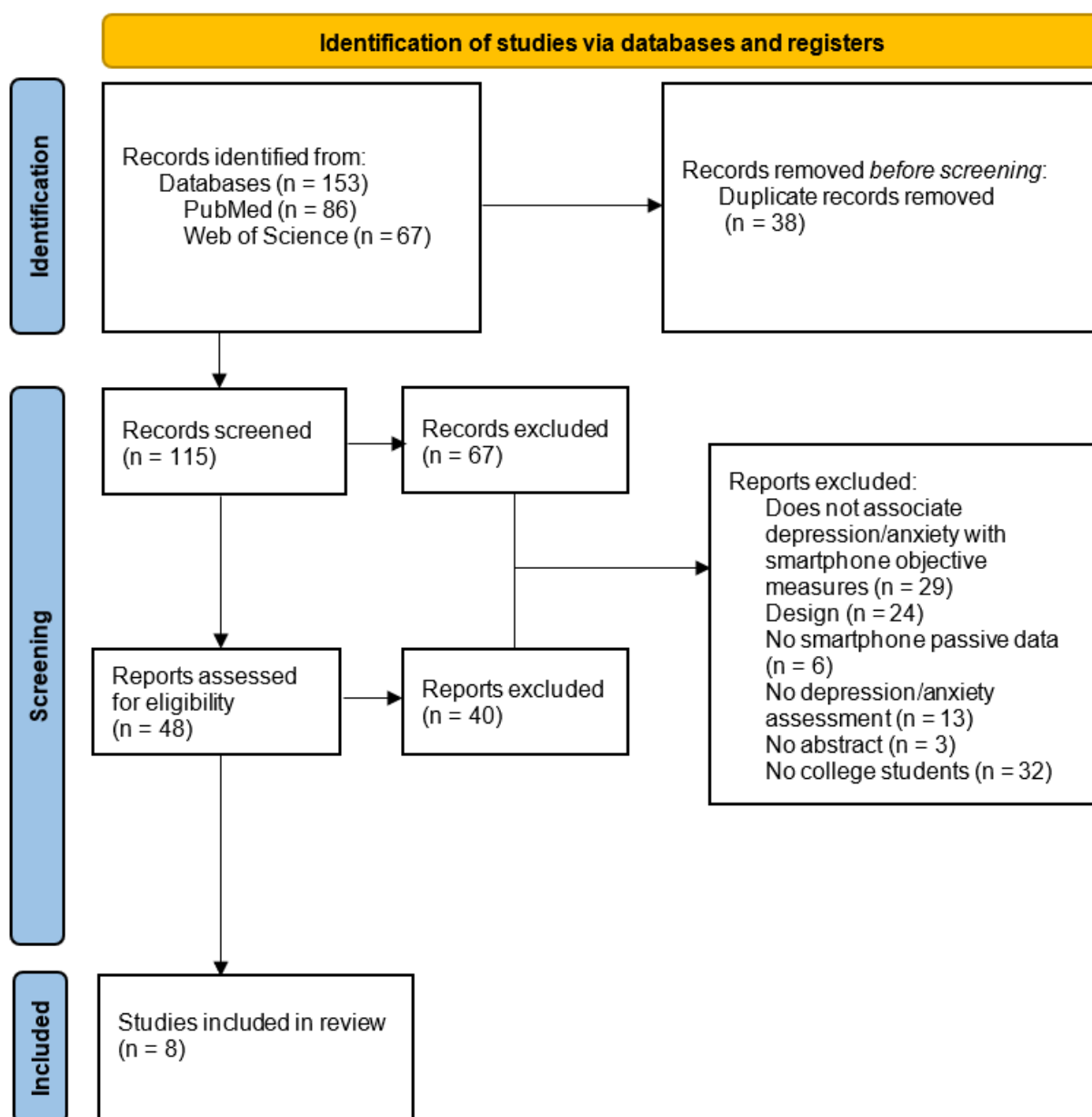
Discussion

Expected Findings

We expect that the findings of this systematic review will have the potential to inform researchers and practitioners about how passive smartphone data has been used to monitor depression and anxiety among college students. In particular, since smartphones are an artifact of everyday life, we expect passive smartphone data to act as proxies for anxiety and depression symptoms in our targeted population.

Comparison to Prior Work

College students are a specific population, both in the way they use their smartphones [60] and in how they experience anxiety and depression [4]. Their living habits are different from the general population, and their smartphone usage is likely to reflect this fact. Yet, previous systematic reviews [18,19,23,36]

focused on a general population (ie, no age restriction beyond limiting to 18- to 65-year-olds), and we do not necessarily expect their conclusions to generalize to college students.

Preliminary Results and Future Steps

Following our study selection process, we found 8 published articles that satisfied our eligibility criteria [42,61-67]. Three articles studied depression only [42,66,67], 1 studied anxiety only [65], and 4 included both depression and anxiety [61-64]. Other mental disorders—or behaviors related to mental disorders—were analyzed in these studies, such as loneliness, disturbed sleep, or stress. Two studies based on the same data sets included 816 participants. The number of participants included in the other 6 studies ranged from 20 to 100. Three studies [61,64,65] examined the use of passive smartphone data to predict mental health. The remaining studies either examined associations between passive smartphone data and mental health indicators [62-65] or aimed to extract the key features from

smartphone data that could help identify depression [42]. Our initial examination of these studies suggests that some features based on passive smartphone data, when appropriately used, could indeed help monitor depression or anxiety among college students.

To the best of our current knowledge, no other work has systematically reviewed the use of passive smartphone data to monitor depression and anxiety among college students. We have registered this protocol for our systematic review on the International Prospective Register of Systematic Reviews (CRD42022316263). We will conduct and report our systematic review according to the PRISMA checklist and guidance [52]. Through this process, we aim to design the appropriate research questions and a search strategy able to extract all the relevant studies' findings. We will provide a synthesis of this, including a flowchart that summarizes the search strategy, as well as tables and figures presenting the extracted data and the results of the study quality assessment. We intend to make our results available to an international audience through publication in a peer-reviewed journal.

Strengths and News Value

We believe that our observations will help increase knowledge of how passive smartphone data can be associated with indicators of depression and anxiety among college students. We estimate that focusing on college students is crucial since they are a specific population, both in the way they use their smartphones and how they experience anxiety and depression. Therefore, we believe that our observations could provide knowledge on how to use passively collected smartphone data to monitor depression and anxiety among college students. It could prove valuable in order to increase the quality of care by providing better identification and follow-up of these disorders through digital solutions.

Limitations

We chose to restrict the set of selected articles to those that have used clinically validated tools to measure anxiety and depression. We did not consider loneliness, well-being, and stress levels even though they may be related to anxiety or depression [68-70]. Additionally, our preliminary search has identified only 1 article based on data collected after March 2020. Therefore, the conclusions drawn from this systematic review might not strictly generalize to lockdown periods during the COVID-19 pandemic.

Data Availability

No data were generated for this research protocol.

Authors' Contributions

EG and NV devised the study's scope, research questions, and study design. They wrote, edited, and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Case-Finding Strategies for Drug-Resistant Tuberculosis: Protocol for a Scoping Review

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Abstract

Background: Transmission of drug-resistant tuberculosis (DR-TB) is ongoing. Finding individuals with DR-TB and initiating treatment as early as possible is important to improve patient clinical outcomes and to break the chain of transmission to control the pandemic. To our knowledge systematic reviews assessing effectiveness, cost-effectiveness, acceptability, and feasibility of different case-finding strategies for DR-TB to inform research, policy, and practice have not been conducted, and it is unknown whether enough research exists to conduct such reviews. It is unknown whether case-finding strategies are similar for DR-TB and drug-susceptible TB and whether we can draw on findings from drug-susceptible reviews to inform decisions on case-finding strategies for DR-TB.

Objective: This protocol aims to describe the available literature on case-finding for DR-TB and to describe case-finding strategies.

Methods: We will screen systematic reviews, trials, qualitative studies, diagnostic test accuracy studies, and other primary research that specifically sought to improve DR-TB case detection. We will exclude studies that invited individuals seeking care for TB symptoms, those including individuals already diagnosed with TB, or laboratory-based studies. We will search the academic databases including MEDLINE, Embase, The Cochrane Library, Africa-Wide Information, CINAHL, Epistemonikos, and

PROSPERO with no language or date restrictions. We will screen titles, abstracts, and full-text articles in duplicate. Data extraction and analyses will be performed using Excel (Microsoft Corp).

Results: We will provide a narrative report with supporting figures or tables to summarize the data. A systems-based logic model, developed from a synthesis of case-finding strategies for drug-susceptible TB, will be used as a framework to describe different strategies, resulting pathways, and enhancements of pathways. The search will be conducted at the end of 2021. Title and abstract screening, full text screening, and data extraction will be undertaken from January to June 2022. Thereafter, analysis will be conducted, and results compiled.

Conclusions: This scoping review will chart existing literature on case-finding for DR-TB—this will help determine whether primary studies on effectiveness, cost-effectiveness, acceptability, and feasibility of different case-finding strategies for DR-TB exist and will help formulate potential questions for a systematic review. We will also describe case-finding strategies for DR-TB and how they fit into a model of case-finding pathways for drug-susceptible TB. This review has some limitations. One limitation is the diverse, inconsistent use of intervention terminology within the literature, which may result in missing relevant studies. Poor reporting of intervention strategies may also cause misunderstanding and misclassification of interventions. Lastly, case-finding strategies for DR-TB may not fit into a model developed from strategies for drug-susceptible TB. Nevertheless, such a situation will provide an opportunity to refine the model for future research. The review will guide further research to inform decisions on case-finding policies and practices for DR-TB.

International Registered Report Identifier (IRRID):   DERR1-10.2196/40009

Introduction

With the emergence of *Mycobacterium tuberculosis* strains resistant to first-line antituberculosis drugs, strategies to control tuberculosis (TB) became even more challenging [1]. It is estimated that almost half a million people have developed rifampicin-resistant TB, of whom 78% had multidrug-resistant TB in 2019 [2]. Although drug-resistant TB (DR-TB) is not as prevalent as drug-susceptible TB, it is more difficult to diagnose, treatment is longer and more toxic, outcomes are worse, and costs are higher. Overall, 67%-100% of people with DR-TB in their households face catastrophic costs (total costs equivalent to >20% of their annual household income) [2].

Finding individuals with DR-TB and initiating treatment as early as possible is important to improve patient clinical outcomes and to break the chain of transmission to help control the pandemic. But despite new diagnostic technologies, only 38% of the estimated number of people who developed DR-TB initiated treatment in 2019 [2,3].

TB can be detected after an individual presents passively to health services or through one of several different screening pathways depending on the case-finding strategy of a TB program [4]. Pathways can also be enhanced via several activities such as health promotion in the community, improved access to TB diagnostic services or training of health workers to identify presumptive TB at general health services. Multiple activities often result in complex interventions and heterogeneous trials, which are difficult to meta-analyze in systematic reviews [5,6].

To our knowledge, systematic reviews assessing effectiveness, cost-effectiveness, acceptability, and feasibility of different case-finding strategies for DR-TB to inform research, policy, and practice have not been conducted, and it is unknown whether enough research exists to conduct such reviews. It is also unknown whether case-finding strategies are similar for DR-TB and drug-susceptible TB and whether we can draw on findings from reviews on drug-susceptible TB to inform decisions on case-finding strategies for DR-TB.

We therefore aim to conduct a scoping review to chart existing literature on case finding for DR-TB and identify priority questions for a systematic review [7,8]. We will also describe existing strategies and how they fit into a model of case-finding pathways for drug-susceptible TB.

Methods

The Arksey and O'Malley framework [9,10], the Joanna Briggs Institute scoping review methodology [8], and the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews [11] will guide the methods for this scoping review.

Defining of the Research Question

The question for our review is as follows: what literature is available on case-finding for DR-TB and which case-finding strategies are described? We will screen studies that have sought to improve case detection for DR-TB.

Identification of Relevant Studies

Table 1 outlines the eligibility criteria for this scoping review.

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Table 1. Eligibility criteria.

Domain	Included	Excluded
Participants	Participate regardless of symptoms; for example, contacts, people living with HIV attending HIV care, and whole communities	Individuals with tuberculosis (TB) symptoms seeking care, individuals diagnosed with TB, and laboratory samples and isolates
Concept or intervention	Strategies specifically aiming to improve or enhance participants' pathways to drug-resistant TB case detection	Intervention strategies aiming to improve finding of TB cases in general, even if they report the yield of drug-resistant TB cases
Outcome	Reporting the yield of drug-resistant TB	Do not report the yield of drug-resistant TB
Context	Community and primary, secondary, or tertiary care centers	Laboratory-based
Study design	Primary studies; systematic reviews; qualitative studies, where the experiences of individuals who receive the intervention or those who provide the intervention are investigated; studies of diagnostic test accuracy if they describe a drug-resistant TB screening strategy; and trials comparing different screening or diagnostic tools within a case-finding intervention for drug-resistant TB	Meta-reviews (review of reviews); narrative reviews; editorials; opinion articles; meeting summaries; guidelines; prevalence surveys, except if the survey includes an intervention strategy to specifically find drug-resistant TB cases; and conference abstracts

With assistance from an information specialist, we will search MEDLINE (PubMed), Embase (Ovid), and The Cochrane Library because they are top academic databases for biomedical research, medicine, and health care; Africa-Wide Information (EBSCOhost) owing to the high prevalence of TB in sub-Saharan Africa; CINAHL (EBSCOhost) because nurses and allied health staff are often the ones carrying out the actual case-finding; and Epistemonikos and PROSPERO to complement the search for systematic reviews. To obtain the highest possible yield, we will use no language or date restrictions; however, if we are not able to translate the articles, we will report them under excluded articles with reasons for exclusion. Reference lists of included studies will be searched.

The preliminary search string will include combinations of the following 3 domains: terms related to "tuberculosis," terms related to "drug resistance," and terms related to "case finding," "case detection," "screening," "contact investigation," and "contact tracing."

Appropriate MeSH (Medical Subject Headings) terms will be added to the different databases. Search strategies from each electronic database are detailed in Multimedia Appendix 1. The search strategy will be piloted and refined in consultation with an information specialist. We will also contact experts working in the field to collect information about ongoing primary research or relevant research missed by the electronic search.

Study Selection

We will use Rayyan systematic review software [12] to screen titles, abstracts, and full-text articles. We will use the "blind" function in Rayyan for screening, except when resolving conflicts. Four reviewers (SvW, MN, LV, and MC) will screen abstracts in duplicate for inclusion. They will resolve conflicts via discussion and meet at the beginning of and after screening 50 abstracts to discuss challenges and possible refinement of the search strategy. Three reviewers (SvW, LV, and MN) will then screen full-text articles for inclusion. Disagreements will

be resolved with a third reviewer (MC) to determine the final studies for inclusion.

Charting of the Data

We will develop a data extraction form in Excel (Microsoft Corp). The data extraction form will be applied to all primary research reports to collect standard information on each study. Information will include the following: authors, journal name, and year of publication; aim or purpose of the research; study design; country characteristics (including income, TB prevalence, HIV prevalence, and urban or rural setting); participants' characteristics (including age, sex, HIV status, and other reported risk factors); target group and how the group was identified, if applicable; interventions (including all components [ie, activities] of the intervention, types of providers, and screening and diagnostic tools used); treatment support, including preventive therapy; and outcomes assessed.

Five authors (SvW, MN, LV, MC, and GH) will extract the data (1 author per paper). A second reviewer (SvW or MC) will check extracted data from each study. The data extraction team and other coauthors will meet regularly after each round of screening of 5-10 studies to determine whether their approach is consistent and in line with the research question.

Patient and Public Involvement

This paper describes the protocol for a scoping review; hence, we did not deem it appropriate to involve patients or the public in the design, conduct, reporting, or dissemination plans of our research.

Results

Collating, Summarizing, and Reporting of the Results

We will provide a narrative report with supporting figures or tables to summarize the data. Textbox 1 contains the definitions we will use in charting, collating, summarizing, and reporting our results.

Textbox 1. Definitions.

Definitions used in the scoping review:

- **Drug-resistant tuberculosis (TB):** all types of drug-resistant TB, including single drug–resistant TB, multidrug-resistant TB, extensively drug-resistant TB, and any other drug-resistant TB reported by the authors.

- **Systematic screening for active TB:** "The systematic identification of people with suspected (presumptive) active TB, in a predetermined target group, using tests, examinations or other procedures that can be applied rapidly. Among those screened positive, the diagnosis needs to be established by one or several diagnostic tests and additional clinical assessments, which together have high accuracy" [3].

- **A screening tool:** tests, examinations, or other procedures used for systematic screening for active TB. Examples of TB screening tools include a structured symptom-based questionnaire, chest radiography, or an algorithm [4]. Algorithms may include sequential or parallel tests. With sequential tests, only those who screen positive with the initial test receive a second test. With parallel tests, those who screen positive on any of the tests are regarded as screen positives.

- **A diagnostic tool:** tests, examinations, or other procedures used to establish a diagnosis of TB in people identified with presumptive TB. Examples of TB diagnostic tools include a clinical algorithm, sputum smear microscopy, the Xpert MTB/RIF test, or cultures [4].

- **TB symptoms:** any TB symptom, including cough, fever, night sweats, weight loss, or a combination of TB symptoms as defined by the study authors.

- **Care seeking:** people seeking care for a perceived health problem.

- **TB care seeking:** people seeking care specifically for TB symptoms.

- **A risk group:** any group of people in whom the prevalence or incidence of TB is significantly higher than that in the general population. Examples of risk groups include a whole population within a geographical area or TB contacts [3].

- **A clinical risk group:** individuals diagnosed with a specific disease or condition that increases their risk for TB; for example, people living with HIV.

- **Presumptive TB:** presumptive TB is identified when a provider identifies a patient with suspected active TB. In the context of screening, a person who screens positive is a presumptive TB case.

- **Passive case finding, passive case finding with an element of systematic screening, triage, enhanced case finding, active case finding, contact tracing or contact investigation, and intensified case finding:** some of these definitions overlap and are used inconsistently within the literature. We will therefore use our logic model (Figure 1) to clearly describe pathways rather than labeling them with these terms.

Figure 1. A systems-based logic model depicting types of services and associated pathways to tuberculosis (TB) case detection.
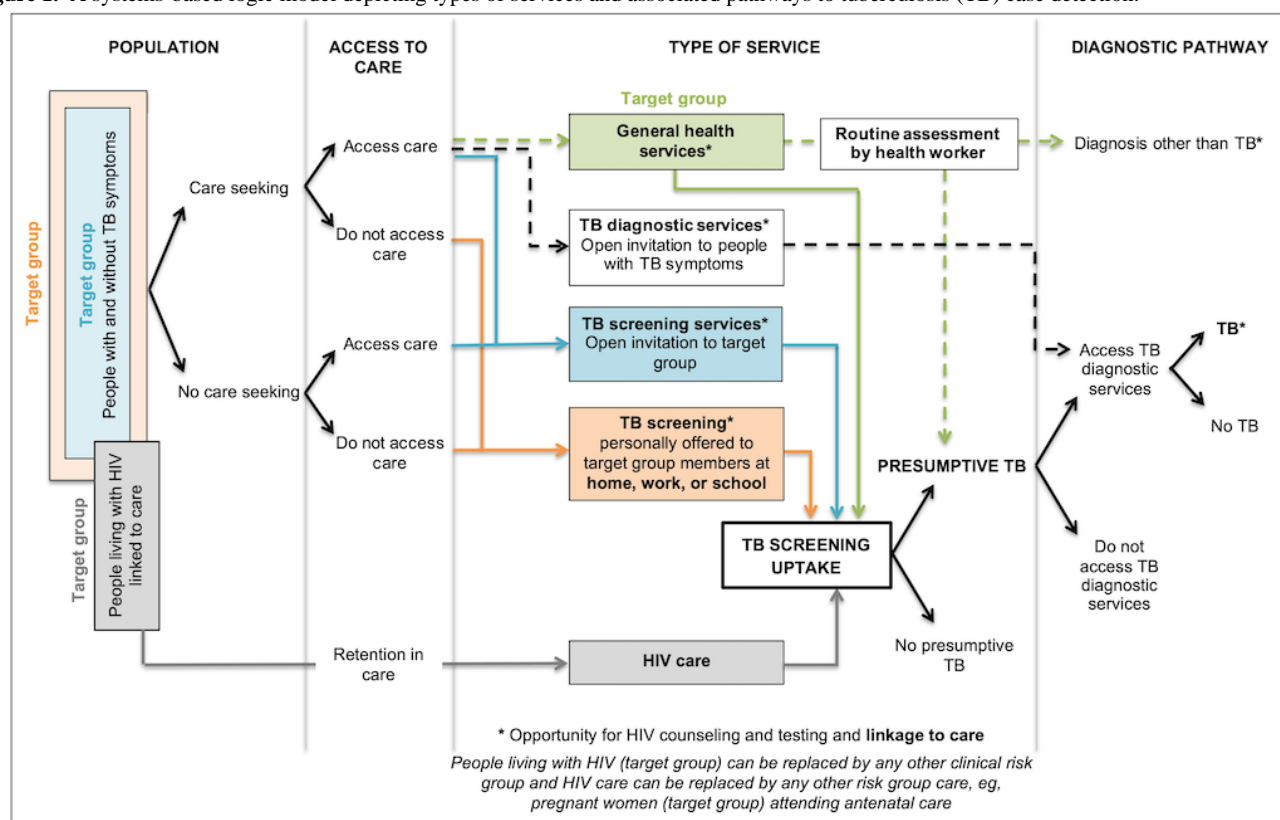
A systems-based logic model developed from a synthesis of case-finding strategies for drug-susceptible TB (Figure 1) will be used as a framework to describe different strategies and resulting pathways [13]. As an example, a target group—for example, household contacts from a TB source case—can be invited to the clinic if they develop symptoms (care-seeking pathway); they can be invited regardless of symptoms (blue screening pathway); or they can be screened at home, resulting in yet a different pathway (orange pathway). Enhancements to pathways will also be described and may include enhanced care-seeking (eg, health promotion), improved access to care for those seeking care (eg, mobile clinics), improved access to TB screening (eg, incentives), improved identification of presumptive TB by health workers (eg, training of health workers and incentives), and improved access to TB diagnostic services for individuals identified with presumptive TB (eg, transport, sputum collection in the community, and mobile laboratories). For screening pathways, we will report on target groups and screening and diagnostic tools used.

Quality appraisal will not be conducted because this is a scoping review and our interest is in the existing evidence base, regardless of study design and quality.

Timeline

The search will be conducted at the end of 2021. Title and abstract screening, full text screening, and data extraction will be carried out from January to June 2022. Thereafter, analysis will be conducted and results written up.

Discussion

Expected Findings

This scoping review will chart existing literature on case finding for DR-TB; this will help us determine whether primary studies on effectiveness, cost-effectiveness, acceptability, and feasibility of different DR-TB case-finding strategies exist. This will assist us in formulating potential questions for a systematic review. We will also describe case-finding strategies for DR-TB and how they fit into a model of case-finding strategies for drug-susceptible TB.

Strengths and Limitations

Our multidisciplinary review team consists of researchers with extensive experience in TB-related research and the conduct of systematic reviews and qualitative evidence synthesis. Their experience would be invaluable in collating and summarizing diverse literature in a sensible way. Another strength of our review is the use of a systems-based logic model that was developed from a synthesis of case-finding strategies for drug-susceptible TB. The model will help construct meaningful pathway descriptions for possible comparisons in future research and to assess whether case-finding pathways for DR-TB are similar to those for drug-susceptible TB.

One limitation to the review is the diverse, inconsistent use of intervention terminology within the literature, which may result in missing relevant studies. Although we cannot completely overcome this problem, we will work with an information specialist to pilot and optimize our search strategy, and we will discuss potential refinements to our search at regular meetings during the screening phase. Poor reporting of intervention strategies may also cause misunderstanding and misclassification of interventions. However, we do not assess effectiveness as an outcome; therefore, bias due to misclassification would be a minor issue. Lastly, case-finding strategies for DR-TB may not fit into a model developed from those for drug-susceptible TB. Nevertheless, such a situation will provide an opportunity to refine the model for future research.

Conclusions

This scoping review will chart the existing body of literature on case-finding strategies for DR-TB and will guide further research to inform decisions regarding case-finding policies and practices for DR-TB.

Data Availability

Data sets will be deposited in a publicly available repository, if applicable.

Authors' Contributions

MC and SSvW conceived the study. SSvW drafted the protocol. All authors read and approved the final protocol.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Search strategies from electronic databases.
[DOC File , 59 KB - resprot_v11i12e40009_app1.doc]

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Abbreviations

DR-TB: drug-resistant tuberculosis
MeSH: Medical Subject Headings
TB: tuberculosis

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Protocol

Maximizing Oral Health Outcomes of Aboriginal and Torres Strait Islander People With End-stage Kidney Disease Through Culturally Secure Partnerships: Protocol for a Mixed Methods Study

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Abstract

Background: Dialysis for end-stage kidney disease (ESKD) is the leading cause of hospitalization among Aboriginal and Torres Strait Islander individuals in Australia. Poor oral health is commonly the only obstacle preventing Aboriginal and Torres Strait Islander people with ESKD in Australia from receiving kidney transplant.

Objective: This study aims to improve access, provision, and delivery of culturally secure dental care for Aboriginal and Torres Strait Islander individuals with ESKD in South Australia through the following objectives: investigate the facilitators of and barriers to providing oral health care to Aboriginal and Torres Strait Islander patients with ESKD in South Australia; investigate the facilitators of and barriers to maintaining oral health among Aboriginal and Torres Strait Islander people with ESKD in South Australia; facilitate access to and completion of culturally secure dental care for Aboriginal and Torres Strait Islander individuals with ESKD and their families; provide oral health promotion training for Aboriginal health workers (AHWs) at each of the participating Aboriginal Community Controlled Health Services, with a specific emphasis on oral health needs of patients with ESKD; generate co-designed strategies to better facilitate access to and provision of culturally secure dental services for Aboriginal and Torres Strait Islander people living with ESKD; and evaluate participant progress and AHW oral health training program.

Methods: This collaborative study is divided into 3 phases: exploratory phase (baseline), intervention phase (baseline), and evaluation phase (after 6 months). The exploratory phase will involve collaboration with stakeholders in different sectors to identify barriers to providing oral health care; the intervention phase will involve patient yarns, patient oral health journey mapping, clinical examinations, culturally secure dental care provision, and strategy implementation workshops; and the evaluation phase will involve 6-month follow-up clinical examinations, participant evaluations of dental care provision, and AHW evaluation of oral health training.

Results: Stakeholder interviews were initiated in November 2021, and participant recruitment commenced in February 2022. The first results are expected to be submitted for publication in December 2022.

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Conclusions: Expected outcomes will identify the burden of oral disease experienced by Aboriginal and Torres Strait Islander people with ESKD in South Australia. Qualitative outcomes are expected to develop a deeper appreciation of the unique challenges regarding oral health for individuals with ESKD. Through stakeholder engagement, responsive strategies and policies will be co-designed to address participant-identified and stakeholder-identified challenges to ensure accessibility to culturally secure dental services for Aboriginal and Torres Strait Islander individuals with ESKD.

International Registered Report Identifier (IRRID):   PRR1-10.2196/39685

KEYWORDS

Introduction

Background

Oral health is a fundamental indicator of overall health and well-being [1]. Despite the importance of oral health, oral disease is commonly experienced by children and adults around the world, with periodontal disease and dental caries being the 2 leading indicators of poor oral health [1]. Periodontal disease is an inflammatory and infectious condition of the supporting bone and soft tissues around teeth, characterized by gingival bleeding, receding gum tissues, and tooth mobility [2]. Dental caries is a result of prolonged carbohydrate metabolism catalyzed by acidogenic bacteria, leading to demineralization of tooth structures [3]. When left untreated, dental caries and periodontal disease can cause substantial pain and fatal infections that spread to other areas of the head and neck [1]. According to the Global Burden of Disease 2017 [4], untreated dental caries in permanent teeth is the most common health condition, and >530 million children worldwide experience dental caries of primary teeth. Severe periodontal disease affects approximately 10% of the global population [4,5].

The direct effect of poor oral health includes pain, functional impairment, and esthetic concerns. However, the indirect effects can be more detrimental to overall health and include difficulties in eating, chronic inflammatory conditions, poor quality of life, and systemic infections that aggravate other comorbidities [6]. In Australia, Aboriginal and Torres Strait Islander communities experience a disproportionate burden of oral disease in comparison with their non-Indigenous counterparts, across all age groups and oral health indicators [7]. This inequity has been attributed to several factors, including the impacts of colonization and assimilation policies [8], neoliberal policies and ideologies [9], experiences of racism in health settings [10], inaccessibility of health services [11], high costs of dental care [12], and inability of mainstream services to meet the health needs of Aboriginal and Torres Strait Islander people [13,14]. Notably, Aboriginal and Torres Strait Islander communities receive less preventive dental care than non-Indigenous Australians [15].

The relationship between oral health and end-stage kidney disease (ESKD) and its precursor, chronic kidney disease (CKD), is well understood. The biological pathway between the mouth and kidney is primarily via the inflammatory response to oral pathogens entering the circulation through bleeding gums

and stimulating C-reactive protein production by the liver. Poor oral health commonly experienced by patients with CKD has been attributed to endocrinological, uremic, metabolic, and immunological imbalances [16], and it is evidenced by changes in patients' teeth [17-21], oral mucosa [22-26], bone [18,27], periodontium [28-30], salivary glands [23,31,32], and tongue [33]. A study in Australia's Northern Territory reported that Aboriginal and Torres Strait Islander individuals with kidney disease exhibited more indicators of poor oral health when compared with both non-Indigenous populations and general Aboriginal and Torres Strait Islander populations [34].

Oral health has a profound effect on the well-being of patients with kidney disease not only because of the biological pathways but also because optimal oral health is a prerequisite for kidney transplant [35]. For patients with ESKD, poor oral health can increase delays in kidney transplant wait-listing or completely prevent individuals from receiving a kidney transplant. Oral health is necessary for successful kidney transplant because of the infective and inflammatory environments created by dental disease in the body, which have the potential to lead to fatal septic conditions among patients who are immunocompromised, such as those with kidney disease. In addition to the commonly experienced challenges in maintaining oral health among Aboriginal and Torres Strait Islander people, individuals with ESKD face unique circumstances that make optimal oral health more difficult to achieve. For example, dialysis is time consuming; the average patient has 4- to 6-hour sessions, 3 to 4 times per week, meaning that scheduling dental appointments can be difficult. Studies from Central Australia estimated the prevalence of severe periodontal disease among Aboriginal and Torres Strait Islander people with ESKD to be 54%, which is approximately 20 times the national prevalence reported in the 2017 to 2018 National Survey of Adult Oral Health.

According to the Australian Bureau of Statistics, in 2019, 3.4% of Australia's population identified as Aboriginal and Torres Strait Islander but represents >7% of patients receiving treatment for kidney disease nationally [36]. In 2019, 157 out of 2091 (7.5%) South Australians receiving dialysis identified as Aboriginal and Torres Strait Islander, despite comprising only 2% of the total South Australian population. Of the 1100 Australians who received a kidney transplant in 2019, 33 (3%) were Aboriginal and Torres Strait Islander patients [36]. It has also been estimated that 50% of the non-Indigenous population with ESKD has received a renal transplant, whereas only 13% of the Aboriginal and Torres Strait Islander people with kidney

disease have received a transplant [37]. Dialysis in South Australia's public sector is provided through the Royal Adelaide Hospital's Central and Northern Adelaide Renal and Transplantation Service (CNARTS) and Flinders Medical Centre. Aboriginal and Torres Strait Islander people in South Australia generally receive primary health care, including kidney-related health care, through Aboriginal Community Controlled Health Services (ACCHS). The ACCHS facilitates transport and accommodation [37] for off-site services; counseling; and management of other chronic care needs, such as type 2 diabetes. Owing to limited provision of dialysis and ESKD care in remote locations, some Aboriginal and Torres Strait Islander individuals with kidney disease are forced to relocate to a city to receive dialysis [34,37]; this dislocation has a profound social and emotional impact on patients and their families, communities, and spiritual connection [37] to Country. Leaving Country also manifests impacts on subsequent care pathways, including dental care [37].

This project focuses on oral health services research, using a culturally secure mixed methodology approach and a multidisciplinary team. The study will use a decolonizing [38] and interpretive [39] theoretical framework, grounded by a critical realist epistemology [40] and guided by an advocacy perspective.

Study Aims

The overall aim of this study is to improve access, provision, and delivery of culturally secure dental care for Aboriginal and Torres Strait Islander individuals with kidney disease in South Australia. In this project, cultural security is understood as a doctrine that moves beyond cultural awareness and cultural safety to directly link understanding and actions with policies and procedures that create processes automatically applied to all Aboriginal and Torres Strait Islander people from the first point of seeking dental care. Although distinct from cultural awareness and cultural safety, both are necessary foundations for attaining cultural security [41]. This study is based in South Australia and is designed to support Aboriginal and Torres Strait Islander individuals with kidney disease in improving oral health via culturally secure dental management strategies to a standard that will meet the eligibility criteria for kidney transplantation. By working in partnership with Aboriginal and Torres Strait

Islander patients, ACCHS, Aboriginal health workers (AHWs), and other kidney disease and dental stakeholders in South Australia, this study will achieve the following objectives:

1. Investigate the facilitators of and barriers to providing oral health care to Aboriginal and Torres Strait Islander patients with kidney disease in South Australia, by capturing the perspectives of the following stakeholders: ACCHS, AHWs, dental service providers, and renal service providers
2. Investigate the facilitators of and barriers to maintaining oral health among Aboriginal and Torres Strait Islander patients with kidney disease
3. Facilitate access to and completion of culturally secure dental care for Aboriginal and Torres Strait Islander individuals with kidney disease and their families
4. Provide oral health promotion training for AHWs at each of the participating ACCHS, with a specific emphasis on oral health needs of patients with ESKD
5. Generate co-designed strategies to better facilitate access to and provision of culturally secure dental services for Aboriginal and Torres Strait Islander people living with dental disease

Methods

Study Design

Overview

This study is a result of community consultation and identification of the oral health care provision gap for Aboriginal and Torres Strait Islander patients with kidney disease in South Australia. This research collaboration is rooted in long-standing partnerships between the University of Adelaide's Indigenous Oral Health Unit, 3 ACCHS (Yadu Health Aboriginal Corporation in Ceduna, Nunyara Aboriginal Health Service in Whyalla, and Umoona Tjutagku Health Service in Coober Pedy), South Australian Dental Service, Aboriginal Kidney Care Together – Improving Outcomes Now (AKction) group, and CNARTS. This study will be conducted over three consecutive phases: (1) exploratory phase, (2) intervention phase, and (3) evaluation phase. A schematic outline of the study design is presented in Figure 1.

Figure 1. Project outline illustrating the 3 phases of the research project. ACCHS: Aboriginal Community Controlled Health Services; AHW: Aboriginal health worker; CEO: chief executive officer; CNARTS: Central and Northern Adelaide Renal and Transplantation Service; SA: South Australia.
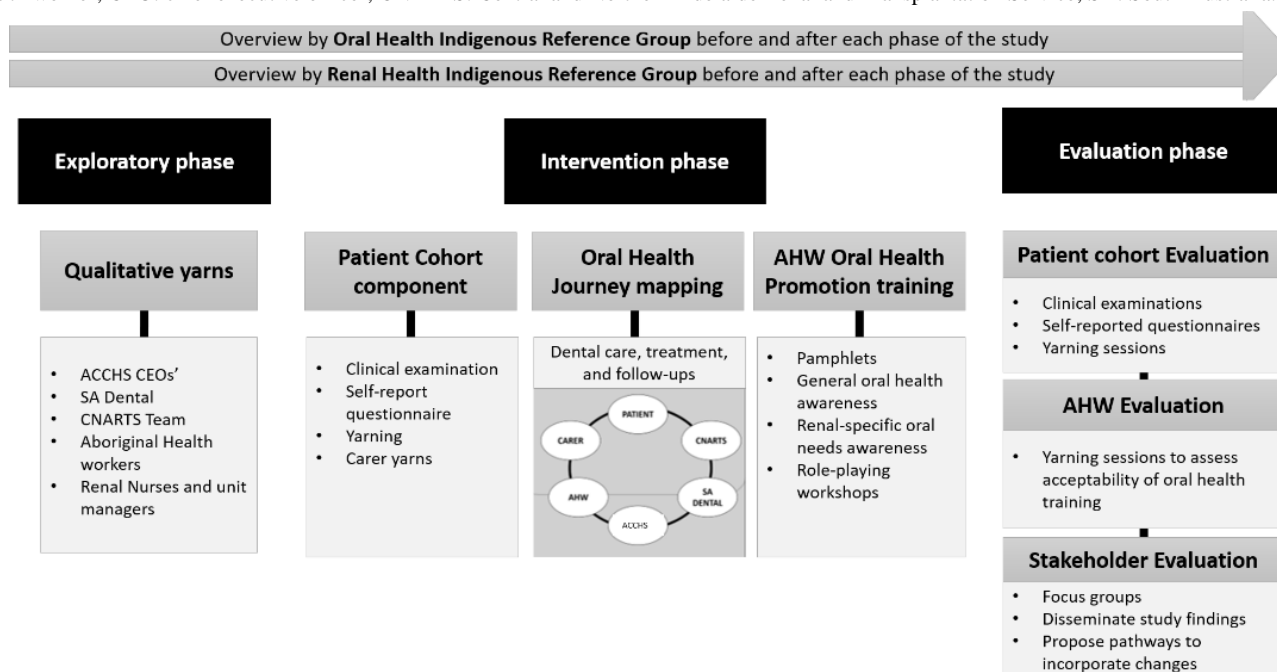
Exploratory Phase

The exploratory phase will focus on further developing relationships with dental and renal stakeholders involved in the project and understanding existing oral health care pathways for Aboriginal and Torres Strait Islander patients with kidney disease. This phase will use a qualitative study design involving stakeholder interviews, focus groups, and yarning sessions (where culturally appropriate) [42-45]. The data gathered during the exploratory phase will inform multidisciplinary collaborative workshops between stakeholders, where stakeholders will be brought together to discuss and investigate potential organizational-level solutions to the burden of oral disease preventing Aboriginal and Torres Strait Islander patients from receiving kidney transplants in South Australia. In addition, this phase will provide rich and diverse narratives regarding the organizational experiences and challenges in accessing and facilitating oral health care provision and renal replacement therapy. This phase is a critical step toward building the foundation for the intervention phase of this project and developing a deep understanding of the practical and existing pathways of oral health care.

Intervention Phase

The intervention phase will use a mixed methods approach and will comprise 3 components: patient cohort, patient oral health journey mapping, and AHW oral health promotion training.

The patient cohort component will involve epidemiological clinical examinations and provision of culturally secure oral health care. Overall, three types of data will be collected during initial visits with participants: (1) clinical examinations to assess periodontal disease, according to American Academy of Periodontology–2017–modified classification [46]; (2) self-report questionnaires to collect participant demographics, self-reported oral and kidney health indicators, and associated

behaviors; and (3) participant yarns to generate an appreciation for past oral health experiences, related challenges, and current needs. Family members and carers will be invited to participate in the yarns, and there will be an optional self-report questionnaire for carers to complete. This initial visit with participants will end with a discussion about the necessary steps for organizing and obtaining comprehensive oral health care, as deemed complete when participants are satisfied with their oral health. By participating in this project, participants will receive oral health care at no cost, they will have the option to be accompanied by members of the research team at each dental visit, and their family members with oral health needs will also be invited to access these services. Execution of this step is the chief priority of the project, with focus on highlighting the culturally secure dental care pathways among community members. To ensure continuity of care, members of the research team will be in contact with each participant on an ongoing basis, with frequency determined by participant-defined need. All dental staff in the public sector in South Australia receive cultural competency training and are evaluated according to the South Australian Health Aboriginal Competency framework [47].

The patient oral health journey mapping component will document patient journeys from the first point of dental contact to weekly or monthly follow-up according to patient-defined or clinician-defined needs. Follow-up will include research team visits, dental appointments, phone calls, and emails to the patient, families, dental managers, and AHWs, as necessary, by research team members. Each patient will have a unique management strategy and oral health plan, which will be coordinated by an appointed research team member (SS, BP, or JH). Patient journeys will be overseen by the Aboriginal and Torres Strait Islander Advisory Group, CNARTS, and special needs dental specialists. Documenting patient oral health journeys will be used to elucidate patient-centered challenges

and enablers for accessing culturally secure dental care for Aboriginal and Torres Strait Islander people with kidney disease in South Australia. This approach is patient-centered and aims to identify barriers and solutions through a patient lens in the context of primary care services and wide health systems. The documentation of patient oral health journeys will be key to generating real-time solutions to challenges experienced by participants supported by this project during the evaluation phase. Interweaving multiple perspectives will enable an increased understanding of the complexities and gaps in dental care service provision and help to facilitate the most responsive and achievable improvements that can be readily translated.

There is strong evidence that supports the role of AHWs in improving health outcomes and health service provision for Aboriginal and Torres Strait Islander communities in Australia [48,49]. AHWs aid Aboriginal and Torres Strait Islander patients in navigating mainstream services and provide cultural brokerage between Indigenous and Western understandings of well-being [48,50-52]. Relationships of trust are imperative to holistic identification of patient needs, appointment attendance, and use of health services; AHWs successfully build upon familiar relationships in health care settings to the benefit of patients [53]. Although AHWs have been successful in providing oral health education to mothers [54] and applying fluoride varnish to children's teeth in New South Wales [55], the use of AHWs for oral health promotion in South Australia has been sporadic and poorly defined [55]. Given the significant burden of oral disease experienced by Aboriginal and Torres Strait Islander people, provision of oral health education must align with community values that best meet the needs of Aboriginal and Torres Strait Islander patients. As such, the research team will work in partnership with AHWs at each of the ACCHS to develop, pilot, and evaluate basic oral health promotion training. Owing to the nature of this project, there will also be a component specific to CKD-related and ESKD-related oral health needs.

The expected outcome of the intervention phase is to develop evidence regarding the implementation of culturally secure dental care, where patients and families are supported by a multidisciplinary team. These findings will substantiate the arguments for policy translation that demands access to culturally secure primary dental services. Ultimately, the intervention phase aims to improve the oral health status and, subsequently, the eligibility for kidney transplantation among Aboriginal and Torres Strait Islander individuals with kidney disease in South Australia.

Evaluation Phase

The evaluation phase will use a mixed methods approach and will be similar in design to the intervention phase, with patient cohort evaluations, AHW evaluations, and stakeholder evaluations. The patient cohort component will involve epidemiological clinical examinations and evaluation of culturally secure oral health care provision. Overall, three types of data will be collected during follow-up visits after 6 months with participants: (1) clinical examinations to assess any changes in periodontal disease, according to the American Academy of Periodontology–2017 classification system [46]; (2) self-report questionnaires to collect any changes in self-reported oral and kidney health indicators and associated behaviors; and (3) participant yarns focused on participant evaluation of and reflection on the experience of dental care provided through this project. Family members and carers will again be invited to participate in the yarns, and there will be an optional self-report questionnaire for carers to complete. The clinical examinations and self-report questions will be compared with baseline measures collected during the intervention phase to assess the differences in clinical oral health and self-reported oral health. Evaluation of the usefulness of oral health promotion training and tools provided to AHWs at each of the 3 partnering ACCHS will be collected via yarns, with focus on the acceptability and relevance of the training and ways to improve the usefulness of these sessions.

Evaluation workshops or focus groups will be conducted with key stakeholders engaged throughout the duration of the project, including Aboriginal and Torres Strait Islander people with lived experience of kidney disease, ACCHS representatives, South Australian Dental Services, and CNARTS to (1) disseminate findings from the mapping exercises, (2) revisit strategies proposed during the workshop in the exploratory phase, and (3) develop realistic and specific pathways to incorporate strategies developed through this project. The evaluation workshops will be critical to ensure the translation of key elements of culturally secure dental care into existing primary health service records and monitoring structures to improve oral health experiences and kidney transplant eligibility among Aboriginal and Torres Strait Islander patients with kidney disease in South Australia.

Participants and Recruitment

All Aboriginal and Torres Strait Islander people with kidney disease living in South Australia are eligible for inclusion in this study. However, our recruitment strategies will focus on Whyalla, Ceduna, Coober Pedy, and Adelaide. As of November 2021, CNARTS is providing nephrological care to 157 Aboriginal and Torres Strait Islander people with ESKD in South Australia, with primary health care needs delivered by each patient's ACCHS. All efforts will be made to recruit all 157 patients. Over the past 10 years, the research team has developed strong relationships with the ACCHS stakeholders across South Australia, and each of the 3 ACCHS sites have been involved in project design, grant submission, and ethics obtainment for this project. Recruitment of participants will occur concurrently with stakeholder communications and ACCHS visits during the exploratory phase. Recruitment will use a purposive sampling strategy [56] to identify eligible patients willing to participate in this research project, using existing networks; patients will be recruited by word of mouth. Project information will also be posted in high-traffic areas at each of the 3 partnering ACCHS and renal sites. To be included in this study, participants must identify as Aboriginal or Torres Strait Islander, be aged ≥18 years, and have been clinically diagnosed with CKD. Patients eligible for inclusion in this study with low English literacy or comprehension will be provided with the option to have a translator from the Aboriginal Language Interpreting Service. Individuals who meet the inclusion criteria but are not enrolled during the original

recruitment period will not be eligible to participate in the follow-up phases.

Ethics Approval and Consent

Ethics approval for this study has been obtained from the Aboriginal Health Council of South Australia Human Research Ethics Committee (04-21-936) and University of Adelaide Human Research Ethics Committee. All study participants, including family members or carers who participate in the study, will be required to provide written informed consent.

Aboriginal and Torres Strait Islander Advisory Group

This study is governed by an Aboriginal and Torres Strait Islander Advisory Group, which will oversee project orchestration, intervention delivery, project evaluation, and knowledge dissemination of the study findings. The Aboriginal and Torres Strait Islander Advisory Group will provide cultural guidance on all aspects of the study, including community engagement, staff recruitment and training, data collection and management, and dissemination of findings appropriate to communities and ACCHS. Secondary governance will be sought from the AKction reference group, a research team led by Aboriginal and Torres Strait Islander individuals with ESKD and carers of those with ESKD, whose lived experiences are invaluable. The involvement of the AKction reference group in an advisory capacity will be especially critical in terms of translation of findings to policy and health services, as the AKction team has already been successful in improving kidney service delivery for Aboriginal and Torres Strait Islander individuals with ESKD in South Australia.

Data Collection

Questionnaires

Quantitative and descriptive data pertaining to kidney disease diagnosis, comorbidities, quality of life, health behaviors (including alcohol, tobacco use, and oral health), and indicators of social determinants of health will be obtained through self-report questionnaires completed in the intervention phase and followed up during the evaluation phase. Data collection will be overseen by a senior Aboriginal researcher (JH) and conducted by a team of Indigenous and non-Indigenous researchers with experience in working with the ACCHS and communities partnering in this project. All participants will be supported to complete a questionnaire containing items on oral health–related quality of life, social and emotional well-being, and dental behaviors.

Clinical Examinations

Hard and soft tissue status in the mouth will be assessed by recording caries experience, periodontal disease indicators, and gingivitis through standardized oral epidemiological examinations based on national oral health survey guidelines [57]. All epidemiological clinical examinations will be led by an experienced oral health specialist with extensive experience of working in partnership with Aboriginal and Torres Strait Islander communities. Patient convenience and comfort will be prioritized, and clinical examinations will be performed at participants' homes, ACCHS, or another location preferred by the participant. Didactic, clinical, and cultural security training

for examining teams will be conducted during the exploratory phase, before baseline collection in the intervention phase, with refresher sessions provided throughout the duration of the project. Daily reflexive debriefing sessions will be standard practice for all team members conducting field work. Examiners will be tested in the field to estimate interexaminer reliability. Intraclass correlation coefficients for caries, gingivitis, and periodontal disease scores will be used.

Oral Health Interventions

Aboriginal liaison project officers of the oral health promotion team from the South Australian Dental Services will aid the research team with the facilitation of dental appointments at public dental clinics, mobile dental vans, or private services, when necessary. The research team will be responsible for keeping detailed records of dental appointments and experiences, as informed by participants, which will be collated into the oral health journey mapping component. The oral health intervention will be based on the technique described by Tonetti et al [58]. This involves removal of subgingival dental plaque biofilms by scaling, root planing, and removal of teeth that cannot be saved, following administration of local anesthesia. It will additionally involve the removal of dental caries in the dental hard tissues, including replacement of insufficient restorations, and comprehensive prophylactic cleaning with fluoride varnish. The intervention will be performed by registered oral health professionals who will be overseen by registered periodontal and special needs dental specialists. The oral health intervention will occur for each participant at the facilities provided by South Australian Dental Services (including mobile dental vans). Dental care will commence immediately after the baseline visit, and the research team will provide transportation and liaise with participants, families, and dental services to ensure patient satisfaction and security. Where desired, research team members will accompany participants during dental appointments and support them in advocating for their dental needs.

Qualitative Data

Participants involved in the cohort component of the study and their family members will be invited to share their dental journeys via yarning sessions using Dadirri (deep listening approach) [42-45,59]. Yarning is a culturally secure research methodology that prioritizes a reciprocal 2-way approach to information sharing and negotiating. Yarning works to reduce power dynamics in research settings by eliminating the formality of researcher identity and demanding engaged interactions between individuals who each assume the position of learner and knower. The specifics of various approaches to yarning are as diverse as the Aboriginal and Torres Strait Islander communities across Australia, but fundamentally, yarning is built on relationships that require responsibility and accountability between people [42-44]. The mechanisms for information sharing in yarning sessions include storytelling and narratives, which enable connection between personal experiences regardless of place, culture, or time [60-62]. Yarning sessions with participants will explore each individual's oral health journey regarding experiences of kidney disease, family, community, and Country.

Statistical Analysis

Overview

The prevalence, extent, and severity of dental diseases will be calculated using the decayed, missing, and filled teeth index; loss of clinical attachment for periodontal disease; and bleeding on probing for gingival disease or gum disease. Data from the 2017 to 2018 National Survey of Adult Oral Health [63], which includes nationally representative data for both Aboriginal and Torres Strait Islander and non-Indigenous population-level estimates, will be used as benchmark oral health indicators. General analysis will comprise chi-square test and student 2-tailed *t* test within the study sample and nonoverlapping 95% CIs when comparing with population estimates.

Qualitative Analysis

Qualitative analysis will be grounded by a critical realist [40] approach and will use decolonizing [38] and interpretive [39] theoretical frameworks. Reflexive thematic analysis will be used to analyze both stakeholder interviews and participant yarning sessions, as guided by the framework by Braun and Clarke [64-66]. Reflexivity in thematic analysis not only embraces research subjectivity but also challenges researchers to continually analyze and explore the ways in which their lived experiences are influencing the analysis of qualitative data [65]. Aboriginal and Torres Strait Islander leadership and consultation throughout the analytic process will be critical to ensure that data are interpreted in a way that honors participant experiences and reflects participant meaning. Data will be inductively analyzed, without a structured codebook, to provide space for engaged and organic identification of themes [64,66]. Data will be coded line by line using NVivo software (version 12.6.1;

QSR International). Initial coding will remain close to the data and maintain participant wording; once initial coding of all transcripts has been completed, data will be revisited, similar codes will be aggregated, and data will continually be reconceptualized for an iterative thematic development process [64-66].

Patient Mapping

The oral health journey of each participant will be mapped against the National Aboriginal and Torres Strait Islander Kidney Clinical Guidelines [67-69] health standards and frameworks for comparison against current clinical standards and best practices. Data from clinical examinations in the intervention phase will be used to categorize participants according to the level of dental care needed (ie, routine dental care vs emergency care). Details from dental appointments, aspects of yarning sessions, and self-reported measures from questionnaires will be collated to represent the journey of each study participant. Each journey will be written as a unique case study and comparatively analyzed against experiences of participants with both similar and differing needs. Findings from the dental journal mapping will be used to tabulate dental journey quality improvement strategies, which will be discussed with stakeholders in South Australia.

It is a well-established fact that Aboriginal and Torres Strait Islander communities face multiple barriers while accessing and maintaining good oral health. A strength of this project is that it addresses these barriers at the individual or family, community, institutional, and organizational levels (Table 1). The methodology used to address the barriers at each level and which phase of the study will focus on those particular barriers are presented in Table 1.

Table 1. Scientific framework of the project, with methodology mapped into the levels of a socioecological model.

Level addressed	Methods used	Phase of study
Individual	• Yarning • Participant satisfaction with oral health • Increased eligibility for kidney transplant	Intervention
Community	• Oral health promotion workshops for AHW[a] • Oral health promotion resources for ACCHS[b] (posters and pamphlets) • CKD[c]-specific oral health resources for ACCHS (posters and pamphlets)	Intervention
Institutional	• Advocating for and facilitating the provision of culturally secure oral health, in partnership with dental teams • Advocating for inclusion of oral health specialist in the multidisciplinary team for renal disease management • Increasing awareness in dental services about CKD-specific oral health care needs in Aboriginal and Torres Strait Islander patients	Intervention and evaluation
Organizational	• Advocating for policy changes that align with project outcomes	Evaluation
Organizational	• Identifying key stakeholders and relationships in CKD within SA[d] • Organizational-level barriers to oral health provision	Exploratory

[a]AHW: Aboriginal health worker.

[b]ACCHS: Aboriginal Community Controlled Health Services.

[c]CKD: chronic kidney disease.

[d]SA: South Australia.

Results

The funding for this project is obtained from a Department of Health (Government of Australia) grant, which was acquired in February 2021. The exploratory phase including stakeholder interviews was initiated in November 2021, and participant recruitment commenced in February 2022. The project has recruited 35 participants by October 2022, and it is estimated that a total of 40 to 42 participants will be recruited into the study according to the inclusion criteria specified in the grant. The first results (baseline) are expected to be submitted for publication in December 2022. The estimated date of project completion, along with the completion of 6-month follow-up with participants, is April 2023.

Discussion

This study presents a unique opportunity to make significant gains in primary health care to not only improve oral health of Aboriginal and Torres Strait Islander communities of South Australia with kidney disease through timely and culturally secure dental care but also to reduce the burden of chronic disease that defines morbidity and mortality in this group. Improved oral health will lead to increased eligibility of Aboriginal and Torres Strait Islander people of South Australia

with kidney disease to receive a kidney transplant, which improves longevity and quality of life for individuals, families, and communities. This study also aims to provide actionable strategies that can be translated into policy through stakeholder relationships and consultations. Evaluating the provision of culturally secure dental care will also contribute to cultural training for dental students. The evaluation of AHW oral health training will be used to enhance training resources developed for this project, which will be disseminated for use in all ACCHS across South Australia, through the Aboriginal Health Council of South Australia, thus creating more opportunities for dental education among communities.

Another strength is the use of interpretive and decolonizing theoretical frameworks and yarning as a methodology, all of which align with and respect Aboriginal and Torres Strait Islander values. An essential component of this project is the advocacy perspective, which aims to yield real-time results for participants and develop realistic strategies for policy implementation through stakeholder consultation. Finally, the foundational multidisciplinary relationships and engagement between the research team and the strong Aboriginal and Torres Strait Islander leadership will ensure that the project continually strives to meet community needs, thus improving the well-being of all those who are engaged in the study.

Data Availability

The data sets generated and analyzed during this study are available from the corresponding author upon reasonable request. The authors confirm that supporting data and material in the study will be made available through Springer Nature's Data Support Services, where possible.

Authors' Contributions

All authors are named investigators of the project. All of them contributed to the intellectual input of the study design and in writing this protocol.

Conflicts of Interest

None declared.

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Abbreviations

ACCHS: Aboriginal Community Controlled Health Services
AHW: Aboriginal health worker
AKction: Aboriginal Kidney Care Together – Improving Outcomes Now
CKD: chronic kidney disease
CNARTS: Central and Northern Adelaide Renal and Transplantation Service
ESKD: end-stage kidney disease

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Protocol

Behavioral Skills Training for Teaching Safety Skills to Mental Health Clinicians: Protocol for a Pragmatic Randomized Control Trial

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Abstract

Background: Workplace violence is an increasingly significant topic, particularly for staff working in mental health settings. The Centre for Addiction and Mental Health (CAMH), Canada's largest mental health hospital, considers workplace safety a high priority and consequently has mandated staff safety training. For clinical staff, key components of this training are self-protection and team-control skills, which are a last resort when an individual is at an imminent risk of harm to self or others and other interventions are ineffective (eg, verbal de-escalation). For the past 20 years, CAMH's training-as-usual (TAU) has been based on a 3D approach (description, demonstration, and doing), but without any competency-based assessment. Recent staff reports indicate that the acquisition and retention of these skills may be problematic and that staff are not always confident in their ability to effectively address workplace violence. The current literature lacks studies that evaluate how staff are trained to acquire these physical skills and consequently provides no recommendations or best practice guidelines. To address these gaps described by the staff and in the literature, we have used an evidence-based approach from the field of applied behavior analysis known as behavioral skills training (BST), which requires trainees to actively execute targeted skills through instruction, modeling, practice, and feedback loop. As part of this method, competency checklists of skills are used with direct observation to determine successful mastery.

Objective: Our objectives are to evaluate the effectiveness of BST versus TAU in terms of staff confidence; their competence in self-protection and team-control physical skills; their level of mastery (predefined as 80% competence) in these skills; and their confidence, competency, and mastery at 1 month posttraining.

Methods: We are using a pragmatic randomized controlled trial design. New staff registering for their mandatory safety training are randomly assigned to sessions which are, in turn, randomly assigned to either the BST or TAU conditions. Attendees are informed and consented into the study at the beginning of training. Differences between those consenting and those not consenting in terms of role and department are tracked to flag potential biases.

Results: This study was internally funded and commenced in January 2021 after receiving ethics approval. As of May 2022, data collection is complete; half of the baseline, posttraining, and 1-month videotapes have been rated, and three-fourths of the interrater reliability checks have been completed. The analysis is expected to begin in late summer 2022 with results submitted for publication by fall 2022.

Conclusions: The findings from this study are expected to contribute to both the medical education literature as well as to the field of applied behavioral analysis where randomized controlled trial designs are rare. More practically, the results are also expected to inform the continuing development of our institutional staff safety training program.

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Introduction

The promotion of health and safety in the workplace is globally recognized as a critical issue. Addressing workplace violence directly contributes to the achievement of several of the sustainable development goals set out by the International Labour Organization including health, gender equality, and decent work and economic growth [1,2]. According to the Centers for Disease Control and Prevention, workplace violence can be categorized into 4 types: criminal intent (the perpetrator has no legitimate relationship to its employees), customer or client (violence to employees from clients, family members, and visitors), worker-on-worker (horizontal violence), and personal relationship (perpetrator has a relationship to an employee outside of work setting) [3]. Globally, health care workers are at a higher risk of experiencing "customer or client" workplace violence than any other category of workers [4,5]. Two meta-analyses, representing 393,344 health care workers, demonstrated a 19.3% pooled prevalence of workplace violence in the past 12 months and 24.4% and 42.5% of respondents reported experiencing physical violence and psychological violence, respectively [6,7].

In Canada, 61% to 68% of nurses and personal support workers experienced a serious incidence of workplace violence, and 20% experienced at least 9 physical assaults in the last year [8]. In Ontario, health care workers, representing 11.7% of the province's workforce, were also noted to be at the greatest risk of experiencing and being disproportionately affected by workplace violence compared to all other workers [9]. Within health care, psychiatric care facilities and their staff are at high risk for customer or client violence in the form of aggression from patients [10,11].

Experiencing workplace violence has been associated with negative psychological, physical, emotional, financial, and social consequences, which impact the staff's ability to provide care and function at work [12]. More specifically, behavioral emergencies or psychiatric behaviors such as yelling, demanding, cursing, manipulating, acting out, or threatening danger are disruptive to the functioning of the unit and place the safety of everyone at risk [13].

In response, health care organizations have committed to creating a safe work environment by adopting a myriad of strategies [9]. In 2017, the Centre for Addiction and Mental Health (CAMH) adopted a major initiative to ensure the physical and psychological safety of all patients and staff. A priority component of this initiative is a mandatory training program for all new direct care staff that teaches trauma-informed crisis prevention, de-escalation skills, and, in particular, safe physical intervention skills. The physical skills curriculum focuses on self-protection and team control skills with the first set of skills targeting how staff can protect themselves when faced with physical violence and the second set related to physical restraint in the hospital. Manual restraint carries a risk of injury for all those involved and in some circumstances can provoke aggressive behavior and staff injuries [14].

The current curriculum (hereafter, "training-as-usual" [TAU]) was developed over 20 years ago. It uses the 3D approach ("describing," "demonstrating," and "doing" the skill through practice). However, this approach is not competency based and thus inconsistent with the contemporary directions in health care and education of using competency [15,16] and evidence-based approaches [17,18]. Furthermore, recent staff reports indicate that the skills acquired using this method are not always retained over time and that staff are not always confident about their ability to use them.

The study described in this protocol seeks to address some of these issues by evaluating 2 forms of training for all new clinical staff in a mental health care setting. We have used an evidence-based approach from the field of applied behavior analysis known as behavioral skills training (BST). BST is a competency and performance-based training model that requires trainees to accurately demonstrate targeted skills through a loop involving instruction, modeling, practice, and feedback. Checklists are used throughout the training to evaluate whether competency in a skill is achieved [19,20], and a predetermined threshold can be applied to these competency ratings to determine whether the skill has been mastered [20]. An important feature of BST is that skill rehearsal and trainer feedback are continued until the predetermined mastery criterion is achieved.

There is a large body of evidence that indicates that individuals who receive BST demonstrate significant improvement in targeted skills posttraining and maintain those skills over time and across settings [21-23]. This model has been used to train a wide range of participants including behavior analysts, parents, and educators to build safety-related skills and manage aggressive behavior [21,24].

The objective of this study is to compare the real-world effectiveness of BST and TAU in terms of physical safety skills acquisition and retention after 1 month as well as staff confidence in their use of these skills.

The following are the null hypotheses being tested: there will be no significant differences between BST and TAU in terms of (1) the competence scores or the percentage of study participants who attain mastery (predefined as a score of 80% or higher) for self-protection or team control physical skills at the end of the mandated training session; (2) the competence scores or the percentage of study participants that continue to

demonstrate mastery at 1 month posttraining for either self-protection or team-control skills (retention); and (3) the percentage of study participants who express confidence in their skills at 1 month posttraining.

Methods

Design, Setting, and Recruitment

Because we are interested in comparing the effectiveness, rather than the efficacy, of the two training methods, we are using a pragmatic randomized controlled trial (RCT) design. The study setting is a large mental health hospital in Ontario, Canada, which delivers inpatient, outpatient, and emergency health care across a wide range of patient populations.

Newly hired staff that are classified as clinical direct service staff must undergo 2 weeks of onboarding, which includes the trauma-informed de-escalation education for safety and self-protection (TIDES) program. Within those 2 weeks, physical skills training is a full-day, in-person session scheduled on the last day. Because the onboarding is tightly scheduled, there is limited time for the typical processes of providing information about the study, gaining agreement and informed consent, and randomization. Consequently, the following procedures have been introduced.

Prior to the 2-week onboarding training, all newly hired clinical direct-service staff will be randomly assigned to their physical skills training session, and the physical skills training sessions will be randomly assigned to either BST or TAU. On the day before the physical skills session, the study will be introduced by a research team member to all attendees at the end of the last session on the previous day; during that introduction, consent will be obtained via a WebEx poll to send interested attendees a copy of the informed consent, and all attendees will be informed that a question-and-answer session along with obtaining informed consent will be carried out before the start of the physical skills session the next day, and then the informed consent form will be emailed to those who provided permission.

Just before the physical skills session, questions about the study or informed consent will be answered, and one-on-one meetings will be conducted with each attendee in a separate room to further review the informed consent and to sign indicating whether they agree or decline to participate in the study. This procedure is designed to protect against attendees identifying who is involved in the study (hereafter "study participant") and who is not (hereafter "trainee").

Ethical and Safety Considerations

This study was internally funded and has been approved by the CAMH Research Ethics Board (#101-2020).

The study processes are designed to ensure that all attendees receive the same attention from the research team and facilitators and the same assessments during the training sessions. The goals are to provide equivalent training experiences, regardless of whether the person is a study participant or a trainee and regardless of whether they are in a TAU or BST session, as well as to minimize the possibility that attendees can identify who among them are or are not study participants. For example, in gaining informed consent, all attendees meet one-on-one privately with a research team member, and all sign the consent form by indicating whether they agree or decline to be study participants. In addition, skill assessments for all attendees are done individually in a separate room, but only the study participants (ie, those providing consent) are videotaped.

Sample and Sample Size

Potential study participants include all newly hired clinical staff attending the mandatory training. There are no exclusion criteria (except the attendee's desire not to be a study participant).

There is no published information on the expected effect size of BST versus other training methods. Indeed, most of the published BST studies have focused on efficacy and consequently have involved relatively small sample sizes. Consequently, we have opted for a sample size of 80 participants total (ie, 40 each in the BST and TAU groups) consistent with sample sizes providing 80% power for an expected medium to large effect size [25].

Recruitment began in January 2021, after REB approval was received. We reached our recruitment goal in September 2021.

Interventions

Both the TAU and BST methods teach the same skills for protecting a person against aggression (eg, someone attempting to punch or choke the staff member) as well as to help a team of staff members physically restrain a patient who is becoming an increased risk of harm to self or others. There are 11 target skills (6 for self-protection and 5 for team-control) that are mandatory for all newly hired staff (Textbox 1). Each skill has a number of defined components, and the same sequence of steps is followed to teach each component. However, the 2 training methods differ in how these steps are administered and monitored (Table 1). The BST protocol involves attendees actively performing the targeted skills through a loop involving instruction, modeling, practice, and feedback using competency checklists [20]. This is continued until the competency of the target skill is demonstrated based on the observation of the trainer [20]. While the common practice as described in the literature is for the attendee to demonstrate successful performance of a skill 2 to 3 times before moving to the next skill on the checklist [26], we have chosen a more stringent threshold of requiring correct execution 5 times consecutively with the expectation that this will further consolidate skill acquisition and possibly retention. In contrast, TAU does not assess competency or require trainees to reach a specific level of competence for a skill before moving on to the next skill. It does, however, include modeling, practice, and feedback.

Each training session is run by 2 facilitators, each training half of the attendees to make the most efficient use of the allotted time. To be compliant with COVID-19 restrictions at the time of the study on the numbers of in-person attendees (maximum of 10 individuals including the trainer), 1 trainer is present at the session, while the other delivers the same material virtually.

Textbox 1. List of 11 target skills.

Self-protection skills

- Same-side push/punch/grab defense

- Cross-arm grab defense

- Roundhouse or open-handed slap defense

- Same-side grab defense

- Two-handed front choke defense

- Rear choke defense

2-5–person team control (physical restraint) skills

- Level 1, 2-person team control

- Level 2, 2-person team control

- Level 3, 2-person team control

- Additional hand controls

- Anchor

Table 1. Comparison of training-as-usual (TAU) and behavioral skills training (BST) training steps.

Training strategy	TAU	BST
Target physical skills (self-protection and 2-5 person team-control)	Yes	Yes
Description of skill	Verbal with no structure	Verbal and written with systematic step-by-step instruction
Demonstration of skill by trainer	Yes	Yes
Practice of skill	Two stages (controlled practice and free practice)	Practice opportunities
Feedback	General feedback	Specific feedback using competency checklist
Repetition of description, demonstration, practice, and feedback	At the instructor's discretion	Yes, the learner must demonstrate correct performance of 80%-100% of component steps 5 times consecutively before moving to train for the next skill
Use of competency checklist	No	Yes
Predetermined mastery criteria for each skill	No, attendees practice until the end of the allotted time	Yes, mastery for each skill defined as demonstrating correct execution of 80%-100% of component steps 5 times consecutively

Variables Assessed

The variables to be assessed include skill competence, mastery, and retention; participant confidence in using each skill; the frequency of skill use in the previous month; and overall satisfaction with the training. Skill competence, mastery, and retention will be evaluated using checklists which were created guided by the considerations proposed by Stufflebeam [27] as well as through consultations with 2 coauthors who are board-certified behavior analysts (KB and LB). These are designed to evaluate the 11 mandatory skills being taught in the TIDES training program. The checklist creation process involved the following steps: (1) observing the training experts performing the skills and consulting with them; (2) having the organizational experts and trainers define and agree to the written descriptions in the training curriculum of the mandatory 11 target skills; (3) presenting the checklist drafts to key

organizational stakeholders (professional practice office, union representatives, staff coaches, and executive leadership); (4) field-testing the resulting checklists in the mandatory staff training and making appropriate revisions; (5) and finally, making final edits based on the results of the interobserver agreement (IOA) assessment (please see further description of IOA below).

The questions assessing participant confidence, the frequency of skill use in the previous month, and overall satisfaction with the training are either adapted from existing questions used in the research team's department or developed specifically for this study. Where applicable, 10-point Likert scales were used to improve accuracy.

The checklists (see self-protection checklist example, Multimedia Appendix 1) will be used during training for the BST sessions and for the baseline, posttraining, and 1-month

study assessments for all study participants. On the training day, attendees will be asked individually to go to a separate room. They will be asked once to demonstrate each of the 11 skills prior to the start of training for baseline and just after the training for posttraining. Only those attendees who have consented to be study participants will have their baseline and posttraining assessments videotaped. For the 1-month follow-up, study participants will be asked to come in to have their skills assessed and videotaped. Videotaping will be done through WebEx (Cisco) and will be rated by a research team member using the predefined competency checklists. On these checklists, each skill component will be judged to be performed "correctly" or "incorrectly." The final competency rating for each skill will be the percent of its component skills that were rated as correctly performed.

The reliability and validity of these ratings will be assessed using IOA calculations [28]. Prior to the study, raters had been trained on a test set of videotapes drawn from a previous study and had reached agreement levels of at least 90% for self-protection and team-control skills. For this study, all videotapes are rated by a primary rater. At the same time, a 30% random sample of videotapes from training months 1, 3, 4, 6, and 9 will be independently rated by a designated secondary (reliability) rater. IOA with the ratings from the primary rater will be calculated after every 2 videotapes rated by the secondary rater and, if the IOA is less than 90%, a recalibration discussion is held and recorded between the 2 raters with a third neutral rater available if needed to resolve any remaining differences. Recalibration decisions are then applied to all subsequent videotape ratings.

A predetermined threshold of 80%, consistent with clinical practice [29,30], is then applied to each competency rating to define skill mastery. Retention between posttraining and the 1-month follow up is measured in terms of whether the competency ratings changed as well as whether the percentage of study participants meeting the mastery threshold has changed.

Study participants complete self-reported evaluation forms covering descriptive information, confidence, training satisfaction, and frequency of skill use. The participants also provide information regarding their professional role and service department at CAMH. For confidentiality reasons, personal characteristics such as age and gender or sex were not provided to the research team, and, for the same reasons, we chose not to collect this information. All participants are asked to evaluate their confidence on a 0-10–point scale (0=not at all confident to 10=extremely confident) in using the 11 self-protection and team-control skills at baseline, immediately after the training, and at 1-month follow-up (Multimedia Appendix 2). All participants were asked to rate for satisfaction with the training on a 4-point scale immediately after the training and 1 month later. The number of times in the past month that self-protection or team-control skills were used is asked at baseline and 1-month posttraining. Finally, an open-ended item is provided in the posttraining assessment form for any comments that trainees want to communicate to the facilitators.

Data Management and Statistical Analyses

Data from the competency checklists, completed by raters on the research team, and data from the self-reported evaluation completed by participants are collected via REDCap, which is CAMH's designated web-based application for research data capture and then exported to Excel (Microsoft Corp) spreadsheets [31]. After data cleaning, these spreadsheets will be imported to a statistical software package (eg, SPSS, R) for analysis.

Testing of the 3 hypotheses will be done using repeated measures ANOVA. In addition, the study participants will be compared to all attendees in terms of their role and department to evaluate whether there are any striking differences despite our randomization methods. We also plan to assess the association between the frequency of physical skills used in the past month and our measures of skill competence, mastery, retention, confidence, and satisfaction.

Results

As of May 2022, raw data collection is complete; half of the baseline, posttraining, and 1-month videotapes have been rated, three-fourths of the IOA checks have been completed, and data cleaning has begun. Analysis of the cleaned data is expected to begin in late summer 2022 with results submitted for publication by fall 2022.

Discussion

Because there have been no previous comparisons between TAU, as used in our institution, and BST, the results we anticipate are based primarily on face validity—that is, a competency-based approach will be better for the acquisition and retention of both skills and mastery. The literature based on health care workers in general [32] suggests that both methods will improve staff confidence, although there are no published results indicating whether one will be superior to the other in either improving or maintaining confidence.

The primary strength of our study is the pragmatic RCT design, which supports a relatively rigorous comparison between the TAU and BST methods. In addition, the study is situated in a mental health setting and includes both nurses and other health care workers addressing 2 other recommendations by Geoffrion et al [32]. However, there are important limitations. First, we were not able, for confidentiality reasons, to collect personal information such as age, sex or gender, education, or ethnicity, which are likely important influences in learning. Second, for practical reasons, we were not able to assess retention beyond 1 month posttraining. These gaps are ones that we hope to address in future investigations of the impact of BST training.

We intend to share our findings with both scientific audiences, in terms of conference presentations and peer-reviewed articles, and administrative and clinical audiences, in terms of in-house and other presentations to health care and other community stakeholder organizations. Through these dissemination efforts, we hope to add to the evidence base in medical education by providing information on the utility of competency-based assessments in training staff under conditions where the desired

target skills can be clearly defined and measured [20]. There is also the potential to explore in greater detail whether methods such as BST or TAU are more suitable for achieving competency, mastery, and retention of specific self-protection and team-control skills and skill components. Our findings should also add to the applied behavioral analysis field where the use of a pragmatic RCT design is relatively novel. From a practical standpoint, the study findings are expected to influence the ongoing development and delivery of physical skills training for staff within our own institution.

Data Availability

Owing to privacy and ethical reasons, access to the supporting data is restricted to the members of the research team.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Competency checklist (self-protection skills example).
[[DOCX File , 80 KB](#) - [resprot_v11i12e39672_app1.docx](#)]

Multimedia Appendix 2
Confidence level assessment example.
[[DOCX File , 16 KB](#) - [resprot_v11i12e39672_app2.docx](#)]

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Abbreviations

BST: behavioral skills training
CAMH: Centre for Addiction and Mental Health
IOA: interobserver agreement
RCT: randomized controlled trial
TAU: training-as-usual
TIDES: trauma-informed de-escalation education for safety and self-protection

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Protocol

Collective Action for Wellness in the Malaysian Workplace: Protocol for a Feasibility Study

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Abstract

Background: Chronic diseases and the associated risk factors are preventable with lifestyle changes such as eating a healthier diet and being more physically active. In Malaysia, the prevalence of chronic diseases, including diabetes, hypertension, and heart diseases, has risen. In the present study, we explore the potential of co-designing and implementing a digital wellness intervention to promote socially-driven health knowledge and practices in the workplace in Malaysia, drawing on social cognitive theory, social impact theory, and social influence theory.

Objective: This study aims to co-design and assess the feasibility of a socially-driven digital health intervention to promote healthy behavior and prevent chronic diseases in a workplace in Malaysia.

Methods: This study involves two phases: (i) identifying the barriers and facilitators to healthy behaviors at work and co-designing the intervention activities with the employees, (ii) implementing and evaluating the intervention's feasibility. Phase 1 will involve qualitative data collection and analysis through semi-structured, in-depth interviews and co-design workshops with the employees, while Phase 2 will consist of a feasibility study employing quantitative measurements of health behaviors through accelerometers and questionnaires.

Results: This study was funded in June 2021 and ethics approval for Phase 1 was obtained from the Monash University Human Research Ethics Committee in January 2022. As of August 2022, qualitative interviews with 12 employees have been completed and the data has been transcribed and analyzed. These results will be published in a future paper with results from all Phase 1 activities.

Conclusions: The study will help us to better understand the mechanisms through which digital technologies can promote socially-driven health knowledge and behaviors. This research will also result in a scalable wellness intervention that could be further tailored and expanded to other employers and social groups across the region.

International Registered Report Identifier (IRRID): PRR1-10.2196/39238

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Introduction

Background

Chronic diseases, such as diabetes, hypertension, and cardiovascular disease, have been a growing public health concern in the Southeast Asian region [1]. In Malaysia, the prevalence of diabetes in adults rose to 18.3% in 2019. About 8% of the adult population in Malaysia, or 1.7 million people, have risk factors for diabetes, hypertension, and hypercholesterolemia [2,3]. These chronic diseases and associated risk factors are preventable or manageable with lifestyle changes, such as eating a healthier diet, getting more exercise, quitting smoking, and reducing stress.

Previous studies suggest that workplace wellness initiatives can benefit individuals and employers through lower health care costs and reductions in absenteeism [4-6]. As the working age population is large and many adults spend the majority of their daytime hours at work, the workplace has been recognized as a favorable setting for health promotion. The World Health Organization has also identified workplace wellness programs as a strategic method to prevent and treat noncommunicable diseases (NCDs) [7]. Further evidence suggests that peer support, such as that found from friends, family, or colleagues, can be more effective at producing behavior change [8]. Messages with health information or peer support can also serve as a "nudge" to influence healthier daily choices [9].

From activity trackers that monitor physical activity levels to smartphone apps that provide personalized health education, the incorporation of digital technologies is becoming commonplace, especially in this digital age. Digital health interventions have been shown to have a positive effect on workplace health promotion [10-12]. Over the past 2 decades, growing research has been conducted to evaluate the effectiveness and feasibility of digital health interventions in the workplace context of many countries [13-15], but relatively few studies have been conducted in low- and middle-income countries (LMICs). Among the broad range of health issues that can be addressed by digital workplace wellness tools, NCDs are one of the most common areas of focus, likely due to the fact that behaviors such as eating and sitting are common in workplaces and contribute to NCD risk. Building on this body of research, this study will use digital tools in the workplace to facilitate health promotion and leverage the fact that 91% of people in Malaysia have smartphones and use messaging apps like WhatsApp and Facebook Messenger regularly [16,17].

However, the global coronavirus SARS-CoV-2 (COVID-19) pandemic has created unprecedented challenges to the research activities of this study. To stem the rising number of COVID-19 cases, countries around the world have announced nationwide quarantines and put people on various forms of lockdown. In Malaysia, movement control orders have been imposed by the Malaysian government from March 18, 2020, with a series of restrictions on movement and mass assembly. As of February 17, 2022, there were a total of 3,111,514 confirmed cases of COVID-19 with 32,201 deaths in Malaysia reported to the World Health Organization [18]. Owing to movement restrictions and frequent changes from COVID-19, we have developed alternative plans for all study activities, including interviews, co-design workshops, and intervention testing to be carried out remotely, if needed.

Aims

Our project aims to develop and assess the feasibility of a digital intervention (referred to for now as Collective Action for Wellness in the Workplace [CAWW]) to improve employees' health behaviors and well-being, thus reducing the risk of chronic diseases in the workplace. Based on the current evidence, there is a need to develop sustainable interventions to support employees' well-being in LMICs. In the current project, we will focus on co-designing and implementing an intervention in a Malaysian company, drawing on social cognitive theory, social impact theory, and social influence theory.

This study has 3 aims. Aim 1 is to understand the barriers and facilitators to healthy behaviors among employees from the target company, both within the workplace and at the work-home interface. Aim 2 is to co-design intervention activities with the employees that deliver collective education and action around healthy behaviors using digital communication or coordination, such as WhatsApp. Aim 3 is to assess the feasibility of measuring health, behavioral, and social outcomes, as well as the cost–benefit to the target company before and after the implementation of the intervention.

Objectives

In order to obtain the aims outlined above, the study will achieve the following objectives:

- identify factors that influence employees to engage in healthier or less healthy behaviors at work, including social influences from others;
- explore workplace wellness activities and digital communication or coordination tools that are of interest to employees;
- co-design specific wellness activities with employees as part of the CAWW intervention;
- test the implementation of these activities with employees over the course of 6 months; evaluate the feasibility of measuring the outcomes of interest through employees completing questionnaires and wearing fitness trackers; and
- assess the feasibility and acceptability of collecting employee attendance and participation data.

Research Questions

The following research questions will be examined throughout the study. The qualitative interviews and workshops (phase 1) will investigate the following:

1. What factors influence employees to engage in healthier or less healthy behaviors at work?
2. How do the behaviors, opinions, or actions of others in the workplace influence employees' health?
3. What types of workplace wellness activities are interesting to employees, and can they be supported or sustained by the organization?
4. Do employees think that digital communication or coordination tools, such as WhatsApp, can be used to coordinate healthier behaviors or activities in the workplace?
5. How can existing social influence within the workplace be leveraged to create new wellness activities and encourage employee participation?

The quantitative feasibility portion of the study (phase 2) will investigate the following:

1. Will employees agree to participate in wellness activities at work, complete questionnaires, and wear fitness trackers, and what proportion will complete these tasks at both baseline and follow-up?
2. Are the selected measures sufficiently sensitive and suitable for measuring the outcomes of interest?
3. What is the variability observed in the outcome measures of interest?

4. Is it feasible to collect data on work attendance from an employer for consenting employees?

Methods

Study Setting

This study will be conducted with employees from a Malaysian biotechnology company. The company employs around 2000 people across functions such as research and development, manufacturing, and marketing. Employees from a range of departments and demographic backgrounds will be included in this study. This company provides an interesting setting for this study as its employees reflect the unique multiethnic composition of Malaysia, and includes employees working in desk or laboratory jobs, as well as employees working in manufacturing positions that require more manual labor.

Study Design

This study will employ a mixed method approach and consist of two phases. Phase 1 will consist of 8 months of co-design activities, and phase 2 will consist of a 6-month feasibility study of the CAWW intervention. Figure 1 shows an overview of the timeline of the study.

Figure 1. Overview of the timeline of the study. CAWW: Collective Action for Wellness in the Workplace.
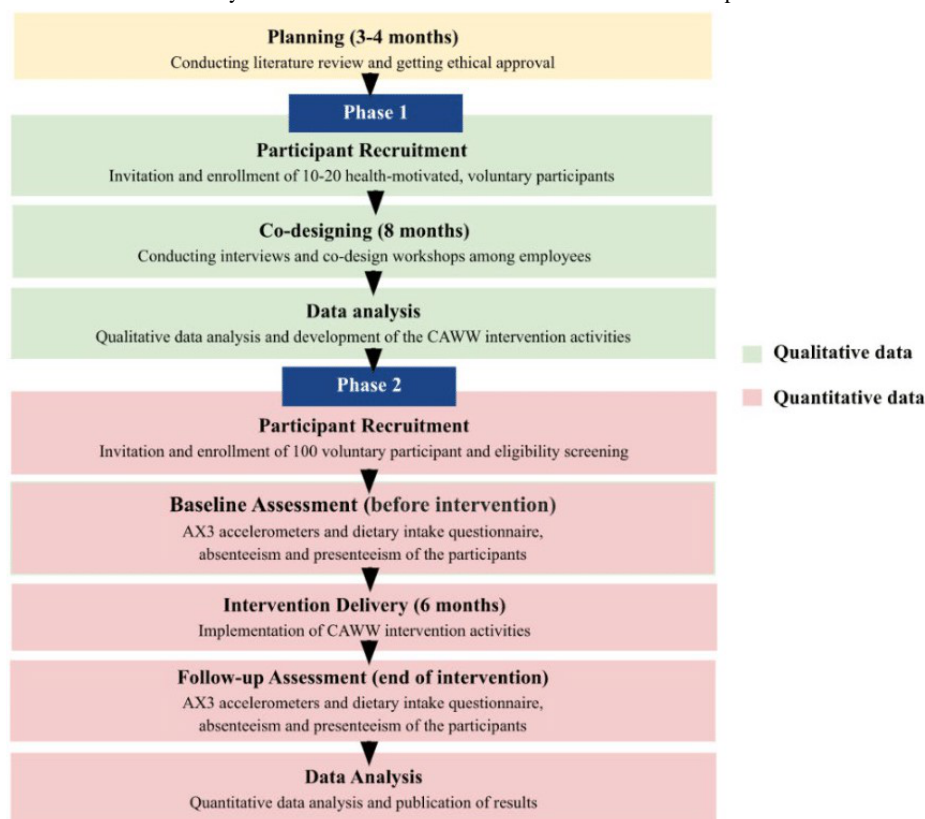
Theoretical Framework

The design of the phase 1 interviews, the phase 2 intervention, and our planned phase 2 measurement framework will be informed by the social cognitive theory (SCT) [19], social influence theory [20], and social impact theory [21], which

acknowledge that behavior is influenced by factors at both the individual and social levels. Even though most of the past studies of workplace health behavior change in LMICs have focused on individual-level factors [10,22-24], we argue that social-level factors and the environmental context are also equally important in behavior change. SCT was selected as an appropriate

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theoretical lens for the study owing to its incorporation of individual environmental and behavioral factors. SCT proposes that health behaviors are influenced by dynamic and reciprocal interactions among individual, environmental, and behavioral factors [19]. Individual factors include cognitive, affective, and biological processes, such as knowledge, expectations, learned behaviors, beliefs, and attitudes [25]. Self-efficacy, a key construct of the theory, refers to an individual's belief in his or her ability to execute a particular behavior necessary to obtain the intended results. Environmental factors include the external social context, which can contribute to observational learning and reinforcements to continue or discontinue a behavior. Finally, behavioral factors, or responses to stimuli to achieve goals, include factors like expectations and capability.

Our understanding of social-level factors can be further expanded by drawing on the social influence theory, which explains how motivations—to be accurate, to affiliate, and to maintain a positive self-concept—can drive behavior [20]. More specifically, factors such as authority and conformity can influence an individual's decision to adopt certain behaviors [26,27]. The social impact theory adds that the amount of influence a person experiences in a social context will depend on the strength or power of the group, the psychological or physical proximity of the group (immediacy), and the number of people exerting the influence in the group [21]. These theoretical constructs have been synthesized into a theoretical framework informing this study in Figure 2.

Figure 2. Theoretical constructs influencing changes in health behaviors at the individual and social levels. Sources: [1]Latané, 1981[21], [2]Cialdini & Goldstein, 2004 [20], [3]Bandura, 2011[25].
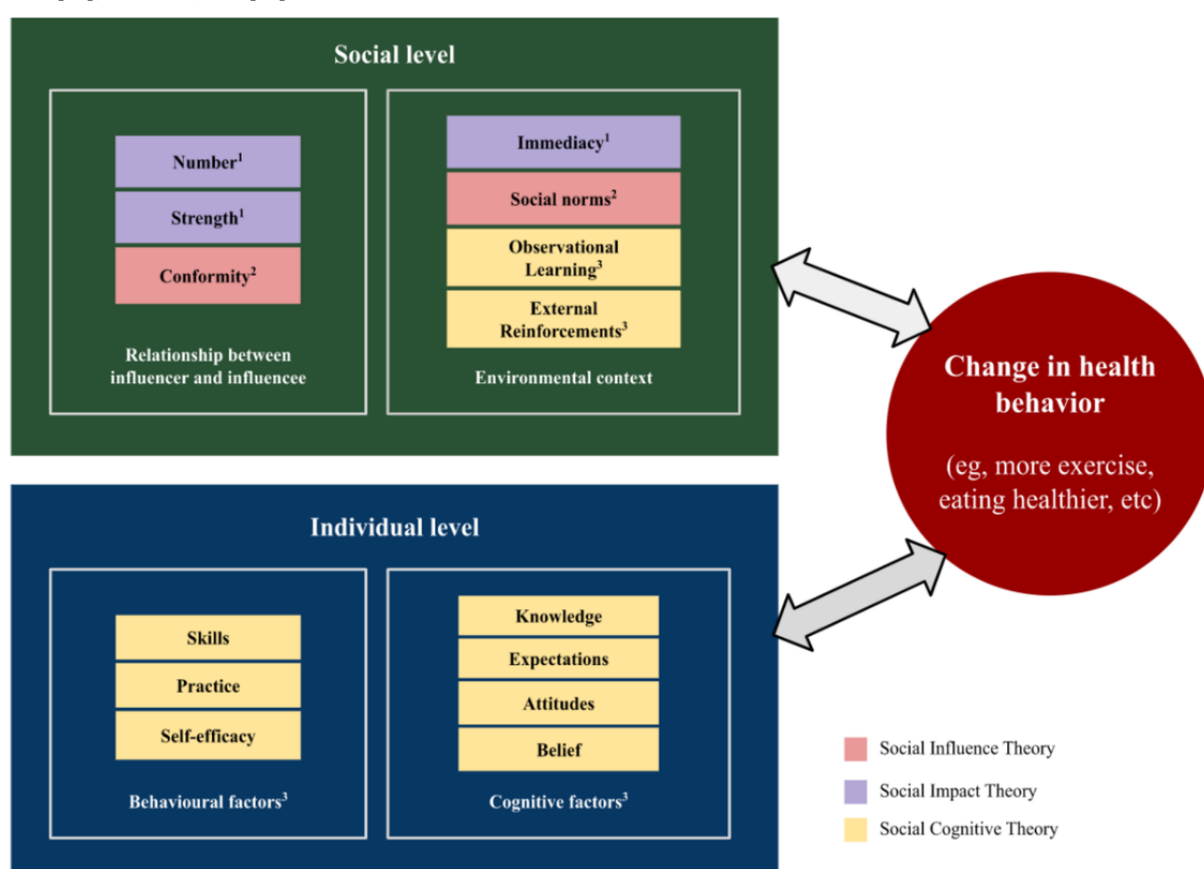
Phase 1: CAWW Intervention Development using a Qualitative Co-design Approach

Co-design is a process involving the collective creativity of all stakeholders, including researchers, designers, developers, and users [28]. It aims for better design through a rich and deep understanding of the user's knowledge, behaviors, and thoughts [29]. By employing the co-design methodology, we will engage the company employees from the beginning of the design process, discussing ideas and developing the CAWW intervention activities to be culturally relevant (both at a societal level and fitting with company culture) and meet their true needs [30]. More detail on the co-design methods that will be used is provided in the following sections.

Qualitative Interviews

First, qualitative, in-depth, individual interviews will be conducted with a purposive sample of highly motivated and health-focused employees (target N=10-15). The sample will be balanced by age, gender, ethnic groups, and working departments. The purposive sampling of motivated and health-focused individuals is based on the idea that these employees may be more likely to help identify new ideas and opportunities for a healthier workplace. A few pilot interviews will be conducted prior to the actual interview to refine the interview questions. The research team members or a trained research assistant will administer the interviews and follow a semistructured protocol that will be developed from primary research questions, the theoretical framework, and project goals.

In relation to the theoretical framework, questions about how individual-level and social-level factors shape employees' perceptions and workplace health behaviors were included in the interview protocol. For example, to explore the social-level relationships between influencers and influencees, participants will be asked, "Who are the key people that make decisions or influence people in your workplace? Why are they influential?" Each interview will take approximately 60 minutes and will be conducted via an web-based platform (eg, Zoom; Zoom Video Communication Inc) without the involvement of a third party to ensure confidentiality. The interview will be conducted in English or Malay based on the participants' language preferences and transcribed using Descript software. All data will be stored in an institution-approved secure space.

Co-design Workshops

Second, we will conduct 2 co-design workshops with employees to design the format and content of the intervention. A target of 10-15 participants will be recruited to participate in each co-design workshop. Flyers will be sent by the human resources (HR) team to recruit voluntary and interested employees. Depending on the current unstable pandemic context of COVID-19 in Malaysia, the co-design workshops will be held through either the Zoom platform or face to face in a private room of the company.

The activities of the workshops will be governed by the findings from the qualitative interviews. For instance, based on the interview data, we will identify which variables of the theoretical framework are more prominent in encouraging individuals to practice healthy behaviors in the workplace. Following this, the workshop activities will be designed to incorporate these variables. The participants of the co-design workshops will then be asked to help design workplace wellness activities integrating the variables that encourage the employees to focus more on their health.

The first workshop will be held with the company's HR department to identify the nature of the activities that can be sustainably supported and financed. Initial ideas for evidence-based intervention activities will be shared with the group, based on a review of the literature on workplace wellness interventions. The employees from the HR department were selected for the first workshop as it is likely that they will be able to provide more holistic input from their perspectives both as employees and HR professionals, owing to their dual role in the company. For the second workshop, we will conduct an activity with other company employees outside the HR department to refine and prioritize potential activities resulting from the first workshop.

Phase 1 Data Analysis

Following transcription of the interview data, a reflexive thematic analysis approach [31] will be used. In reflexive thematic analysis, the researchers deeply immerse themselves in the collected data and follow an "organic" process through "reflexive interpretation" [32]. Given that reflexive thematic analysis encourages researchers to actively engage with research data and make transparent decisions, all decisions from data collection to data analysis in phase 1 will be designed to align with strategies outlined in this approach. For example, when determining the sample size, we will pay attention to the adequacy of the data gathered from interviews in relation to the purpose of our research, the relevance of the gathered data to research questions, and whether the sample is representative of different departments within the organization [32]. Thus, the target sample size (N=10-15), which has currently been determined based on the representation of workers from different departments, may be modified as necessary during data collection depending on the richness and complexity of data gathered from the interviews in relation to the research questions. Further, since the study is informed by a theoretical framework designed by considering individual, cognitive, social, and environmental factors that influence health behavior change, we will adopt a theoretical (deductive) approach in conducting the reflexive thematic analysis [33].

Employee input during the workshops will be recorded and subsequently analyzed as well. Common themes will be concluded from the findings across workshops, and the final components of the CAWW intervention will be identified via consensus. With the input from the participants during the co-design phase, the research team will identify the intervention wellness activities, the potential channels (eg WhatsApp, Zoom, in-person, etc) to coordinate and conduct the wellness activities, ways to motivate participation in wellness activities, and the timing and frequency of the wellness activities.

Phase 2: CAWW Testing and Evaluation of Acceptability and Feasibility Using a Quantitative Approach

Phase 2 will consist of testing the feasibility of the intervention through baseline data collection, followed by the 6-month intervention, and then the collection of follow-up data. Participation data (number of messages sent, attendance to events, etc) will be collected throughout the intervention. In this phase, we aim to enroll 100 participants in the feasibility study. The study was funded to include 100 participants. This is a conservative sample size for a feasibility study and is comparable to many other feasibility and pilot studies, given the lack of consensus on the best methods to calculate sample size for a feasibility study [34]. Employees will be invited by their employer to contact the research team if they are interested in participating. Participants with the following criteria will be eligible for inclusion in the study: adults aged 18 years and older, are employed through the study completion date, do not have a mobility impairment, working in the office or at home at least 3 days a week, and have access to a mobile device. Participants who are away on extended leave for more than 2 weeks or who are pregnant or lactating will be excluded from this study. Additional employees can participate in the intervention activities, but their data will not be collected. Informed consent will be obtained from participants who meet the inclusion criteria and participation will be voluntary. Financial incentives will be provided for participation in research activities including surveys and data collection, but no compensation will be given for participating in the intervention wellness activities.

Study Measures

The research team will collect data at baseline before the intervention starts and at follow-up after the intervention ends (after 6 months). The baseline and follow-up data collection will include 4 aspects: (1) health, including health-related quality of life (HRQoL); (2) behaviors, including physical activity and dietary intake; (3) social, including employees' sense of community [35]; and (4) economic, including absenteeism, presenteeism, and total cost of implementing the program for employers.

Primary Outcomes

The primary measured outcomes of this study are physical activity and diet. The AX3 accelerometer will be used on wristbands to monitor the physical activity levels of participants for a 7-day period at baseline and follow-up. Participants' dietary data will be collected at baseline and follow-up through a self-administered questionnaire that asks about participants' food and beverage consumption on the previous day. This questionnaire, the Diet Quality Questionnaire, has been developed and validated to measure diets worldwide as part of the Global Diet Quality Project, and the country-specific questionnaire for Malaysia will be used [36].

Secondary Outcomes

The HRQoL will be measured through an extensively used questionnaire, the Short Form-12 Health Survey Version 2 (SF-12v2). The SF-12v2 was developed from the Medical Outcomes Study (MOS) 36-item Short-Form Health Survey (SF-36) [37], and its brevity reduces the burden on participants and researchers [38]. The 12-item SF-12v2 has also been shown to be reliable and valid in measuring HRQoL of a wide range of population groups [38-42]. The employees' sense of community will be assessed using Sense of Community Index version 2 (SCI-2) [43]. SCI has been frequently used as a quantitative measure of a sense of community, being proven as a strong predictor of behaviors and a valid measurement tool. It has been used with different cultures in many different contexts [43]. The employees' health-related productivity will be assessed through absenteeism and presenteeism. Absenteeism will be examined through recorded sick days taken in the previous 6 months (reported by the employer at baseline and follow-up). Sickness absence by definition is the absence from work owing to illness and has been used as the measure of health and well-being in the population [44-46]. Presenteeism will be measured using the 6-item Stanford Presenteeism Scale (SPS-6) [47]. SPS-6 has strong psychometric characteristics in measuring health and productivity [47]. Finally, data will also be collected on the estimated costs of the intervention.

Feasibility and Acceptability

Satisfaction with the intervention will be assessed by a modified version of the client satisfaction questionnaire (CSQ) [48]. The 8-item CSQ has been recognized as a useful measure of general satisfaction and takes only 3-8 minutes to complete [48]. It is associated with therapists' estimates of client satisfaction and has good reliability due to its high internal consistency. The CSQ will be modified to fit the workplace context and to measure the general satisfaction with the intervention activities.

Phase 2 Data Analysis

For the quantitative outcome measures in phase 2, a descriptive analysis will be conducted. As this is only a feasibility study and the sample size is appropriately small, we will not make statistical inferences on the effectiveness of the intervention [49]. The data will be used to assess the sensitivity and suitability of the instruments, estimate the levels of variability in outcomes for future sample size calculations, and determine the willingness of participants to participate in activities, wear fitness trackers, and complete our measures. These results can help to inform a potential future larger-scale study to examine the intervention's effectiveness. A preliminary economic cost–benefit analysis will also be performed to better understand the potential for this intervention in the workplace for employers.

Ethics Approval

We have obtained ethics approval from the Monash University Human Research Ethics Committee (Review reference: 2022-30670-71503) for phase 1 of the study. The necessary precautions will be taken to maintain privacy and confidentiality, including using institution-approved secure data storage space, which is password-protected and only accessible by research team members. All participants will provide written consent prior to their participation in activities. Ethics approval for phase 2 will be obtained prior to commencing those study activities.

Results

This protocol summarizes the initial study plan. This study was funded in June 2021, and ethics approval for Phase 1 was obtained in January 2022. As of August 2022, qualitative interviews with 12 employees have been completed, and the data have been transcribed and analyzed. The findings and more details will be included in the following study results publication.

Discussion

Projected Principal Findings

Once completed, this study will further our understanding of the factors that influence healthier behaviors in the workplace, including social influence between employees. It will also result in co-designed, culturally relevant workplace wellness activities with the goal of promoting better health and reducing chronic disease. Finally, the results will also indicate the feasibility of implementing and studying a digital workplace wellness intervention in this setting and can be used to inform a future, larger-scale effectiveness study.

Comparison to Prior Work

Prior to planning and commencing this study, our team conducted a scoping review of digital workplace wellness interventions in LMICs. This review is under submission, but its main findings include that most research on digital workplace wellness interventions has taken place in high-income countries, and relatively few interventions have been studied in LMICs. Among those studies that have been done in LMICs, digital workplace wellness interventions focus on a range of health

issues, including physical activity [22], nutrition [50], smoking cessation [51], and stress [52]. The most common focus is on health behaviors related to chronic disease prevention, as in our study. For example, Ganesan et al [53] studied a digital stepathalon among 26,562 adult employees in India and found evidence of improvements to outcomes such as step count and body weight. Most studies found some evidence of effectiveness and were feasible to implement and acceptable to employees, suggesting that a similar approach in the Malaysian workplace context holds promise in this study.

Strengths and Limitations

This study has three major strengths. First, this study was designed using 3 theoretical frameworks that describe the individual and social-level factors that contribute to behavior change, and it will leverage the social connections and influence within a workplace to drive healthier behaviors. Based on our recent scoping review (under submission), many previous studies of digital workplace wellness interventions in LMICs either did not use any theory to inform their design or were informed by individual behavior change theories only. Second, this study will employ the co-design methodology to develop the intervention and will contribute to the literature in this area. Though co-design methods are becoming more commonly used in health studies, they are seldom described or evaluated in detail [54]. Further, existing research suggests that the co-design approach is beneficial for researchers, practitioners, research processes, and outcomes [54]. Finally, as mentioned above, most research on digital workplace wellness interventions has taken place in high-income countries. This study will contribute to the evidence from LMICs by studying an intervention in a Malaysian workplace, taking into account the unique multiethnic cultural context of Malaysia, as well as an individual company's workplace culture.

This study has an important limitation. Phase 2 employs a small sample size and uses nonrandom sampling methods that will not make it possible to test the intervention's effectiveness. However, the sample size and sampling methods are appropriate for testing feasibility, which is this study's aim.

Data Availability

The qualitative data sets generated from interviews and co-design workshops (phase 1) will not be made available, owing to the need to protect data that could lead to the potential identification of employees by their employer. The quantitative, deidentified data sets generated from phase 2 will be made available to other researchers following the study.

Authors' Contributions

JYT performed the background literature review and drafted the manuscript with support from JW. JW, JYT, and DC developed the theoretical framework section, PO contributed to the co-design workshop methodology, and DC contributed to the qualitative methods section. JW, TM, and AR refined and revised the manuscript. All authors provided input on the study aims and design and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CAWW: Collective Action for Wellness in the Workplace
CSQ: client satisfaction questionnaire
HR: human resources

HRQoL: health-related quality of life
LMICs: low- and middle-income country
MOS: Medical Outcomes Study
NCDs: non-communicable disease
SCI-2: Sense of Community Index version 2
SCT: social cognitive theory
SF-12v2: Short Form-12 Health Survey Version 2
SF-36: 36-item Short Form Health Survey
SPS-6: 6-item Stanford Presenteeism Scale

A Video-Based Mobile App as a Health Literacy Tool for Older Adults Living at Home: Protocol for a Utility Study

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Abstract

Background: People aged ≥65 years are more likely to have health problems related to aging, polypharmacy, and low treatment adherence. Moreover, health literacy levels decrease with increasing age.

Objective: The aim of this study is to assess an app's utility in promoting health-related knowledge in people aged ≥65 years.

Methods: We developed a simple, intuitive, and video-based app (DigiAdherence) that presents a recipe, nutritional counseling, and content on physical activity, cognitive exercise, motivation to adhere to treatment, fall prevention, and health literacy. A convenience sample of 25 older adults attending the Personalized Health Care Unit of Portimão or the Family Health Unit of Portas do Arade (ACeS Algarve II – Barlavento, ARS Algarve, Portugal) will be recruited. Subjects must be aged ≥65 years, own a smartphone or tablet, be willing to participate, and consent to participate. Those who do not know how to use or do not have a smartphone/tablet will be excluded. Likewise, people with major cognitive or physical impairment as well as those living in a long-term care center will not be included in this study. Participants will have access to the app for 4 weeks and will be evaluated at 3 different timepoints (V0, before they start using the app; V1, after using it for 30 days; and V2, 60 days after stopping using it). After using the app for 30 days, using a 7-point Likert scale, participants will be asked to score the mobile tool's utility in encouraging them to take their medications correctly, improving quality of life, increasing their health-related knowledge, and preventing falls. They will also be asked to assess the app's ease of use and visual esthetics, their motivation to use the app, and their satisfaction with the app. Subjects will be assessed in a clinical interview with a semistructured questionnaire, including questions regarding user experience, satisfaction, the utility of the app, quality of life (EQ-5D-3L instrument), and treatment adherence (Morisky scale). The proportion of participants who considered the app useful for their health at V1 and V2

will be analyzed. Regarding quality of life and treatment adherence perceptions, comparisons will be made between V0 and V1, using the *t* test for dependent samples. The same comparisons will be made between V0 and V2.

Results: This study was funded in December 2019 and authorized by the Executive Board of ACeS Algarve II – Barlavento and by the Ethics Committee of NOVA Medical School (99/2019/CEFCM, June 2020). This protocol was also approved by the Ethics Committee for Health (16/2020, September 2020) and the Executive Board (December 2020) of the Regional Health Administration of the Algarve, IP (Instituto Público). Recruitment was completed in June 2021.

Conclusions: Since the next generation of older adults may have higher digital literacy, information and communication technologies could potentially be used to deliver health-related content to improve lifestyles among older adults.

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Introduction

Following the trend observed in other developed countries, Portugal's population is aging rapidly, and Eurostat estimates it will be the oldest country in the European Union by 2050 [1]. Although medical and scientific progress has made it possible to increase the average life expectancy, this rapid aging of the population is associated with an increasing number of people with multiple chronic diseases and disabilities.

In the 2015 National Health Examination Survey, 3.9 million Portuguese people (57.8%) reported having at least one chronic condition. The occurrence of chronic disease was more frequent in people aged 65-74 years and in those with a lower educational level [2]. Four years later, the tendency remained. According to Portugal: Country Health Profile 2019, 53% of people ≥65 years of age have at least one chronic disease. Nonetheless, many reported having two or more chronic illnesses [3].

Additionally, data from the Epidemiology of Chronic Diseases (EpiDoC) cohort, a prospective cohort study based on a representative sample of the Portuguese population, showed that there is a high prevalence of multimorbidity among older adults and that the frequency of coexisting multiple diseases increases with age (72.8% in people aged 65-69 years vs 83.4% in people ≥80 years). Importantly, this was associated with unhealthy lifestyle behaviors, such as physical inactivity [4]. Multimorbidity and polypharmacy, which are of particular concern in an aging population, are also associated with poor treatment adherence [5-7].

The literature suggests that low health literacy levels are associated with worse health outcomes. For instance, those with lower health literacy tend to resort to emergency services more frequently, have higher health expenditures, and do not make as much use of preventive medicine services [8-10].

Income, age, race, and education level are considered contributing factors to health literacy levels. Authors have reported that even minor cognitive decline in older nonimpaired adults is associated with health literacy decline [11].

Because of the current COVID-19–related need for social distancing, it is essential to implement new nonpharmacological strategies to support older adults living at home by promoting their physical, mental, and nutritional health and increasing their treatment adherence and health-related knowledge. Digital patient-centered solutions can potentially help us create these much-needed alternatives. Studies have reported several apps for older adults to promote social interaction, health, and well-being [12-15]. An example is STARFISH, a smartphone-based app that monitors users' physical activity by counting their daily steps and facilitates social support [12]. In terms of treatment adherence, evidence suggests it can be improved with apps designed for older adults, even if they have no smartphone or tablet experience [16].

We have previously developed an informative and motivational, home-based, 12-week program (Saúde.Come) aimed at promoting healthy eating at a low cost and the practice of regular physical exercise. The program was delivered by an interactive television application [17]. The pilot study showed Saúde.Come was well accepted, reduced food insecurity, and improved the participants' physical function [18].

Several projects are being developed under the umbrella of the Portuguese Health Literacy Action Plan 2019-2021 [19], which aims to continuously, consciously, and sustainably improve the health literacy level of those living in Portugal. The Portuguese Directorate-General for Health plans to disseminate, free of charge, an educational mobile app to promote physical activity, mental health, and nutritional health in older adults. Given our experience [17], we have joined them in the effort and developed such an app (DigiAdherence). In this study, we aim to assess the DigiAdherence mobile app's utility in promoting health literacy.

Methods

The DigiAdherence App

We have developed a simple, intuitive, and video-based mobile app using the Android Studio software and the following programming languages:

- Java for operations, such as user interaction when clicking a button, and the various video-linked options including pause, fast-forward, rewind, and full-screen mode
- XML for the system design implementation and each of the app's actions

- Gradle for Java development and implementation, enabling the app's adaptation to different types of Android systems/mobile phones

Our user interface was developed with a reader-friendly mindset (straightforward content coupled with eye-catching, simple, and consistent design). Color and contrast were used for optimal visibility (#02796B for the foreground and #FFFFFF for the background; contrast ratio of 5.31:1). Videos are stored locally within the app, allowing it to function on demand and without connecting to the internet. To build the executable file (APK), we used Android Studio's "Build APK" option.

The aging process is associated with the development of various chronic noncommunicable diseases (like high blood pressure or rheumatic diseases) and the decline of one's senses, motor function, and cognition. Altogether, these may compromise a person's ability to perform certain physical and mental tasks, making them vulnerable to life-threatening events such as falls. We have previously shown there is a high prevalence of chronic diseases and unhealthy lifestyle behaviors among the Portuguese older adult population, highlighting the need for dedicated interventions [4]. The DigiAdherence app integrates 6 short videos designed to motivate older adults, encourage the consumption of healthy food, improve the practice of physical activity, prevent falls, encourage cognitive exercise, and increase treatment adherence. The app's contents were developed by a multidisciplinary team of professionals, including 1 chef, 1 nutritionist, 1 personal trainer, 1 psychologist, and 2 rheumatologists. Video length varies between 2 and 8 minutes. In essence, the DigiAdherence app is intended to be an extension of the comprehensive care provided by a person's primary care health care professional.

The app can be accessed using an Android smartphone or tablet. DigiAdherence's launch screen appears instantly when the app starts up and is quickly replaced with the app's 6-option main menu, with each menu button leading to a distinct health-related thematic video (wireflow depicted in Figure 1). Half of the video content was used in a previous successful study conducted by our research group [17,18]. In the first section, a chef teaches the users how to make a healthy carrot soup; in option number 2, a personal trainer demonstrates a series of physical activity exercises that older adults can do while sitting in a chair; in section number 3, a nutritionist talks about sugar replacement options; in option number 4, a psychologist talks about the importance of doing cognitive exercises, giving some examples of the types of exercises that older adults can do; in section number 5, a rheumatologist lists a series of techniques that can be adopted by older adults to prevent falls on the street or at home; finally, in section 6, a rheumatologist talks about the risk of polypharmacy and gives tips on what older adults should do to ensure they take their medication as prescribed. Note that every professional made sure to speak clearly, without using medical or technical jargon, keeping their messages simple and easy to understand. Full-screen mode is enabled by rotating the smartphone or tablet horizontally.

DigiAdherence is an offline app that users can access multiple times and at any time. Even though there are no notifications sent by the app, we believe the participants will access its contents when, for instance, they feel the need to exercise without leaving the house or want to learn more about nutrition. The app was designed to get users to see a health-related video of their choice with just 2 taps.

As an offline app, we will not be quantifying the app's engagement metrics such as frequency of use, exit rate, or repeat usage. Our focus will be on the app's content utility in improving self-reported health-related knowledge (7-point Likert scale). For more details on the variables this study will assess, please read the Data Collection subsection.

Figure 1. DigiAdherence app wireflow.
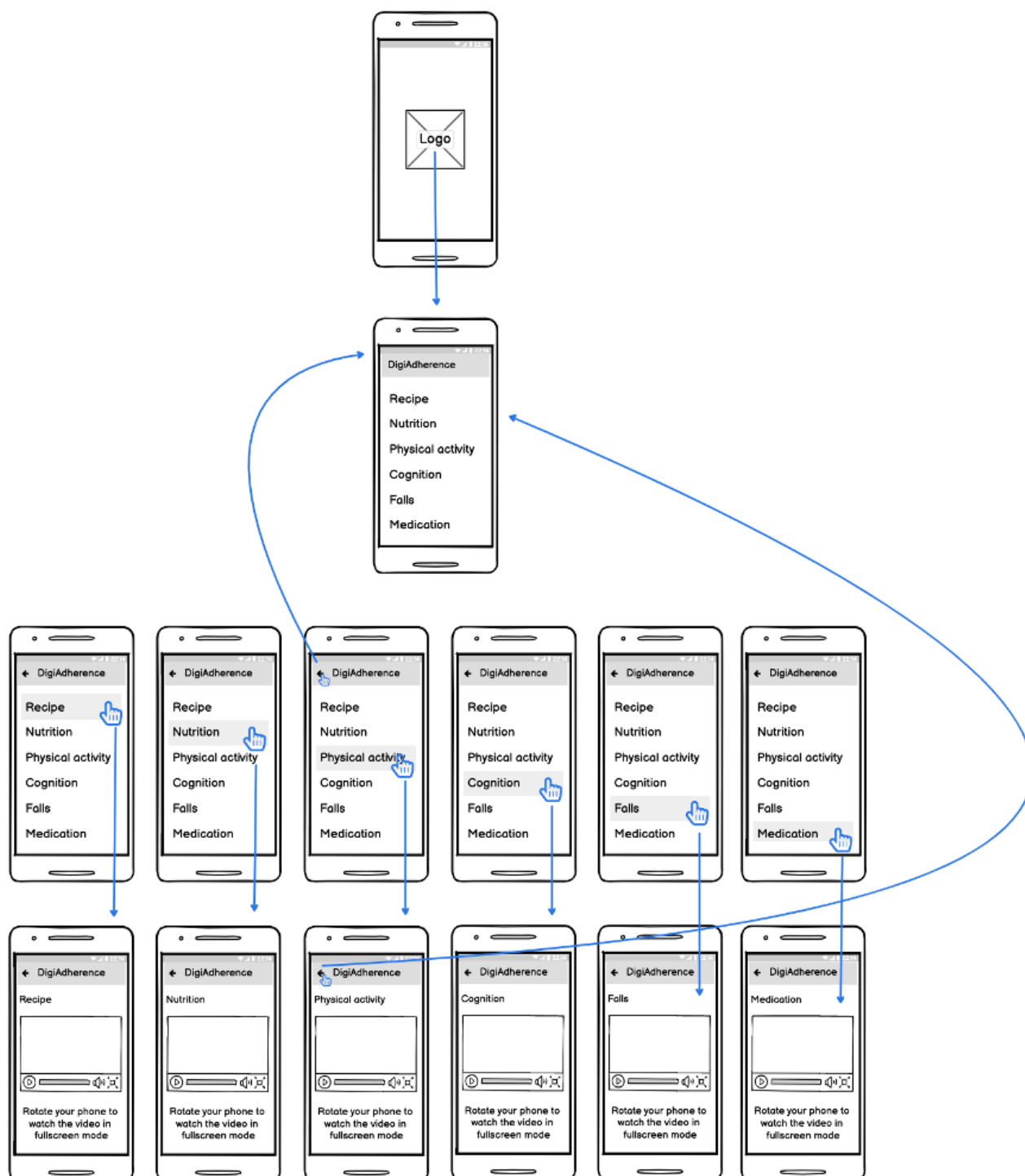
Study Description

Participants and Recruitment

This study will include a convenience sample of 25 patients, aged 65 years or older, who attend the Barlavento Health Center Cluster (ACeS), Regional Health Administration (ARS) of the Algarve, Portugal (Figure 2). The selection of potential participants will be carried out by their primary health care physician. Subjects' recruitment will occur at the Personalized Health Care Unit of Portimão and at the Family Health Unit Portas do Arade, both belonging to ACeS Algarve II – Barlavento, Portugal. Those who show an interest in participating in the study will be contacted by a Public Health physician who will invite them to an in-person visit at the Public Health Unit of ACeS Algarve II – Barlavento. At this visit, the physician will explain the study to the older adult and, if he/she agrees to participate and meets the study's inclusion criteria, ask him/her to sign the informed consent. The recruitment phase is expected to last 2 months.

Figure 2. DigiAdherence study design overview. UCSP: Personalized Health Care Unit; USF: Family Health Unit.
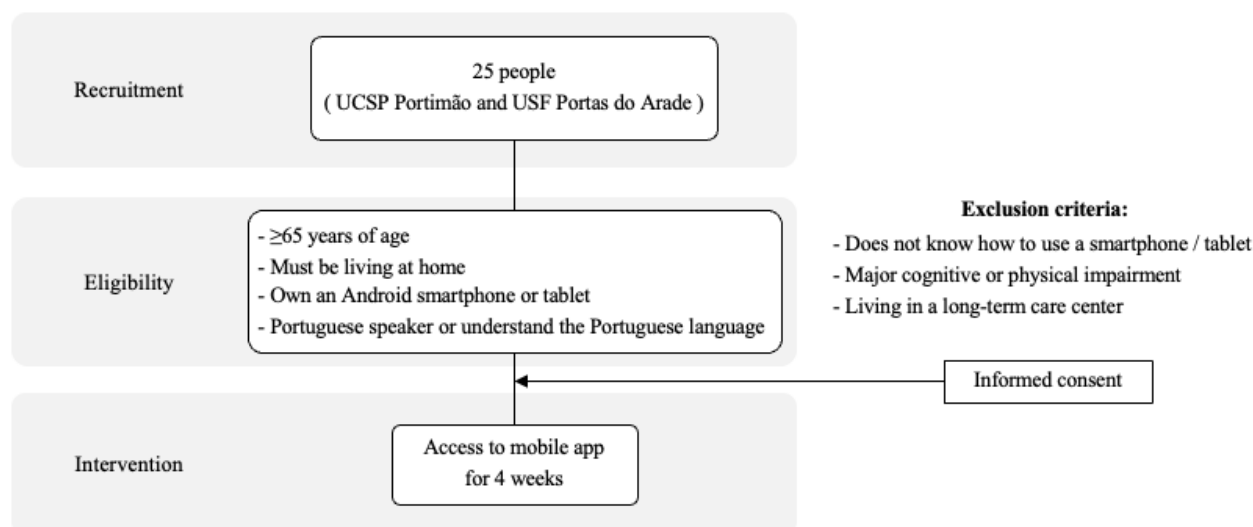
To be eligible for participation in this pilot study, inclusion criteria are as follows. Participants (male/female) must (1) be aged ≥65 years, (2) be living at home, (3) own an Android smartphone or tablet, (4) be a Portuguese speaker or understand the Portuguese language, (5) visit the Personalized Health Care Unit of Portimão or the Family Health Unit of Portas do Arade (ACeS Algarve II – Barlavento, ARS Algarve, Portugal), and (6) be willing and consent to participate.

Inclusion criteria were not limited to a specific set of chronic diseases or medications to increase the odds of older adults who are smartphone owners joining our pilot study.

Exclusion criteria include the following: (1) individuals who do not understand Portuguese, (2) individuals who do not know how to use or do not have an Android smartphone/tablet, (3) individuals who have a major cognitive or physical impairment and/or (4) individuals who are living in a long-term care center.

Study Design and Procedures

After being recruited and consenting to their participation, subjects will have to attend 3 scheduled visits at their primary health care center. All clinical evaluation and data collection visits will be carried out at the Public Health Unit of ACeS Algarve II – Barlavento, Portugal.

At the first visit (V0), we will collect information about the participant's health status, medication, health literacy, quality of life, and frequency of falls (if subjects fell in the last month, how many times did they fall? Answer options: 1, 2, 3, 4, 5, >5). After participants install the app on their smartphone or tablet, they will be given a demonstration on how the app works and have the chance to clarify any questions that may arise

regarding the app's functioning. The health care professional performing the participants' recruitment will also encourage them to use the app. Access to the DigiAdherence app will be granted for 4 weeks. There will be no notifications or triggers.

After a month, there will be a second visit (V1) to reassess the subjects' health status, adherence to technology, quality of life, frequency of falls, and health literacy. The third visit (V2) will occur 2 months after the end of the exposure to the app. The participants' health status, quality of life, frequency of falls, and health literacy will be reassessed in this consultation.

This study does not comprise an app usability testing, since DigiAdherence's content was adapted from the Saúde.Come project [17,18], a multidisciplinary 12-week, home-based program focused on improving dietary and physical activity through an interactive television app. Saúde.Come has been fully implemented and tested in a similar population and shown to be feasible and acceptable for use by users [18]. Furthermore, DigiAdherence is an offline app with no interaction or dynamic elements, consisting mainly of educational content for which no difficulties in engaging with the app were anticipated.

Data Collection

As previously described, this study entails three evaluation moments: the initial one (V0; before the participant starts using the app), after using the app for 30 days (V1), and 60 days after stopping using DigiAdherence (V2) (Table 1). In terms of variable selection, we selected knowledge as the target determinant since it is one of the main factors contributing to the adoption of self-management practices, according to various theories of behavior change such as the Capability, Opportunity, Motivation, Behavior Model [20,21].

Table 1. Variables to be assessed within the DigiAdherence study.

	Baseline	Visit 1	Visit 2
Visit number	V0	V1	V2
Timing (weeks)	0	4	12
Informed consent	X		
Inclusion/exclusion criteria	X		
Participant identifier	X		
Birth date	X		
Sex	X		
Weight and height	X	X	X
Educational level	X		
Concomitant medications	X	X	X
Self-reported chronic diseases	X	X	X
Self-reported number of falls in the last month	X	X	X
Self-reported health literacy	X	X	X
Health-related quality of life (EQ-5D-3L instrument; score from –1 to 1)	X	X	X
Treatment adherence (8-item Morisky Medication Adherence Scale; score from 0-8; <6 denotes low adherers, 6 to <8 denotes medium adherers, and 8 denotes high adherers)	X	X	X
Self-reported adherence to the technology, including an evaluation of the app's instrumental and noninstrumental attributes on a 7-point Likert scale (1=most negative response, 7=most positive response); attributes include utility in the correct uptake of medication, utility in improving quality of life, utility in improving health-related knowledge, utility in preventing falls, ease of use, visual esthetics, motivation to use the app, and satisfaction with the app		X	

At V1 and using a 7-point Likert scale, older adults will be asked to score the mobile tool's utility in taking their medications correctly, improving quality of life, increasing their health-related knowledge, and preventing falls.

Using the same scoring system, participants will also be asked to assess the app's ease of use and visual esthetics, as well as their motivation to use the app and satisfaction.

All assessments will be based on a structured questionnaire. All visits will focus on treatment adherence (Morisky scale [22]) and the prevention of falls. We will also assess perceptions regarding quality of life (assessed by the Portuguese version of the EQ-5D-3L questionnaire [23], the European Quality of Life questionnaire with 5 dimensions and 3 levels) and health-related knowledge (participants will be asked if they felt that the app's content increased their health-related knowledge and if they made use of the information delivered to prevent falls and to correctly take their medication). At these visits, sociodemographic data (age, gender, level of education) and clinical history will also be collected, including concomitant medication, comorbidities, and history of falls.

Statistical Analysis

Statistical analysis will be performed using the STATA software (version 16; StataCorp LLC). Participants will be characterized in terms of sociodemographic variables, health, quality of life, and fall risk. Normally distributed continuous variables will be described as mean and standard deviation, while nonnormal distributed ones will be presented as median and interquartile range. Categorical variables will be reported as frequencies or proportions.

We will analyze the proportion of participants who considered the app useful for their health in V1 and V2. Regarding quality of life (EQ-5D-3L [23]) and self-reported medication uptake (Morisky scale [22]), comparisons will be made between V0 and V1, using the t test for dependent samples if data are normally distributed; if not, Wilcoxon signed-rank test will be used. The same comparisons will be made between V0 and V2. Statistical significance will be considered when $P<.05$.

Ethical Issues

This study was submitted and authorized by the Executive Board of ACeS Algarve II – Barlavento and by the Ethics Committee of NOVA Medical School (99/2019/CEFCM, June 2020), NOVA University of Lisbon, Portugal. This protocol was also submitted to and approved by the Ethics Committee for Health (16/2020, September 2020) and the Executive Board of the Regional Health Administration of the Algarve (December 2020), IP (Instituto Público). All procedures will follow the principles of Good Clinical Practice and the Declaration of Helsinki (Fortaleza revision, 2013). Participants will be included in the study solely after obtaining their informed consent.

Although this pilot study is based on the use of a mobile phone app, the latter is an educational app that will only deliver short videos with a recipe, nutritional counselling, physical activity content, cognitive exercises, health literacy content, and motivation to adhere to treatment content. It should be noted that this technology will not collect or transmit, through

communication networks, any personal data related to the participants' health. Thus, according to the General Regulation on Data Protection; Regulation (EU) 2016/679 of the European Parliament and the Council of April 27, 2016; and Regulation No. 1/2018, this study is exempt from notification to the Portuguese Data Protection Authority.

Results

Recruitment was completed in June 2021. Data analyses are ongoing. Research findings will be made available to communities of interest through peer-reviewed journals and scientific conferences.

Discussion

Overview

This study aims to assess the DigiAdherence app's utility in improving health-related knowledge among older adults living at home. Based on our experience with information and communication technologies, we anticipate that the accurate educational content of the DigiAdherence app will prove useful for users of the app and contribute to the improvement of their health-related knowledge and encourage them to exercise and eat healthy.

Although older adults can sometimes become overwhelmed by the ever-changing world of technology, the next generation of older adults will be fairly digitally literate. Because people aged 65 years and over often have more health problems related to aging, polypharmacy, and low treatment adherence, information and communication technologies could potentially be used to deliver health-related content to improve lifestyles.

Those with lower health literacy are more receptive to video-based education [24,25]. Our research group has previously implemented a 12-week, home- and video-based intervention program (Saúde.Come) to reduce food insecurity in older adult populations using an interactive television app [17]. Saúde.Come was found to be feasible and well accepted by its users [18]. Moreover, a study [26] showed that 97% of community-dwelling older adults use television as their primary source of health information.

The acceptability of video across different age groups (ie, including older adults) and the exponential adoption of digital technology makes video an attractive communication tool to conveniently deliver health information to older adults no matter where they are.

Limitations

To measure medication uptake, we chose an instrument (Morisky Scale) that only quantifies self-reported oral medication uptake. Hence, injectable medication adherence will not be measured, constituting a study limitation. It should also be taken into consideration that the overall impact of the intervention on participants' health-related knowledge may be diminished, considering the app's short-form content and the lack of dynamic elements like triggers or notifications.

Conclusions

Since the next generation of older adults is somewhat tech-savvy, short mobile videos could potentially be used to deliver accurate health-related knowledge to improve lifestyles among older adults.

Authors' Contributions

Study design was accomplished by AMR, HC, RDS, MA, AC, and CNS. The DigiAdherence app's contents were developed by AMR, HC, MJG, and RDS. AV was responsible for the development of the DigiAdherence app architecture. CNS was a major contributor in writing the manuscript. AC, AMR, AV, HC, LP, MA, ML, and RDS provided essential scientific perspectives and performed the revision of the manuscript for publication. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ACeS: Health Center Cluster
ARS: Regional Health Administration
EQ-5D-3L: European Quality of Life questionnaire with 5 dimensions and 3 levels

Protocol

Development and Exploration of the Effectiveness and Feasibility of a Digital Intervention for Type 2 Diabetes Mellitus (DEsireD): Protocol for a Clinical Nonrandomized Pilot Trial in Brunei Darussalam

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Abstract

Background: The prevalence of type 2 diabetes mellitus (T2DM) is increasing worldwide. Digital interventions that incorporate the use of mobile phones and wearables have been getting popular. A combination of a digital intervention with support from professional management can enhance users' self-efficacy better than a digital intervention alone and provide better accessibility to a lifestyle intervention. However, there are limited studies exploring the feasibility and efficacy of applying a digital intervention in Muslim-majority countries, and none have been conducted in Brunei Darussalam.

Objective: The study aims to determine the effectiveness and feasibility of a proposed 16-week digital intervention program for T2DM self-management and to guide the rollout of a mobile app as part of a population health solution for adults with T2DM in Brunei. The primary outcome of this study is to measure the proportion of participants with a hemoglobin A_{1c} (HbA_{1c}) reduction of at least 0.6% from baseline, and the secondary outcomes include a change in HbA_{1c}, BMI, lipid profile, and EQ-5D-5L score.

Methods: This single-arm nonrandomized pilot study will recruit participants using web-based (with the national health care app [BruHealth] and official social media platforms being used for outreach) and offline (in-person recruitment at health centers) approaches. A target of 180 individuals with T2DM aged between 20 and 70 years that meet the inclusion criteria will be enrolled in a 16-week digital intervention program. Baseline and postintervention markers will be evaluated.

Results: The study received approval from the Medical and Health Research & Ethics Committee of the Brunei Darussalam Ministry of Health (MHREC/MOH/2022/4(1)). The recruitment process is ongoing, and we anticipate that the study will conclude by April 2023. This will be followed by data analysis and the reporting of outcomes with the intention to publish. The results of this study will be disseminated through scientific publications and conferences. This study will serve as a guide to launch T2DM digital therapeutic programs and extend to other noncommunicable diseases (NCDs) if proven as an effective and feasible approach in Brunei.

Conclusions: The Development and Exploration of the Effectiveness and Feasibility of a Digital Intervention for Type 2 Diabetes Mellitus (DEsireD) study will be the first study to investigate the clinical effectiveness and feasibility of the proposed 16-week T2DM digital intervention program tailored for Brunei, a Muslim-majority country. The findings of this study can potentially scale up the proposed model of care to other NCDs as a national approach for health management solutions.

Trial Registration: ClinicalTrials.gov NCT05364476; https://clinicaltrials.gov/ct2/show/NCT05364476

International Registered Report Identifier (IRRID): DERR1-10.2196/43208

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Introduction

Background

The worldwide prevalence of diabetes continues to increase, and the International Diabetes Federation (IDF) estimates the global prevalence of diabetes currently to be 9.1% with Brunei Darussalam reported to be at 12.4% among the 20-75 years old age group [1]. Type 2 diabetes mellitus (T2DM) is associated with a decreased quality of life (QOL) and increased mortality [2] and economic burden on individuals, families, and society in general [3]. Diabetes and its related complications can have devastating costs to health care systems and the national economy. According to IDF Diabetes Atlas, the global health care expenditure for the management of diabetes and diabetes-related complications was approximately US $850 billion in 2017 and is expected to increase to US $958 billion in 2045 [4].

Lifestyle interventions and modifications can effectively reduce the risk of diabetes-related complications. The American Diabetes Prevention Program [5], the Finnish Diabetes Study [6-8], and the UK DiRECT (Diabetes Remission Clinical Trial) study [9] have shown that in various populations lifestyle interventions can delay the development of T2DM and related cardiovascular complications. Lifestyle interventions remain crucial in the management of a patient with chronic disease. These interventions are traditionally performed through an in-person, face-to-face outpatient visit; such means of engagement are often plagued with challenges and often difficult to administer in the outpatient setting due to resource limitations [10,11]. The combination of offline outpatient care with a web-based software remote management model has proven to be effective in recent years [9], providing opportunities to explore further digital interventions.

Accelerated by COVID-19, digital interventions, which use different digital and mobile technologies to support health system needs, have been gaining popularity [11]. They have been shown to be safe and cost-effective in achieving positive health outcomes for T2DM [12,13]. Results from two 2020 systematic reviews and meta-analyses have shown that mobile health interventions (eg, mobile phone SMS text messages, smartphone apps, wearables, portable monitoring devices, or web-based coaching) can significantly improve hemoglobin A_{1c} (HbA_{1c}) with a standardized mean difference of –0.44 [14] and a weighted mean difference (WMD) of –0.4 when compared with traditional treatment and a fasting blood glucose WMD of –0.52 [15]. A more recent systematic review in 2022 has also revealed an overall improvement in HbA_{1c} (–0.9%) compared with usual care for T2DM [16]. Digital interventions have also been used to reduce BMI and waist circumference by 1.7 kg/m^2 and 5.77 cm, respectively [17]. On the contrary, digital interventions did not demonstrate improvement in total cholesterol, low-density lipoprotein cholesterol, or triglyceride levels [17].

Despite the proven effectiveness of digital interventions in the management of T2DM in adults, there are limited studies exploring the feasibility and efficacy of applying digital interventions in Muslim-majority countries, and no studies have been conducted in Brunei, whose population is 82.1% Muslim [18].

Rationale of Study

This study will attempt to address the resource limitations in providing lifestyle management tools to patients with chronic diseases, specifically T2DM, by providing an adaptable and easily accessible platform to administer digital lifestyle interventions in combination with offline support.

This study is a single-arm nonrandomized clinical trial, which is the first study being conducted in Brunei to assess the potential effectiveness and feasibility of using a digital intervention for participants with T2DM. In this study, the digital intervention for participants includes the use of a mobile phone, wearable devices, and hardware to collect participants' health information and provide telehealth consultation by health coaches based on the collected information. Through an integrated online and offline model of management, this digital intervention aims to improve diabetes management for patients in an outpatient setting. This intervention will allow accessibility to nonpharmacological lifestyle treatments outside of the hospital with the long-term goal of improving QOL and decreasing mortality, morbidity, and the economic burden of diabetes on health care resources.

Aims and Objectives of Study

The study is conducted with the following aims: to assess the potential effectiveness and feasibility of a comprehensive digital intervention for people with T2DM, to explore the effects of a combined online and offline intervention for the management of T2DM, to improve the accessibility of a lifestyle intervention among participants with T2DM, and to understand the process of guiding the rollout of an app for T2DM management as part of a health management digital solution [19].

The primary objective is to investigate the proportion of participants with a decrease in HbA_{1c} of 0.6% through lifestyle modifications using a digital intervention after 16 weeks. Secondary objectives include estimating the change in HbA_{1c} and BMI, improvement in lipid profile components at week 16, and change in QOL measured by the EQ-5D-5L compared with baseline measurements.

Methods

Study Design

This study is a single-arm nonrandomized clinical trial that will collect participants' baseline data, apply relevant assessment scales, and collect data using a comprehensive digital intervention in 16 weeks to evaluate the improvement of relevant markers post intervention. Figure 1 provides the standard operating procedure of the Development and Exploration of the Effectiveness and Feasibility of a Digital Intervention for Type 2 Diabetes Mellitus (DEsireD) clinical trial.

Figure 1. The DEsireD pilot trial study protocol. Bru-HIMS: Brunei Darussalam Healthcare Information and Management System; DEsireD: Development and Exploration of the Effectiveness and Feasibility of a Digital Intervention for Type 2 Diabetes Mellitus.
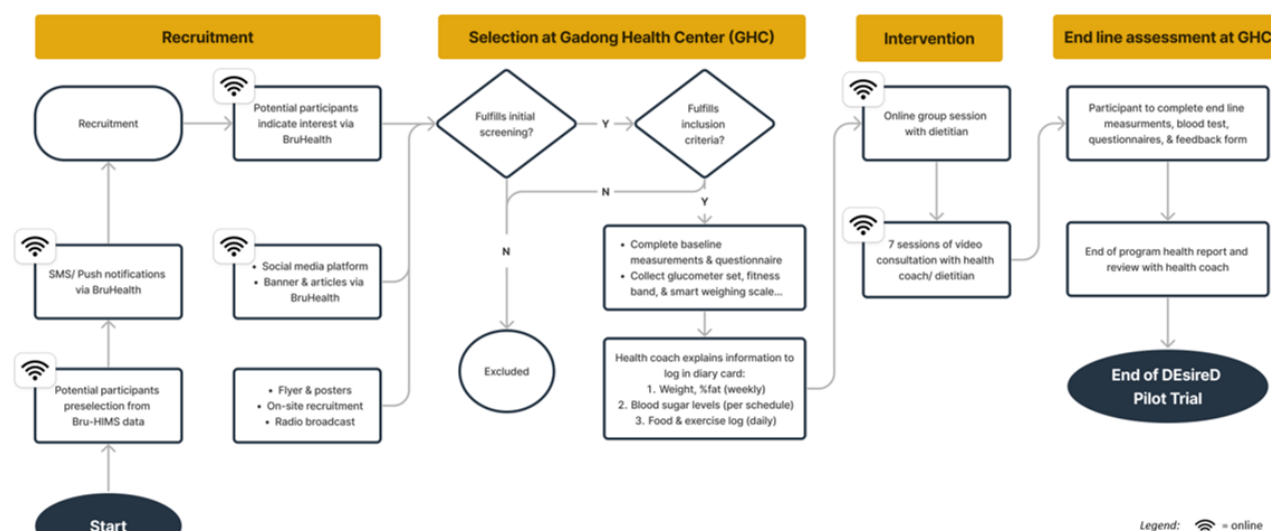
Population

Inclusion Criteria

The study participants will need to meet all the following criteria: diagnosed with T2DM, $HbA_{1c} \geq 7\%$ within 12 months prior to recruitment, age range between 20 and 70 years, and BMI between 23 and 50 kg/m^2.

Exclusion Criteria

Individuals will be removed if they meet any of the following exclusion criteria: pregnant/breastfeeding; on insulin therapy or noninsulin injectable medication; a history of diabetes crisis (hypo- or hyperglycemia) in the past 6 months; blood pressure $\geq 160/100$ mmHg; recurrent history of acute pancreatitis; decompensated liver cirrhosis; estimated glomerular filtration rate <60 ml/min/1.73 m^2; a history of acute myocardial infarction or acute coronary syndrome (within the past 1 year), arrhythmias, or heart failure (New York Heart Association class II-IV); proliferative diabetic retinopathy; foot ulcer or gangrene; deep vein thrombosis of lower limbs (within the past 12 months); intermittent claudication; a history of cerebral hemorrhage or acute cerebral infarction (within the past 12 months); a history of active cancer; posttransplant/perioperative individuals (defined as planned for operation in the next 6 months); a history of hypo- or hyperthyroidism, including subclinical states; musculoskeletal injuries resulting in difficulty in performing physical activities; failure to provide consent; unable to perform activities of daily living; and unable to use WhatsApp and YouTube via mobile devices (eg, phone or tablet).

Recruitment

Participants will be recruited using web-based and offline methods based on the inclusion and exclusion criteria.

Offline Recruitment

For offline recruitment, promotional posters and flyers will be used. These publicity materials will be placed at the front counters of health centers and in the main referral hospital (ie, the Raja Isteri Pengiran Anak Saleha [RIPAS] Hospital). Flyers will be actively given out by health coaches and recruitment teams at health centers; the flyers will be placed in the medication bags of the patients who collect oral diabetic medications from RIPAS Hospital.

Web-Based Recruitment

In addition to traditional on-site outreach via official social media approaches, a technology-assisted adaptive recruitment strategy was used for participant recruitment [20]. Sociodemographics, comorbidities, and medication lists were extracted from the Brunei national electronic medical record system (Brunei Darussalam Healthcare Information and Management System [Bru-HIMS]) for eligibility screening. A push notification for study invitation will be sent via BruHealth to identify eligible patients with T2DM. For users who choose to response to the nudge, they will be directed to a landing page with a questionnaire for them to fill in more required details (Figure 2). While this pilot aims to recruit 180 participants, the recruitment rate was low after 3 months. Therefore, a study invitation linking to the same questionnaire was sent via SMS text message. The recruitment banner to the same link can also be seen by any BruHealth users.

A total of 9990 potential individuals with T2DM who fulfilled the inclusion and exclusion criteria (except BMI due to data unavailability) were extracted from the Bru-HIMS database, and study invitations were sent via push notifications and SMS text messages.

Figure 2. Push notification via the national health care app (BruHealth) for the Development and Exploration of the Effectiveness and Feasibility of a Digital Intervention for Type 2 Diabetes Mellitus (DEsireD) study recruitment.
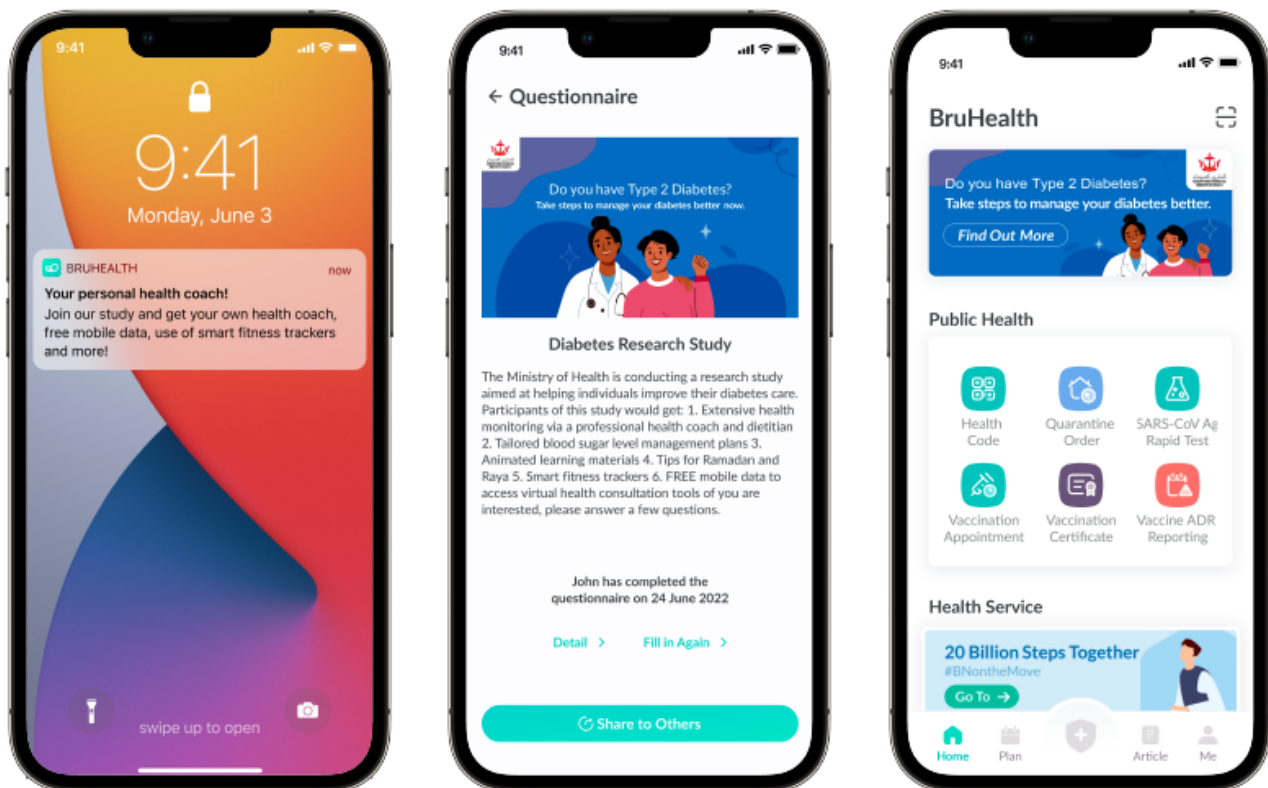
Participant Selection at Baseline

Potential participants will be seen by the health coaches at the health center, where informed consent will be signed by participants prior to undergoing the screening process (see the Data Collection, Management, and Analysis: Baseline Assessment and Endline Assessment sections). The clinical investigators will review the baseline blood test results and determine whether an individual satisfies the inclusion criteria.

Intervention

Participants will be enrolled in a 16-week program that consists of online (web-based consultations and group education sessions) and offline support (baseline and endline assessments) from health coaches and a dietitian. Participants will be given a fitness band, smart weighing scale, and glucometer set to collect one's health information. A diet and exercise recommendation based on their submitted food and exercise log and collected health data will be provided by health coaches. A lesson plan consisting of animations, videos, infographics, and articles will be given on a weekly basis with the intention to empower participants with diabetes self-management knowledge.

The 16-week program was crafted in collaboration with the expertise of a board-certified endocrinologist in Brunei, a registered dietitian, and a physiotherapist according to evidence-based guidelines and national guidelines [21-23]. The intention is to improve the outcome of diabetes care management by influencing the participant through various methods of information via knowledge empowerment.

To ensure the successful implementation of the study and that the designed education materials are able to meet the local context, the team has worked collaboratively with diabetes specialists from the Ministry of Health, Brunei Darussalam, to design the framework of this study, oversee the program, and provide advice regarding the contents of all educational materials. To meet the cultural needs of Muslim participants, education materials that specifically focus on managing T2DM during Ramadan were developed according to relevant studies and guidelines [23-26].

Outcome Measures

Primary Outcome

The primary outcome will be the proportion of participants with a decrease in HbA_{1c} by 0.6% through lifestyle modifications via digital intervention after 16 weeks.

Secondary Outcomes

Secondary outcomes will include a change in HbA_{1c}, BMI, lipid profile, and the EQ-5D-5L components at week 16 compared with baseline readings.

Roles and Responsibilities in the Study

Health Coach

The main objective of a health coach is to facilitate an efficacious and effective lifestyle intervention for the participants. The responsibilities of the health coach include providing personalized nutrition and exercise recommendations for the participants in concordance with digital management to optimize the primary and secondary outcome measures; reviewing participants' daily self-monitoring logs of blood glucose, weight, meals, and exercise on a weekly/biweekly interval; and adhering to the escalation pathway (see Escalation Pathway section) to ensure participants' safety.

Dietitian

The dietitian will lead and provide training to the team the delivery of the diabetes self-management intervention in the study with the intention to ensure the competency level of health coaches. The dietitian will also engage and empower participants' nutrition knowledge for self-managing T2DM with web-based support via small group education sessions and web-based consultations. The dietitian is required to adhere to the escalation pathway to ensure participants' safety. Additionally, the dietitian will assist in the evaluation of the clinical trial effectiveness and outcomes according to the collected biometric data and blood test results.

Study Withdrawal

The participant may withdraw from the trial at any time by withdrawing their informed consent. An end-of-study form will be given, and the reason for withdrawal will be documented.

Statistical Analysis: Sample Size Calculation

A statistical power calculation was performed as follows: a sample size of 120 achieves 80% power to detect a proportion of 0.63 using a 1-sided exact test with a significance level of 0.025. These results assume that the proportion of the population under the null hypothesis is 0.5. Considering a dropout rate of 30%, the target sample size is 180.

Data Collection, Management, and Analysis

Baseline Assessment

During the screening process at baseline, participants will undergo a panel of blood tests to determine eligibility for study participation. Baseline blood tests include full blood count, HbA_{1c}, fasting blood glucose, fasting lipid profile, liver function test, renal panel, and thyroid function test. The clinical investigators will review baseline blood test results and determine whether potential participants satisfy the inclusion criteria. Eligible participants will be enrolled in the study, asked to complete the EQ-5D-5L questionnaire, provided with loaned devices, and requested to submit data required on a weekly basis at enrollment.

Study Assessment

During the 16-week study period, participants will be required to log their blood glucose levels, weight, and heart rate using the loaned devices into a daily report card. They will also be required to manually record their meals and exercise in the same report card. Reviews of logs will be performed on a weekly interval by the health coaches.

Endline Assessment

Upon completion of the 16-week intervention, participants will undergo a second panel of blood tests, which include full blood count, HbA_{1c}, fasting blood glucose, fasting lipid profile, and liver function test as part of the primary and secondary outcome measures. Participants will also be asked to complete the EQ-5D-5L questionnaire to assess participants' QOL in comparison to baseline.

Data Management

A dedicated proprietary research platform called EVYDResearch (EVYD Technology Sdn Bhd) will be used for data management. Data confidentiality will be maintained through EVYDResearch, as only the research team will have access to the full information. Sociodemographic and clinical variables will be extracted from Bru-HIMS and integrated into EVYDResearch. Data collected via questionnaires and diaries will be manually transcribed and housed in EVYDResearch. Physical copies of all the collected data, such as case report forms, informed consent forms, and questionnaires, will be locked in a cabinet that is only accessible to the research team. All data will be stored for 5 years and destroyed thereafter in compliance with the Ministry of Health, Brunei Darussalam regulations.

Statistical Analysis

Descriptive statistics will be performed for both primary and secondary outcomes. Frequency and count will be calculated for categorical variables. Means, SDs, and quartiles will be calculated for continuous variables. EVYDResearch will be used for simple data validation rules, such as uniqueness and missingness; descriptive statistical analysis for primary and secondary outcomes; and simple visualization plots. Additionally, R (R Foundation for Statistical Computing) or other software may be used when necessary to perform more advanced statistical analysis and data visualization.

Event Safety Monitoring

The terms pertaining to events have been adapted from ClinicalTrials.gov [27] and are as follows:

> *Adverse Events are unfavourable changes in health, including abnormal laboratory findings, that occur in trial participants during the clinical trial. Serious Adverse Events include adverse events that result in death or result in either inpatient hospitalization or the prolongation of hospitalization, are life-threatening or result in a persistent or significant disability/incapacity. Other important medical events, based on appropriate medical judgment, may also be considered Serious Adverse Events if a trial participant's health is at risk and intervention is required to prevent an outcome mentioned. Other Adverse Events are adverse events that are not Serious Adverse Events but exceed the indicated frequency threshold.*

All adverse events will be logged in the adverse events form. Any serious adverse events (expected/unexpected) will be reported to the Brunei Darussalam Medical and Health Research & Ethics Committee (MHREC) by the principal investigator within 24 hours of the event through the adverse events form.

For medical events, health coaches will review the weekly report card and follow the escalation pathway as described below.

Escalation Pathway

Health Coach to Dietitian

Participants with poorly controlled capillary blood glucose (defined as blood glucose <4 mmol/L and >16.6 mmol/L) will be referred for web-based counseling by the dietitian.

Dietitian to Clinical Investigators

Participants with any of the following will be referred to the clinical investigators: two episodes of hypoglycemia, which is defined as a blood glucose of <4.0 mmol/L with or without symptoms of hypoglycemia, despite diet and lifestyle modifications, and more than 2 occasions of hyperglycemia, which is defined as a blood glucose of >16.6 mmol/L in a week.

Clinical Investigators to Diabetes Nurse Educators

In the respective clinic where participants see their primary physician for diabetes care, participants who require counseling about the timing of medications to meals and exercise will be referred to the diabetes nurse educators.

Consultations With Clinical Investigators

Consultations with clinical investigators will only be done via the virtual clinics (refer to Figures 3 and 4) that are specifically set up for this study period. Participants with recurrent hypoglycemia and hyperglycemia despite lifestyle modification will be excluded from the study for the participant's safety. The clinical investigators will write a letter to inform the participant's primary physician for an urgent review of their treatment. However, participants who do not experience any of the above issues will continue their routine clinic visits (if any) with their primary physician during the study period, and any changes in medications will be noted. Such changes in medication are allowed as part of participants' usual care and do not constitute an exclusion from the study.

Figure 3. Video consultation appointment arranged via BruHealth app.

Figure 4. Video consultation interphase via the national health care app (BruHealth).

Ethics Approval

This study is being conducted in accordance with Good Clinical Practice, as defined by The International Council for Harmonisation. The trial protocol has received approval from MHREC from the Ministry of Health Brunei (MHREC/MOH/2022/4(1)). The appropriate participant information sheet and informed consent form describing in detail the trial interventions, trial procedures, and risks were approved by the ethical committees. Aside from providing a participant information sheet to all potential participants, the investigator will explain the study and answer any questions posed. After being given adequate time to consider the information, the participant will be asked to sign the informed consent document. The participant may withdraw from the trial at any time by withdrawing their informed consent. The rights and welfare of the participants will be protected by emphasizing to them that the quality of medical care will not be adversely affected if they decline participation.

Results

The enrollment period of this study is between April 18 and November 30, 2022. As of November 4, 2022, a total of 72 participants have been recruited. In this study, participants are recruited in batches, and at the data collection level, there are 12 participants who have completed the endline assessment. Data collection is ongoing. We anticipate this study to conclude by April 2023, followed by data analysis and final reporting with the intention to publish.

Discussion

Overview

This study protocol provides an overview of the methodology used in the DEsireD clinical trial. To our knowledge, this study is the first to examine the effectiveness of a proposed 16-week digital intervention program for T2DM self-management and to explore the feasibility of the proposed model of care—a combination of online and offline management to improve the accessibility of a lifestyle intervention among individuals with T2DM in Brunei.

With resource limitations in providing holistic lifestyle interventions in a conventional manner through face-to-face consultations in outpatient settings, digital interventions can be a scalable and cost-effective solution for diabetes self-management. According to Koh et al [19], COVID-19 has had a negative impact on noncommunicable diseases (NCDs) in Brunei due to the disruption of essential health services. Thus, the government has stated its intention to use BruHealth to prioritize NCD service expansions. This includes a diabetes digital intervention. Globally, there are multiple studies demonstrating the effectiveness of digital interventions [12-17,28,29], but there are limited studies conducted in Southeast Asia, particularly in Muslim-dominant populations [16]. This study will be useful for health care professionals and policy makers to understand the possible barriers to the implementation process during the subsequent phases of rolling out an app for T2DM management as a nationwide digital health solution in Brunei [19]. In addition, a feedback form will be given to any participants who have dropped out or completed

the study to collect their quantitative feedback on the DEsireD trial. This will include overall experience, the usefulness of the designed program to assist them with setting goals, study duration (16 weeks), and qualitative feedback on the overall perception and contextual feasibility.

The majority of studies use the reduction of the HbA_{1c} level as a clinical marker for the effectiveness of digital interventions for patients with T2DM [16,30]. We agree with Stevens et al [16] that a wider measure of clinical effectiveness should go beyond HbA_{1c}. Thus, this study will investigate changes in fasting blood glucose, lipid profile, and health-related QOL (measured by the assessment of the EQ-5D-5L [31,32]).

There are several limitations to this study. The first is achieving the targeted sample size. This will make the evaluation of the primary objective difficult. There is a sample of convenience, which may result in response bias. The nature of a single-arm study will be limited by its nonrandomized design of unknown causal inference. Finally, in the absence of comparison, the reference end point of a 0.6 reduction in HbA_{1c} over 16 weeks was used as a benchmark for clinical effectiveness. Our rationales include the effect of other mobile health interventions on the reduction of HbA_{1c} levels are between a WMD of 0.40 to a mean average of 0.9 [15,16] and the effect of oral diabetic medication as monotherapy is expected to reduce HbA_{1c} by 0.5

to 2.0 [33]. Thus, a lower average number of 0.6 was used. In addition, the absolute and relative decrease in HbA_{1c} will be calculated as secondary outcomes.

This study is expected to conclude in April 2023. The scientific findings will be presented as oral communications and abstracts at regional, national, and international scientific meetings related to T2DM. The findings will also be published in peer-reviewed journals.

Conclusions

The DEsireD study will be the first study to investigate the clinical effectiveness of the proposed 16-week digital intervention program tailored for individuals with T2DM in Brunei.

The evidence will serve as a guide to roll out a nationwide value-based care program via an app as a digital solution. The lessons from the implementation of this study and the feedback and data from participants will be beneficial for further localization of this digital intervention program. Consequently, scaling up to other NCDs and validation with a larger sample size to demonstrate that the digital intervention is a safe, scalable, sustainable, and cost-effective approach in Brunei will be needed.

Data Availability

The data collection process is still underway. The other materials presented in the study are included in the paper. Further inquiries can be directed to the corresponding author.

Conflicts of Interest

HNC, HSL, and YW are full-time employees of EVYD Technology Limited. EVYD Technology Limited is the technology partner and research collaborator of this study. EVYD Technology Limited is the developer of the T2DM digital therapeutics application EVYDResearch and BruHealth mobile app used in this study. The authors declare that there is no other conflict of interest.

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Abbreviations

Bru-HIMS: Brunei Darussalam Healthcare Information and Management System
DEsireD: Development and Exploration of the Effectiveness and Feasibility of a Digital Intervention for Type 2 Diabetes Mellitus
DiRECT: Diabetes Remission Clinical Trial
HbA$_{1c}$: hemoglobin A$_{1c}$
IDF: International Diabetes Federation
MHREC: Medical and Health Research & Ethics Committee
NCD: noncommunicable disease
QOL: quality of life
RIPAS: Raja Isteri Pengiran Anak Saleh
T2DM: type 2 diabetes mellitus
WMD: weighted mean difference

Protocol

Telehealth Care for Mothers and Infants to Improve the Continuum of Care: Protocol for a Quasi-Experimental Study

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Abstract

Background: Ensuring an appropriate continuum of care in maternal, newborn, and child health, as well as providing nutrition care, is challenging in remote areas. To make care accessible for mothers and infants, we developed a telehealth care system called *Portable Health Clinic for Maternal, Newborn, and Child Health*.

Objective: Our study will examine the telehealth care system's effectiveness in improving women's and infants' care uptake and detecting their health problems.

Methods: A quasi-experimental study will be conducted in rural Bangladesh. Villages will be allocated to the intervention and control areas. Pregnant women (≥16 gestational weeks) will participate together with their infants and will be followed up 1 year after delivery or birth. The intervention will include regular health checkups via the Portable Health Clinic telehealth care system, which is equipped with a series of sensors and an information system that can triage participants' health levels based on the results of their checkups. Women and infants will receive care 4 times during the antenatal period, thrice during the postnatal period, and twice during the motherhood and childhood periods. The outcomes will be participants' health checkup coverage, gestational and neonatal complication rates, complementary feeding rates, and health-seeking behaviors. We will use a multilevel logistic regression and a generalized estimating equation to evaluate the intervention's effectiveness.

Results: Recruitment began in June 2020. As of June 2022, we have consented 295 mothers in the study. Data collection is expected to conclude in June 2024.

Conclusions: Our new trial will show the effectiveness and extent of using a telehealth care system to ensure an appropriate continuum of care in maternal, newborn, and child health (from the antenatal period to the motherhood and childhood periods) and improve women's and infants' health status.

Trial Registration: ISRCTN Registry ISRCTN44966621; https://www.isrctn.com/ISRCTN44966621

International Registered Report Identifier (IRRID): DERR1-10.2196/41586

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Introduction

In Sustainable Development Goal 3, maternal, newborn, and child health (MNCH) were identified as essential issues for the world to address [1]. A vital and global framework in improving mothers', newborns', and children's health status is ensuring the continuum of care in MNCH within resource-limited settings. The continuum of care is the series of care throughout the adolescence and prepregnancy periods, the antenatal period, and the motherhood and childhood periods. Further, in terms of the nature of care, the continuum of care spans across community care, primary care, and advanced care [2-4]. Comprehensively monitoring infants' nutrition status has also been emphasized in the context of the continuum of care in MNCH [5]. To ensure infants' physical and psychological development and long-term health, they must receive appropriate care at the right times.

In this context, telehealth care is gaining attention, as it can be used to fill the gaps in the continuum of care [6]. Telehealth care may have the potential to monitor and provide care for high-risk pregnancies [7,8]. According to previous studies, telehealth care provided through either the internet or the telephone for the treatment of postpartum depression showed favorable effects thereon (mean difference: −1.81, 95% CI −2.68 to −0.93) [9]. Further, by using telehealth care monitoring, women with gestational diabetes mellitus showed an improvement in hemoglobin A1c levels (−0.41%, 95% CI −0.25% to −0.04%) when compared with a control group [10]. Another study on gestational diabetes mellitus found lower incidence rates of cesarean sections and maternal and neonatal complications in the telehealth care group [11]. Thus, the need for telehealth care follow-ups is sure to gain importance in the future.

In Bangladesh, the MNCH status has been improving. However, the maternal and neonatal mortality rates in Bangladesh are still among the highest in Asia; 173 maternal deaths per 100,000 live births and 19.1 neonatal deaths per 1000 live births were reported in 2019 [12]. As a considerable number of maternal and neonatal deaths and gestational complications are avoidable through early health intervention, providing appropriate and continuous care is essential. However, only 44% of women receive antenatal care (≥4 times) from a medically trained health care provider, and 47% of women and 46% of newborns do not receive any postnatal care [13], indicating inadequate MNCH services in Bangladesh. Further, Bangladesh's cesarean section rate (30.7%) [12], which is higher than the global mean, may be a consequence of insufficient health care, as the cesarean section rate is often considered a proxy indicator of women's access to care. Several factors have been identified that relate to the lower utilization of MNCH care services, including family wealth, previous experiences of childbirth, autonomy in women [14], and the distance to health facilities [15]. Therefore, financially and physically affordable care needs to be explored further to improve access to care.

Infants' development status has also been recognized as a problem in Bangladesh; 28% of newborns had a low birth weight in 2015 [16], which was the highest low birth weight rate among newborns in the world at the time. Accordingly, undernutrition in 5- to 9-year-old children was also reported, with 18% of children categorized as *thin* (BMI of <−2 SDs below the mean)—the third highest undernutrition rate among 5- to 9-year-old children in the world. Anemia was also detected among 43% of children aged 6 to 59 months [12]. Hence, children's nutrition status is also an essential aspect that needs to be monitored at and after birth.

The Portable Health Clinic (PHC) is a telehealth care system that comprises a set of sensor devices in an attaché case and an information system that can automatically triage health levels once users input the results of a checkup [17]. Originally developed in collaboration with Grameen Communications and Kyushu University, the PHC has been used in Bangladesh for telehealth checkups with over 45,000 people to prevent lifestyle diseases, such as diabetes and hypertension. Receiving care at home is beneficial for people who live in remote areas where access to health care is limited. Later, the MNCH module—PHC for Maternal, Newborn, and Child Health (PHC-MNCH)—was developed and piloted in rural areas of Bangladesh to provide antenatal and postnatal health checkups [18,19]. The PHC-MNCH has been renewed, and its original coverage (16 gestational weeks to 6 weeks after birth) has been expanded to include follow-ups at 1 year after birth for perinatal complications and infants' health and nutrition status (ie, through home visit services).

Our study thus examines the effectiveness of a telehealth care intervention for improving women's and infants' care uptake in rural areas of Bangladesh. Additionally, it examines the effectiveness of telehealth care in detecting health problems among women and infants.

Methods

Study Design and Sites

Our study is quasi-experimental, and it will be conducted in 6 villages within the Chhaygaon Union of Bhedarganj Upazila (subdistrict), Shariatpur District, Bangladesh (Figure 1; trial registration number: ISRCTN44966621). Located approximately 80 km from Dhaka, these villages are in the suburb of the capital. Among the nine villages in the Chhaygaon Union, the East Chhaygaon, Middle Chhaygaon, and Lakarta villages were purposively set as the intervention cluster, and the Gangshar, Nazimpur, and Aterpara villages were set as the control cluster. The villages were allocated to the intervention and control areas such that the population sizes (intervention area: N=6378; control area: N=6178), geographic locations of the villages, and access to health facilities (each area has a health facility) were

similar between the two areas. In the intervention arm, we conducted a pilot study in which we used the PHC system between June 2019 and May 2020 to follow women and infants

from 16 gestational weeks to only 6 weeks post partum, with a shorter postpartum follow-up period than the one described herein.

Figure 1. (A) Project site villages within the Chhaygaon Union of Shariatpur District. Among the nine villages, the six that are not bracketed are the study sites. (B) The location of Shariatpur District in Bangladesh.
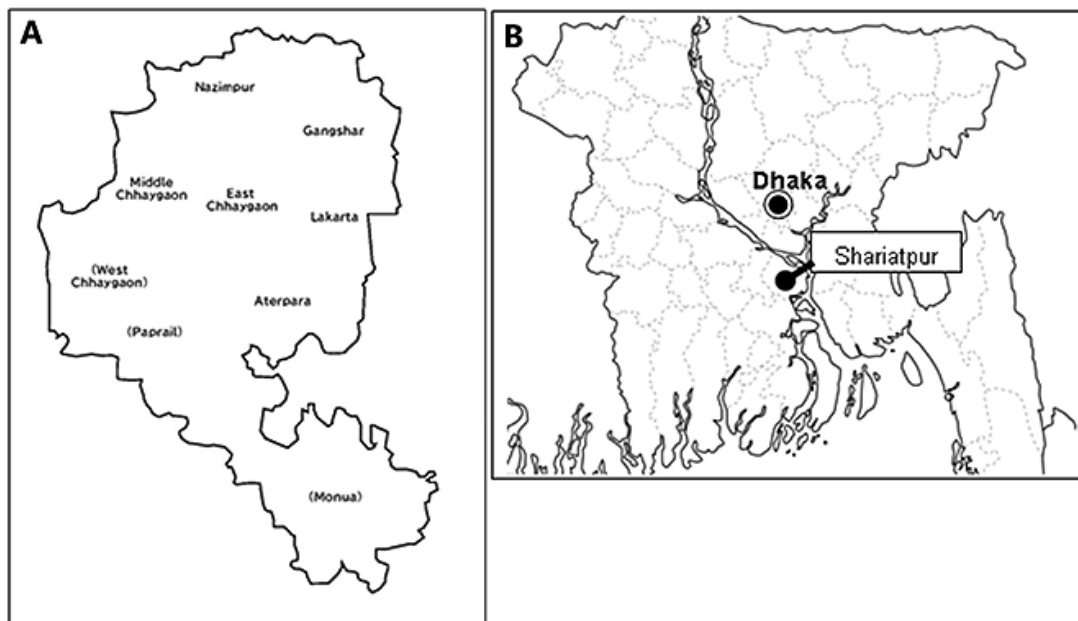
Study Population and Selection Criteria

A flow diagram of participants for the enrollment, allocation, follow-up, and analysis stages is presented in Figure 2. Different selection criteria will be applied to intervention, baseline survey, and end line survey participants. The inclusion criteria for intervention participants are (1) women at reproductive age (between 15 and 49 years), (2) women at ≥16 gestational weeks, and (3) women living in intervention villages at the time of

enrollment. After birth, their infants will also be enrolled in the intervention cluster.

Baseline survey participants will be women in the intervention and control clusters who experienced giving birth between June 2015 and May 2019 (ie, before the pilot study). End line survey participants will be women in the intervention and control clusters who give birth between November 2020 and October 2024. Women who experience a miscarriage or a stillbirth during this period will also be included as participants.

Figure 2. Flow diagram of participants for the enrollment, allocation, follow-up, and analysis stages.
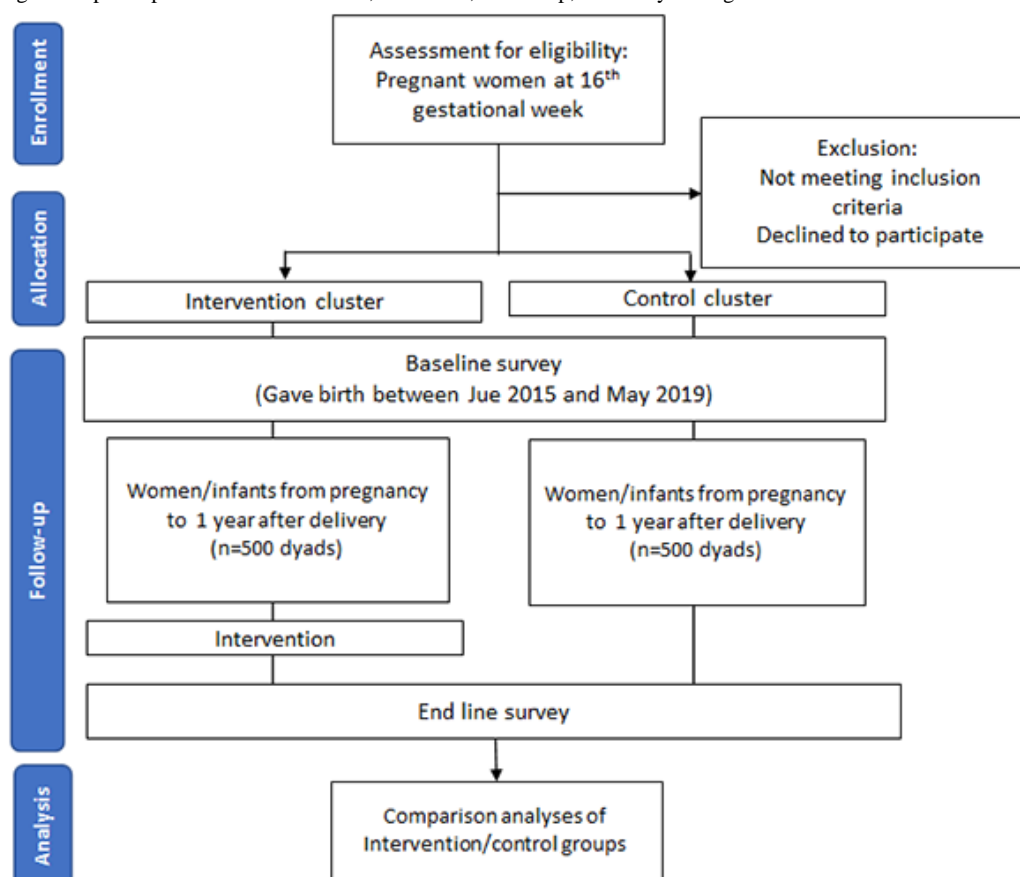
Recruitment and Consent of Participants

All eligible women living in the intervention villages will be recruited for the study intervention. Local informants will collect information about eligible women from local citizens every month in all of the intervention cluster villages by visiting resident reproductive-age women individually. For women who might be pregnant, a test kit will be provided to confirm their pregnancy status. The expected recruitment period for intervention participants is June 2020 to June 2024. Baseline survey participants will be recruited based on information regarding their past pregnancy experiences, which will be obtained through the local informants and individual home visits.

We will explain the study purpose to potential participants, and their consent will be indicated by their participation in the intervention study or the questionnaire surveys. Their participation will be voluntary, and they will be free to join or withdraw at any time.

Interventions

We will conduct a telehealth care intervention for women (from pregnancy [at ≥16 gestational weeks] to 1 year after delivery) and their infants (from birth to 1 year of age). The content and processes of the interventions are detailed below.

The PHC-MNCH

We developed the PHC-MNCH system, which comprises a set of sensor devices that were selected based on international information standards and approved by Japanese pharmaceutical

law. This sensor set also includes an Android tablet, internet router, and portable printer. The sensors include weighing scales, a digital sphygmomanometer, a blood glucose test sensor, a digital thermometer, pulse oximeters for adults and infants, a height measurement tape, a height measurement mat for infants, a blood hemoglobin meter, and urine test strips. The list of devices is presented in Multimedia Appendix 1.

Implementation Team

We created, in advance, a health care worker team that will perform health checkups on participants. The team consists of 2 local residents; one is a qualified paramedic, and the other is a traditional birth attendant. Using the PHC-MNCH system, the team members will act as mediators of health checkup implementation between participant women and physicians.

Telehealth Care Intervention

The health care worker team will visit women's and infants' homes to examine their health status by using the PHC-MNCH system and conducting interviews to check if they are experiencing any complications. All of the data will be inserted into the triage app installed on the tablet, which will automatically categorize the participants' health statuses into the following four severity and color levels: healthy (green), cautious (yellow), affected (orange), and emergency (red). Finally, the health care worker team will print out the health checkup reports for women and infants. The women will be remotely connected to a medical physician stationed at Dhaka by using a video system, and they will receive the physician's consultation on the basis of the results of their checkups, which

will be sent through the app. If necessary, the physician will send prescriptions to the women via the health care worker team, using the same app.

Health Education

In addition to health checkups, the health care worker team will provide health education to mothers during each home visit through educational videos and brochures, with themes related to antenatal and postnatal care, danger signs in each pregnancy stage, and mothers' and infants' nutrition. The education materials were developed based on the regional context of Bangladesh, following a review by a local health expert. The education content is presented in Multimedia Appendix 2.

Maternal and Child Health Handbook

The collected health checkup data will be recorded in a physical maternal and child health handbook, so that the information can be kept for future reference. In addition to the health checkup records, this handbook contains health education information regarding perinatal danger signs, infants' immunization records, and infants' growth records. The handbook was developed based on the maternal and child health handbook that is presently used in Japan.

Health Checkups in the Control Area

Although we will not provide the PHC-MNCH telehealth checkup to the participants in the control area, they can receive any health checkups at any health facilities if they want, as general pregnant women, mothers, and children do in Bangladesh.

Data Collection Methods and Evaluation

We will assess the impact of the intervention by comparing the clusters, using baseline and end line questionnaire survey data.

Baseline and End Line Survey

We will conduct the questionnaire survey at the baseline and end line periods for all eligible women in the intervention cluster and control cluster. The questionnaire items assess sociodemographic and economic status, the health services received and the times they were received, symptoms during pregnancy, and postpartum or neonatal complications. The PHC-MNCH researchers developed the survey in English, and the research assistants translated it into Bengali. A Bengali- and Japanese-speaking researcher then checked the accuracy of the translation.

Health Checkup

We will collect the health checkup data of intervention cluster participants throughout the intervention to identify gestational and maternal complication symptoms and health problems. The health checkups will be conducted during 9 home visits, which will be scheduled at approximately 16, 24, 32, and 36 weeks of gestational age and at approximately 2 to 3 days, 7 days, 6 weeks, 6 months, and 12 months after delivery or birth. The measurement- and interview-based checkup items are presented in Textboxes 1 and 2. Health statuses will be categorized into 4 levels according to the criteria developed by Japanese and Bengali obstetricians and medical professionals. Excerpts of criteria details are presented in Multimedia Appendix 3.

With regard to the control cluster, we will not collect health checkup biometric data. This is because conducting health checkups in the control area may affect the mothers' awareness of health-seeking behaviors and result in bias in the intervention results.

Textbox 1. Health checkup items for mothers at different periods.

Measurements

- All periods from the antenatal period to the motherhood period
  - Weight, pulse, blood pressure, temperature, hemoglobin, urine protein, urine sugar, oxygen saturation, and blood glucose

- Additional measures for the antenatal period
  - Fetal heartbeat, uterus height, edema, and baby's position

Interviews

- Antenatal period
  - Fetal movements, regular contractions, ruptures, vaginal bleeding, smelly vaginal discharge, headaches, vomiting, fevers, convulsions, and depressive symptoms

- Postnatal period
  - Vaginal discharge, bleeding, uterus hardness, nutrition, nipple problems, perineum tear problems, wound infection, urinating problems, calf pain, headaches, shortness of breath, fevers, convulsions, and depressive symptoms

- Motherhood period
  - Vaginal discharge, hematemesis, nutrition, nipple problems, headaches, shortness of breath, fevers, convulsions, depressive symptoms, urination problems, urinary leakages, and fecal leakages

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Textbox 2. Health checkup items for infants at different periods.

Measurements

- Both the after-birth period and the childhood period

  - Weight, height, temperature, heart rate, oxygen saturation, cyanosis, and hemoglobin

Mothers' interviews

- After-birth period

  - Breathing difficulties, feeding frequency, jaundice, pus, irritated cords, diarrhea, bleeding, and convulsions

- Childhood period

  - Breathing difficulties, pus, diarrhea, hematemesis, convulsions, and the start of complementary feeding

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Study Outcomes and Measurements

The following outcomes will be compared based on the baseline and end line surveys: the frequency of antenatal and postnatal care visits by health care providers conducted through health checkups with the PHC or at health facilities; the detection rate of gestational complication symptoms (suspected gestational diabetes, pregnancy-induced hypertension, anemia, preterm birth, and postterm birth); the detection rate for neonates and infants with suspected jaundice, anemia, and growth delay; the percentage of infants who started complementary feeding at 6 months after birth; and the percentage of participants who sought health care or exhibited health-seeking behaviors or self-care behaviors upon experiencing health problems.

Data Monitoring

Data managers will review the accuracy and completion of collected data and thereafter pool them in a project server. Verification checks will be performed to correct any discrepancies in records. Intervention implementation will be monitored by the field monitoring and research team members. All adverse events and unintended effects of the intervention will be reported monthly by the field monitoring team members and followed up by the research team members. Access to all monitoring-related information will be limited to the field monitoring and research team members.

Participants' Timelines

The details of participants' timelines are described in Multimedia Appendix 4. Women will be enrolled at approximately 16 gestational weeks, that is, when they receive the first antenatal checkup. They will be followed up at 9 points in time via health checkups. Infants will be enrolled at birth and followed up at 5 points in time after birth.

Sample Size

All eligible women and infants at the study sites will be included in our study. Approximately 1000 mother-infant dyads have been deemed eligible for this study among all clusters (500 dyads in each cluster). However, the minimum sample size for recruitment was calculated as 925 dyads for all clusters; 771 dyads in a cluster are required for analyses based on our pilot study, in which the percentage of antenatal care increased by ≥4 times (from 29% to 42%). A 2-tailed test will be conducted (power=0.95; α error=.05). A loss to follow-up rate of 20% was estimated.

Statistical Analyses

First, we will conduct descriptive analyses of and comparison tests between the intervention and control clusters to assess their similarities. Second, to evaluate the effectiveness of the intervention and compare the clusters, we will perform a multilevel logistic regression model of end line surveys, adjusting for the effects of clustering. Finally, sensitivity analyses will be conducted to assess the robustness of the model. The statistical significance will be set at a P value of <.05. All data analyses will be performed by using IBM SPSS (IBM Corporation).

Ethics Approval

Our study was approved by the institutional review boards of Kyushu University (approval number: 20202021). Written informed consent will be obtained from all participants. Participation will be voluntary, and confidentiality will be maintained. Participants can withdraw from the study for any reason at any time. The intervention will be introduced to the control cluster after the study is completed.

All of the information obtained in our study will remain confidential. Access to information will be limited to the health care workers and data entry management staff for the duration of the study. Research records will be identified only by study ID numbers.

Dissemination

The results of our study will be disseminated through peer-reviewed journals and international conferences. Additionally, the telehealth care system will be disseminated to other areas in Bangladesh through the collaboration of local communities and research collaborator organizations. Important protocol changes will be communicated to the research ethics committee and the clinical trials registry.

Designing or reporting will not involve patients of the public. However, residents will be involved in interventions, serving as health care workers or local informants. The dissemination plan will be discussed with the local community and research collaborator organizations.

Results

Recruitment began in June 2020, and it is expected to continue until June 2024. We consented 295 mothers in the study by June 2022. Data cleaning and analysis will begin after the data collection is complete.

Discussion

In our study, the intervention arm participants are expected to have better health statuses than those of the control arm, as they will receive care through the PHC-MNCH. Our community-based intervention study is extremely important for realizing the continuum of care in MNCH through a telehealth care system and evaluating the improvement of mothers', newborns', and children's health status. Previous studies that investigated the effectiveness of the continuum of care in MNCH mostly focused on the perinatal period [20,21]. Through our trial, we will attempt to show whether the continuum of care, which extends from the antenatal period to the motherhood and childhood periods, is effective in improving the health of mothers and infants. The study will further accumulate evidence on the effectiveness of the continuum of care.

Our proposed study also has a limitation. The intervention sites include some of the areas where we conducted the pilot study. Therefore, some residents of the intervention sites may have a better understanding of the continuum of care than those in the control group. However, since the participants in the pilot study are not included in the proposed study, the effectiveness of the intervention will be evaluated based on its status prior to the pilot study. As such, we believe that this limitation can be controlled.

Data Availability

The data that have been generated and analyzed during our study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Device specifications.
[DOCX File , 16 KB - resprot_v11i12e41586_app1.docx]

Multimedia Appendix 2
Health education content.
[DOCX File , 27 KB - resprot_v11i12e41586_app2.docx]

Multimedia Appendix 3
Excerpts of criteria for antenatal checkup.
[DOCX File , 19 KB - resprot_v11i12e41586_app3.docx]

Multimedia Appendix 4
Participant timeline of the Portable Health Clinic for Maternal, Newborn, and Child Health intervention study.
[PNG File , 160 KB - resprot_v11i12e41586_app4.png]

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Abbreviations

MNCH: maternal, newborn, and child health
PHC: Portable Health Clinic
PHC-MNCH: Portable Health Clinic for Maternal, Newborn, and Child Health

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<u>Protocol</u>

Evaluating the Acceptance and Usability of an App Promoting Weight Gain Prevention and Healthy Behaviors Among Young Women With a Family History of Breast Cancer: Protocol for an Observational Study

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Abstract

Background: Breast cancer is the most common form of cancer in women, and around 20% of cases are associated with factors such as adult weight gain, overweight and obesity, and potentially modifiable health behaviors including high alcohol intake, smoking, lack of physical activity, and breastfeeding. Significant weight gain occurs between the ages of 18 and 35 years; hence, this age group could benefit from weight gain prevention interventions. Population studies have reported that women at increased risk of breast cancer account for a disproportionate amount of cases. Thus, there is a particular need to target weight gain prevention and other health behavior interventions for women at increased risk. A literature review identified no evidence-based apps that cover all relevant health behaviors. With patient and participant involvement from the target population, we have developed a new app to promote healthy behaviors among young women at increased risk of breast cancer. Alongside the app, a Facebook group provides peer support, and a virtual welcome event provides an overview of the project and the opportunity to meet the research team and other study participants. The aim of the intervention is to prevent weight gain via changes to eating habits and physical activity levels, and improve other health behaviors associated with breast cancer. The app includes goal setting and self-monitoring of health behaviors and provides education about breast cancer.

Objective: This study aims to assess the acceptability and usability of the app in young women at increased risk of breast cancer, and the feasibility of the study procedures for a future, larger efficacy study.

Methods: Young women (n=35, age 18-35 years) at increased risk of breast cancer (>17% lifetime risk) will be recruited via 2 recruitment procedures: mailed invite from the local breast cancer family history, risk and prevention clinic, and advertisements on social media and websites. Participants will have access to the app and the private Facebook group for 2 months. They will complete questionnaires regarding their health behaviors and breast cancer risk belief at the start and end of the study, complete app rating scales in the middle and at the end of the study, and be invited to give feedback on the app during the study period.

Approximately 20 participants will have a semistructured interview at the end of the study regarding their views on the app and trial procedures.

Results: The trial is ongoing, and the publication of results is anticipated in 2023.

Conclusions: The trial will provide evidence regarding the acceptability and usability of the newly developed app for young women at increased risk of breast cancer. Feedback obtained will be used to improve the app. The trial will also assess the feasibility of the study procedures and how these can be refined for a future efficacy study.

Trial Registration: ClinicalTrials.gov NCT05460650; https://clinicaltrials.gov/ct2/show/NCT05460650

International Registered Report Identifier (IRRID): PRR1-10.2196/41246

Introduction

The Importance of Health Behaviors for Breast Cancer Prevention

Breast cancer is the most frequent female malignancy worldwide, with over 2 million diagnoses annually worldwide and over 55,000 diagnoses in the United Kingdom [1]. These figures are predicted to increase [2] in part due to an aging population and increasing trends in modifiable breast cancer risk factors.

Recent estimates show that weight gain, excess weight, and potentially modifiable health behaviors are causally linked with a high proportion of breast cancer in the United Kingdom (~20%) [3]. The estimated attributable risks are 8% for weight gain through adulthood and overweight and obesity, 8% for high alcohol intake, and 5% for the absence of breastfeeding [3]. Other health behaviors that increase risk include smoking and lack of physical activity [4].

A recent UK study reported that a significant proportion of breast cancer cases, around 38%, occur in the 18% of women who are at increased risk (>17% lifetime risk) on the basis of their family history, +/ mammographic density, +/ hormonal factors, +/ high-risk single nucleotide polymorphisms (SNPs) [5]. Excess weight and unhealthy behaviors (high alcohol intake, smoking, unhealthy diet, and lack of physical activity) have an equal or greater effect on the relative risk for breast cancer among women with a family history compared to women without a family history of breast cancer [6-10]. Targeting health behavior interventions to women at increased risk of breast cancer is likely to have a significant impact on reducing rates because the same relative risk reduction will lead to greater absolute risk reductions.

Current Health Behaviors Among Women at Increased Risk

Many women known to be at increased risk attend Family History, Risk and Prevention Clinics (FHRPCs) of which there are around 90 in the United Kingdom. UK guidance from the National Institute of Health and Care Excellence (NICE) recommends FHRPCs to provide advice on health behaviors to lower breast cancer risk [11]. However, our 2016 survey of 21 FHRPCs found that few do in practice, most likely due to limitations on time, skills, and resources (personal communication). Analyses of BMI and health behavior data from women at increased risk (n=136, mean age 41.2, SD 3.5 years) in our clinic at The Nightingale Centre, South Manchester, highlighted the prevalence of overweight and obesity, and unhealthy behaviors that were comparable to women in the general population [12]. Almost 60% had overweight or obesity, 30% did not meet physical activity recommendations, and 45% exceeded alcohol recommendations. Thus, there is an unmet need to provide cancer prevention health behavior programs for women at increased risk.

Our recent overview highlighted that the majority of weight gain in women occurs between the ages of 18 and 35 years [13]. Once the weight is gained, it is very difficult to lose. Hence, this project is focused on preventing weight gain and improving health behaviors among women aged 18 to 35 years.

The Need for a Health Behavior App

Our previous interview study reported that young women (aged 25-35 years) at increased risk of breast cancer are interested in joining a program to prevent weight gain and promote healthy behaviors which could be accessed remotely, potentially via an app [14]. This was in line with the views expressed by our public and patient involvement (PPI) group of women younger than 40 years at increased risk of breast cancer who had been a healthy weight at age 18 years but had since gained at least a stone in weight (unpublished data). A program delivered via an app could also be scalable to all UK FHRPCs without putting additional pressure on each clinic.

While there are a number of weight loss apps already on the market, there are currently no apps designed to prevent weight gain. A search of the literature revealed no publications on the development of such apps; therefore, there is nothing that is currently suitable for testing in FHRPCs. Additionally, there are many breast cancer information and prevention apps, which only provide static information, for example, on risk factors and health behavior advice. They are neither interactive nor grounded in recognized psychological theory; therefore, they are unlikely to elicit behavior change [15].

Development of the App

We have developed an app promoting weight gain prevention and healthy behaviors among young women at increased risk of breast cancer using a codesign process involving young women from the FHRPC, Manchester University NHS Foundation Trust (MFT). The development was based on the person-based approach including performing qualitative research with users in the planning stages and the creation of guiding principles which are the features of the intervention identified as central to achieving the objectives [16,17]. We held 4 web-based PPI groups between September 2020 and October 2021 with between 2 and 7 PPI participants using an iterative approach to app development. Following each meeting, the participants' opinions were fed back to the app development team. Our multidisciplinary team includes researchers with experience of developing health apps, behavioral psychologists, dietitians, and breast oncologists. The app includes behavior change techniques found to be effective within health behavior apps in the literature, including self-monitoring [18-21] and goal setting [18,22-25], and provides education about health and breast cancer topics via an embedded microsite. Users can customize the app by choosing imperial or metric units for height and weight entries, opt to have their BMI or not have their BMI calculated after entering a weight, and choose their desired frequency for completing the 5 health logs (weight, alcohol intake, healthy eating score, smoking, and physical activity). Only weight must be completed at least monthly. Logs that are not relevant, for example, the smoking log for a nonsmoker, will not be displayed. After submitting a log, the participants are prompted to document their next target. Participants receive push notifications when their logs are due and are able to view graphs of their progress. The microsite is embedded within the app and contains information about topics such as alcohol and breast cancer, importance of fruit and vegetables in the diet, how to set health behavior goals, and how to limit weight gain in pregnancy.

The Health Behavior Intervention: Microsoft Teams Welcome Event, App With Embedded Microsite, and Private Facebook Group

The aim of the health behavior intervention is to prevent weight gain (via encouraging healthy behaviors such as healthy eating and physical activity) and improve other health behaviors associated with breast cancer, that is, reduced alcohol, smoking cessation, and breastfeeding. All of the components of the intervention are shown in Figure 1.

Alongside the app, a private, hidden Facebook group allows participants to access social/peer support within the study population for behavior change and contact with the research team. Membership of the private Facebook group is by invitation only by the research team who will also act as moderators. Only the invited members can see the list of members in the group and what members post, comment on and share within the group, and only current, invited or former members of the group can see the group's name and description, and can find the group in a web-based search. The participants' membership of the group and activity within the group are not visible on their personal Facebook profiles. Participants are encouraged to post within the group, and weekly posts from the research team will introduce a new weekly educational topic to promote interaction, for example, a poll or request for a recipe exchange. The research team will check the group at least once daily and reply to comments and private messages.

After consent, participants will be invited to attend one of several 45-minute welcome events hosted on Microsoft Teams with up to 10 other participants. These will provide a simple overview of the evidence for the association between weight, health behavior risk factors, and breast cancer, meet and build relationships with other study participants who will be present in the private Facebook group, and build rapport with the research team.

Figure 1. Components of the app.
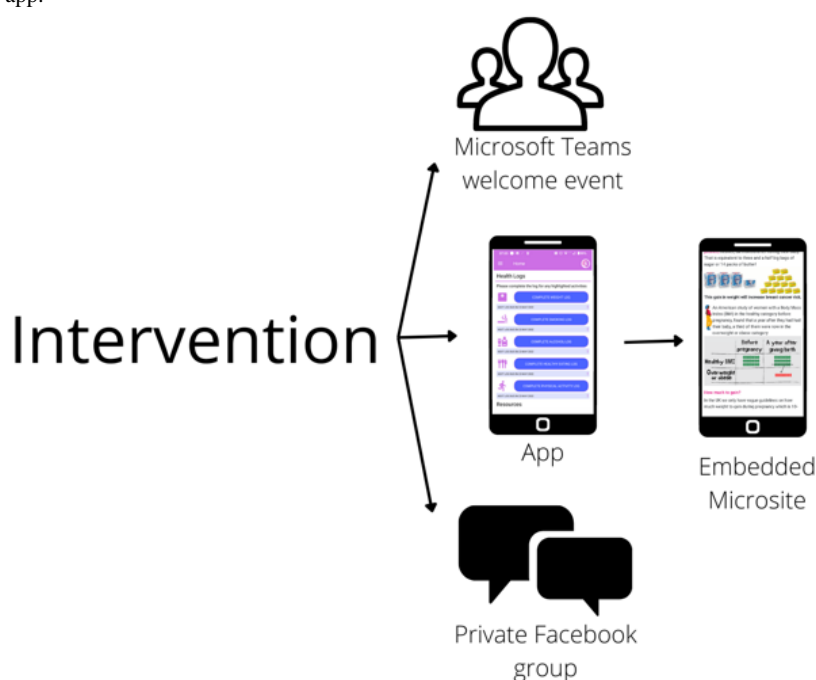
Testing the Complex Intervention

Evidence generation for the developed app will follow "Evidence Standards Framework for Digital Health Technologies" guidance by NICE to Tier C [26]. App design, development, and testing have involved experienced health professionals to ensure content is accurate and up-to-date. This study will involve users for acceptability testing. The intervention is "complex" as it has a number of interacting components (information provision, social/peer support, self-monitoring, and goal setting) and a number of outcomes (weight, alcohol, physical activity, healthy eating, and smoking) [27]. Therefore, we will follow the Medical Research Council framework for developing and evaluating complex interventions, which indicates the need to assess the acceptability and feasibility of a new complex intervention before any evaluation of efficacy or effectiveness [27]. This study is focused on the evaluation of acceptability and usability and will highlight areas to be refined before the next stage of testing. This study will also give us an indication of the feasibility of some of the study procedures we will use in future studies, for example, recruiting via social media and using web-based questionnaires. Following this initial study, we will run a full feasibility study in line with the Medical Research Council framework to assess the feasibility of running a randomized, multicenter efficacy study. Adhering to these frameworks will help to ensure that the correct evidence is gathered to enable the implementation of the intervention in the NHS.

Study Aim

The overall study aim is to assess the acceptability and the usability of the intervention for young women at increased risk of breast cancer, and the feasibility of the study procedures for a planned future efficacy study.

Study Objectives

This study has the following 7 objectives:

1. Explore the views of users on their experience of the 2 different recruitment procedures (targeted mailshot, or social media, newsletters, and websites) and the web-based consent procedure
2. Assess recruitment data to explore how the 2 different recruitment procedures could be improved for the next study
3. Explore views of users on their experiences during and after using the app
4. Assess user data from the app including frequency and patterns of use of the different functions
5. Assemble a list of suggested changes to the recruitment and consent procedures, and to the app itself, to be considered before the next study
6. Quantify health care professional time required for administering the private Facebook chat group, and through email or private message support
7. Quantify researcher time required for the cleaning and analysis of app data

Methods

Overview

This is a single-arm observational study (with embedded qualitative elements). The study team includes a PPI participant who gave feedback on the protocol and all study documents that the participants will receive such as the participant information sheet and questionnaires. A total of 35 young women at increased risk of breast cancer will have access to the app and Facebook group for 2 months followed by an interview.

Participants

The study will recruit 35 participants using the following inclusion criteria: female, age 18-35 years, living in the United Kingdom, moderate or high risk of breast cancer (>17% lifetime risk) [11], ability to communicate (written and spoken) in English, ability to download and use an app (available on both iOS and Android). In addition, the following exclusion criteria will be used: previous breast cancer (other cancers will not be excluded); previous bilateral preventative mastectomy, currently trying to gain weight; previous weight loss surgery; currently taking weight loss medication; prescribed (eg, orlistat, liraglutide, naltrexone/bupropion [Mysimba]) or other medical conditions that influence diet and weight, for example, diabetes, inflammatory bowel disease, or cystic fibrosis; current diagnosis of a psychiatric disorder, for example, bipolar psychotic disorder or current self-harm (self-report); current alcohol or drug dependency (self-report); or current or previous diagnosis of an eating disorder.

Ethical Considerations

The study has been granted ethical approval by Wales Research Ethics Committee 3 Cardiff (reference 22/WA/0164). All participants will be asked to provide informed consent. The study will be performed in accordance with the Declaration of Helsinki. The study is registered online at ClinicalTrials.gov (reference NCT05460650). Data will be anonymized once data collection is complete but before analysis. There are no financial incentives for participating in the study.

Study Procedures

The study flowchart is detailed in Figure 2.

Figure 2. Study flow chart.

Recruitment

Participants will be recruited in 2 different ways: (1) receiving a targeted invite letter from the MFT FHRPC (estimated recruitment of 30 participants) and (2) viewing advertisements on websites/newsletters/social media platforms such as Facebook and Twitter (estimated recruitment of 5 participants).

1. Recruitment from within the MFT FHRPC: We have successfully recruited to health behavior research studies and PPI projects using postal invite letters to FHRPC participants with an uptake of between 9% and 23% (unpublished, in press, and [14]). Based on a 15% predicted uptake, 200 letters will be posted to recruit 30 women.
2. Recruitment from outside of the FHRPC: Other methods of recruitment will be used to expand diversity within the recruited population as the ethnicity of MFT FHRPC attendees is mainly White [28].

Eligibility Check and Consent

All participants will have a telephone eligibility check. Breast cancer risk for participants from MFT FHRPC does not need to be verified as this has already been calculated using the Tyrer-Cuzick method [29]. Participants recruited from outside of the FHRPC will be deemed at increased risk based on their family history of breast and ovarian cancer as per NICE guidelines for referral to secondary care [11]. These women will be advised that they could be at increased risk due to their family history and therefore may meet the criteria for referral into secondary care and will be advised to seek a referral to a local FHRPC via their general practitioner. Following the eligibility check, participants will be asked to complete a web-based informed consent form. In order to report uptake to the study and reasons for screen fail, we will ask interested women who are not eligible if we can store their answers to the eligibility screen. If women consent to this, the information will be anonymized prior to storage.

Intervention

Participants will be invited to attend a Microsoft Teams (Microsoft Corporation) welcome event and will have 2 months' access to the app (Figure 3) and the private Facebook group.

Figure 3. App screenprints.
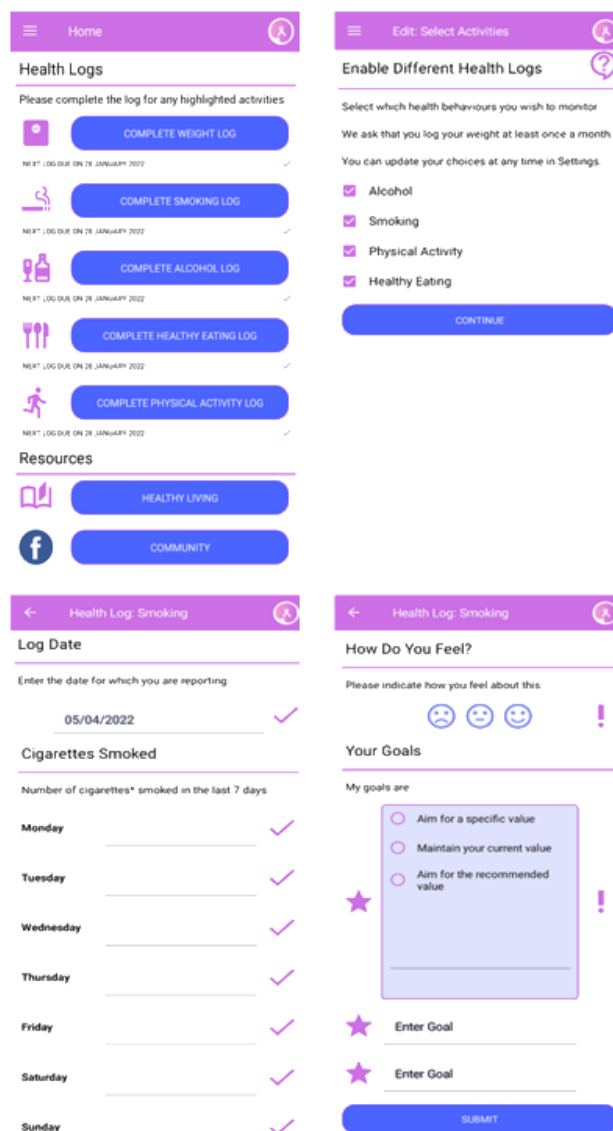
Questionnaires

All questionnaires will be hosted electronically on Qualtrics XM (Qualtrics LLC) and completed following the timeframe in Table 1.

Table 1. Timeframe of study questionnaires.

Questionnaire	Baseline	1 month (midstudy)	2 months (end of study)
Demographics and Health Behaviors Questionnaire	✓	N/A[a]	N/A
Breast cancer risk beliefs questionnaire	✓	N/A	✓
Mobile Application Rating Scale [30] questionnaire	N/A	✓	✓
App feedback questionnaire	N/A	✓ *Optional* as and when the participant wishes to give feedback on the app during the study	✓ *Optional* as and when the participant wishes to give feedback on the app during the study

[a]N/A: not applicable.

Outcome Measures

Outcome measures for the study and how they will be evaluated are detailed in Table 2.

Table 2. Outcome measures and how they will be evaluated.

Process to evaluate and method of data collection	Aims to explore	Method of analysis/data to be presented	Timepoint of analysis
Recruitment methods			
Recruitment data	Recruitment source of the participants	Recruitment data, for example, percentage response to mailshot, percentage uptake, and breakdown of numbers recruited via each method	At the end of recruitment phase
Interviews	Acceptability of recruitment procedure	Analysis of qualitative interviews	Interviews at the end of study
Consent method			
Interviews	Acceptability of consent procedure	Analysis of the qualitative interviews	Interviews at the end of the study
App: participant views			
Interviews, final questionnaire, app feedback questionnaires, and feedback received by email	Acceptability of the app, barriers and facilitators to engagement, likes and do not likes within the app, usability, and likelihood of extended use	Analysis of qualitative interviews, analysis of final questionnaire, and app feedback questionnaires, for example, functions most liked, suggested changes	Middle, during, and the end of the study
App: participant usage			
App usage data	Frequency of use, pattern of use across the 2-month interaction with components within app	Analysis of app analytics: number of times visited the app, clicks on links within the app to external sites, clicks from notifications, clicks on help buttons, flow through the app (which screens in which sequence), duration spent on each page/on the app in total	End of study
App: completion of information including logs			
Download of completed information including logs	Correct completion of the settings information and completion the frequency of the logs	Actual versus chosen frequency of completion of logs and change over time; any errors in information inputted, for example, kg entered as stones and pounds; number of logs completed for each health behavior	End of study
Health care professional time required			
Health care professional time logs	Health care professional time required for moderating Facebook chat group and through email or private message support	Breakdown of health care professional time spent in total and per person on moderating Facebook chat group, responding to private messages and emails	End of study
Engagement with the Facebook group			
Download of data from the group	Number of participant interactions in the Facebook group, pattern of interactions over the 2 months	Analysis of Facebook download	End of study
Time needed to collect, clean, and analyze data			
Staff time logs	Estimate of staff time and costs for larger study	Breakdown of staff time spent on the study, including cleaning the app data	End of study

Interviews

A qualitative researcher will undertake up to 20 semistructured interviews at the end of the 2-month study. Sampling will be purposive, aiming to obtain women with a range of ages, ethnicities, and both heavy and light engagers with the app. The interviews will take place face-to-face or over Microsoft Teams and will be digitally audio-recorded and transcribed verbatim. The interview schedule (Multimedia Appendix 1) explores the participants' experience of using the app, the usability of this app, whether it has been useful to them in changing their health behaviors, and aims to understand how the app may have influenced health behaviors or feelings toward breast cancer. It is predicted that a maximum of 20 interviews will be required, but a decision to stop further interviews will be made when no novel insights appear in the interviews according to the concept of "information power" [31].

Statistical Analysis

This study is to assess the acceptability and usability of the app before a larger feasibility study is planned and as such is not powered according to the outcome measures of that larger study. The study will recruit 35 women, of which up to 20 will be interviewed. The study sample size of 35 will allow for a 20%

dropout and selection of a range of women to interview, for example, both heavy and light engagers with the app. The study is not powered to assess the efficacy of the app at changing health behaviors and preventing weight gain, but 2 months of usage by ≥28 users will enable the quantitative data to give helpful indications of changes required to the app before a larger efficacy study.

Quantitative Analysis

Key baseline information from the demographics and health behaviors questionnaire will be presented, for example, smoking status, alcohol intake and physical activity in the previous week, age, living circumstances, ethnicity [32], education level, employment status, sociodemographic status (deprivation score: English Indices of Multiple Deprivation derived from full postcodes [33]), number and ages of children, and previous attendance at FHRPC using mean (SD), median (25th-75th percentile), and n (%) as appropriate.

Data from the private Facebook group will be extracted by copying and pasting it into Excel and anonymized. Data will be comments, posts (or descriptions of posts in the case of photo or video posts), and numbers of reactions. The use of an application programming interface will not be considered for this small study. Quantitative data will be presented, for example, the number of comments in reaction to weekly educational posts (total, average number per post and range, subjects evoking the highest number of comments, and number of users commenting), number of posts by participants, number of likes and reactions (total, average number per post and range, subjects evoking the highest number of reactions, and number of users reacting), and number of private messages to the moderators (number of users messaging and total number of messages received and sent) [34]. No qualitative analysis is planned on the text.

App usage data (number of times visited the app, clicks on links within the app to external sites, clicks from notifications, clicks on help buttons, flow through the app [which screens in which sequence], duration spent on each page/on the app in total) will be presented descriptively.

Qualitative Analysis

Transcripts will be analyzed using thematic analysis [35]. The analysis will be inductive: open-ended, exploratory, and driven by the data. Thematic analysis is free from theoretical bonds and is therefore adaptable to a wide range of methodologies. This freedom of epistemology means that the qualitative data from this study can provide a parallel and complimentary perspective to the other methods of data collection being used in this study. Thematic analysis can account for both individual and group consensus so that both convergent and divergent experiences across the corpus of the data can be taken into account as the process of analysis involves searching for all salient themes that emerge from the data. The analysis will be conducted by the qualitative health psychology researcher and codes discussed, revised, and refined in conjunction with DF.

Results

The study is currently ongoing, recruitment is predicted to be complete by the end of January 2023, and the results are expected to be submitted for publication by the summer of 2023.

Discussion

Expected Findings

We have developed an intervention including a novel weight gain prevention and health behavior app with PPI participants. This study is aiming to assess the acceptability and usability of the app for young women at increased risk of breast cancer, and the feasibility of study procedures for a planned future efficacy study. Through its objectives, this study will provide evidence for changes required to the study and the intervention that should be implemented in a future study. We are following recognized frameworks in order to enable future implementation in the NHS.

Previous Studies

The literature reveals a paucity of studies using evidence-based smartphone interventions for breast cancer risk reduction. A 2014 review by Mobasheri et al [36] highlighted the lack of evidence-based content in apps related to breast health and found potential safety concerns in 15.7% (29/185) of the apps they reviewed. In 2016, Coughlin et al [37] collated the evidence regarding modifiable behavioral risk factors that should be included in the development of apps for breast cancer risk reduction. They concluded that an app should address multiple modifiable risk factors and different apps may be required to effectively target different populations such as younger women. They highlighted the importance of including proven behavioral techniques such as goal setting. They found that no evidence-based apps currently exist and they planned to develop and test an app but as yet have not published further work. Giunti et al [38] identified 61 apps related to primary or secondary breast cancer prevention of which over 80% were developed by individuals or small-to-medium enterprises, and they, again, raised concerns about the lack of medical professional involvement in app development, many of which aim to sell products or link with paid services [38]. A 2019 systematic review of app studies that aim to reduce breast cancer risk did not find any that addressed all of the necessary behavioral risk factors and concluded that more research is required, especially for apps relevant to young women [39].

Limitations

This 2-month study will be unable to assess app usage over a longer timeframe. The questionnaires and interviews will, however, inform whether longer-term use is likely, and changes that are required to improve engagement and longevity that will be employed in the subsequent feasibility study. The study will not attempt to establish the effectiveness of the intervention for modifying behavior. A longer study duration is required for this. Nor will the study assess changes to breast cancer risk due to behavior modification or weight change, as current risk models are unable to calculate the effect of behavioral changes

such as smoking reduction/cessation or changes in physical activity levels on future breast cancer risk.

Planned Future Steps

The findings of the study will be published. If this study shows that the app is acceptable to the target audience, it will be used in a future planned feasibility study. Any changes required to the app, Facebook page, or trial procedures that have been highlighted by this acceptability study will be completed before the feasibility study. The feasibility study will in turn inform the viability of a larger, definitive multicenter randomized controlled trial to test the effectiveness and cost-effectiveness of the app for the prevention of weight gain, and optimization of health behaviors related to breast cancer among young women at increased risk.

Conclusions

Over 55,000 women are diagnosed with breast cancer in the United Kingdom each year, and many of these cases could be prevented through changes to health behaviors and limiting weight gain. Consideration of the existing literature surrounding health behavior interventions and breast cancer risk reduction, along with input from PPI groups, has led us to develop an app for use in young women at increased risk of breast cancer. In this initial study, we will assess whether the app is acceptable to the target population. The study will add to the literature on the development of interventions for the reduction of breast cancer risk in women at increased risk of the disease. If successful, we plan to run a larger efficacy study. By following recognized frameworks for intervention development, we will increase the likelihood of developing an intervention that can be successfully rolled out within the NHS.

Data Availability

After data analysis is complete, the fully anonymized data will be uploaded to the University of Manchester institutional research data repository and will remain there indefinitely and will be freely available.

Authors' Contributions

AD, JM, and MP designed and created the app and all authors conceived and designed the protocol. RC, DPF, MP, and MH developed the interview schedule. All authors and drafted and gave final approval of the paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview schedule.
[DOCX File , 18 KB - resprot_v11i12e41246_app1.docx]

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Abbreviations

FHRPC: Family History, Risk and Prevention Clinic
MFT: Manchester University NHS Foundation Trust
NICE: National Institute of Health and Care Excellence
NIHR: National Institute for Health Research
PPI: public and patient involvement
SNP: single nucleotide polymorphism

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Protocol

Identification of Clinical Measures to Use in a Virtual Concussion Assessment: Protocol for a Mixed Methods Study

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Abstract

Background: Workplace concussions can have a significant impact on workers. The impact of concussion symptoms, combined with challenges associated with clinical environments that are loud, bright, and busy, create barriers to conducting effective in-person assessments. Although the opportunity for remote care in rural communities has long been recognized, the COVID-19 pandemic has catalyzed the transition to virtual assessments and care into the mainstream. With this rapid shift, many clinicians have been completing remote assessments. However, the approaches and measures used in these assessments have not yet been standardized. Furthermore, the psychometric properties of the assessments when completed remotely using videoconference have not yet been documented.

Objective: Through this mixed methods study, we aim to (1) identify the concussion assessment measures clinicians are currently using in person and are most relevant to the following 5 physical domains: neurological examination (ie, cranial nerve, coordination, motor, and sensory skills), cervical spine, vestibular, oculomotor, and effort assessment; (2) document the psychometric properties of the measures identified; (3) identify measures that appear feasible in a virtual context; and (4) identify practical and technical barriers or challenges, facilitators, and benefits to conducting or engaging in virtual concussion assessments.

Methods: This study will follow a sequential mixed methods design using a survey and Delphi approach, working groups with expert clinicians, and focus groups with experienced clinicians and people living with concussions. Our target sample sizes are 50 clinicians for the Delphi surveys, 4 clinician-participants for the working group, and 5-7 participants for each focus group (roughly 6-10 total groups being planned with at least two groups consisting of people living with concussions). The results from this study will inform the decision regarding the measures that should be included in a virtual assessment tool kit to be tested in a future planned prospective evaluation study.

Results: The study is expected to be completed by January 2023.

Conclusions: This mixed methods study will document the clinical measures that are currently used in person and will identify those that are most relevant to assessing the physical domains impacted by concussions. Potential feasibility of using these measures in a virtual context will be explored.

KEYWORDS

telehealth; virtual care; concussion; mild traumatic brain injury; assessment; examination

Introduction

Background

Concussions or mild traumatic brain injuries affect thousands of Canadians every year [1]. Workplace injuries account for a notable portion of nonsport concussions [2]. Terry et al [3] reported that approximately 25% of adult concussions occur at work. Workplace injuries resulting in concussions pose a significant challenge for employers and insurers while disrupting the lives of the workers due to greater recovery times compared to non–work-related concussions [4]. In general, roughly 10%-20% of individuals who sustain a concussion experience symptoms lasting beyond the one- to two-week typical recovery time frame [5,6]. In the workplace context specifically, prolonged symptoms lead to reduction in productivity at work or even disability, which in turn has an economic impact on people, companies, and government agencies [3]. Although it is apparent that there is a need for further support and research in the workplace concussion rehabilitation field, a focus on the evaluation of concussion will be an important starting point to individualizing care.

Assessing symptoms and function after concussion presents clinicians with challenges due to the complex and diverse symptom presentation and a lack of sensitive and reliable clinical assessment measures [7]. Symptoms may be physical (such as dizziness, balance issues, headaches, neck pain, and vision difficulties), emotional (such as irritability and disinhibition) or cognitive (such as memory and concentration difficulties) [7-11]. All the domains of concussion symptoms must be considered [8]. Currently, however, a gold standard test to evaluate all concussion symptoms does not exist. Commonly, a battery of tests and symptom self-reports are relied upon [7,12,13]. For example, the Balance Error Scoring System and the Sensory Organization Test are used to assess balance deficits following a concussion injury [14]. The King-Device test and the Vestibular Ocular Motor Screen may be used to evaluate oculomotor deficits [14,15]. Furthermore, the psychometric properties of the tools involved are often underdeveloped, and clinical utility varies. There is an additional challenge with all assessments of injured workers because of access to compensation that may interfere with the validity of effort provided during the assessment [3]. Measures that allow the examiner to ensure that a valid effort was made to complete the assessment should be considered.

With the shift in clinical service delivery to virtual health care driven by the COVID-19 pandemic, the need for valid and reliable approaches to virtual concussion assessments has become more pressing. In addition, people living in remote areas or for whom travel is difficult due to comorbidities continue to have a great need for assessment that can be carried out at distance [16,17]. Such assessment would also be helpful for people whose symptoms are aggravated by travel and environmental factors such as noise and light [18].

Clinicians are currently completing virtual concussion assessments using a variety of clinical assessment measures; however, as with in-person assessments, there is no standardized approach to assessing adult concussions virtually. Resources have been developed to support completion of the virtual concussion examination, including a training manual for the examination and a living guideline that outlines considerations for the pediatric examination [19,20]. Comparison of the measures identified in these resources when administered in an in-person and virtual context has not yet occurred.

The psychometric properties of many of the assessment measures being used have not been established for use in person or virtually. Accelerated adoption of information and communication technology has been occurring globally to enhance service delivery during the COVID-19 pandemic; however, it is unclear whether the outcomes of assessments completed virtually are consistent with assessments performed in person [21,22]. It is, therefore, important to understand if the measures used to assess concussions in person could provide equivalent results when used virtually [23].

Overall, there are multiple clinical assessment measures being used by clinicians to assess the physical domains impacted by a concussion injury. There is no standardized tool kit of measures available with established psychometric properties that are relevant and feasible in a virtual context, nor are there guidelines outlining specific measures to use in the adult population [12-14].

Objective

The objective of this mixed methods study is to produce a tool kit of measures that can be used in virtual assessments of concussion's physical symptoms.

Methods

This study will follow a sequential mixed methods design [24] that will include a Delphi survey, a working group consultation, and focus groups. The methodological approach is outlined in Figure 1.

Figure 1. Sequential explanatory approach commencing with survey administration guided by the Delphi methods and working group completion (quantitative) followed by focus group completion (qualitative) to expand on and explain survey and working group results.
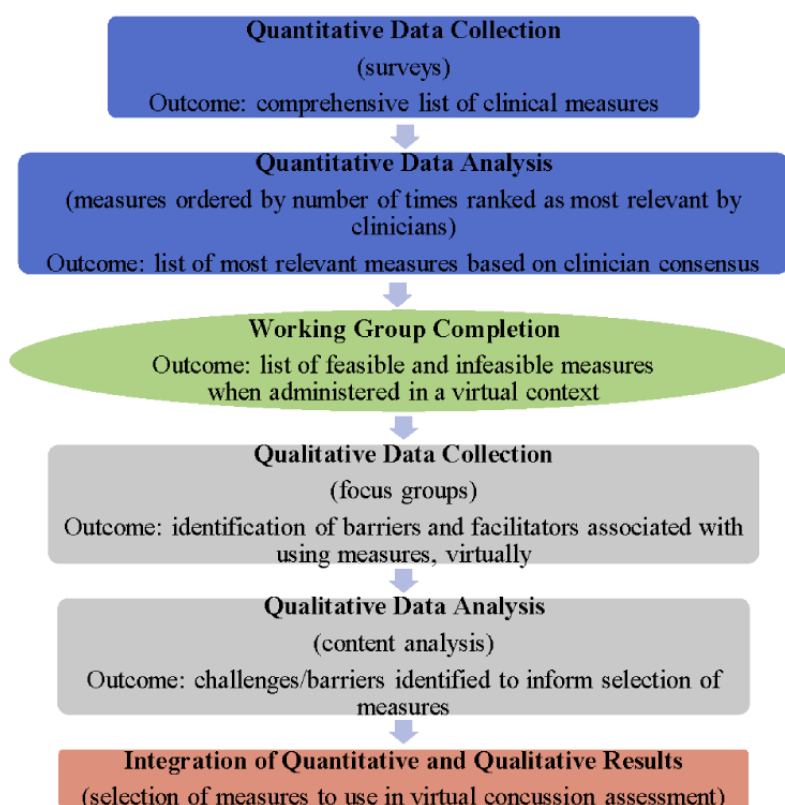
Participants

Delphi Survey

Expert clinicians (ie, physiatrists, neurologists, sports medicine physicians, and physiotherapists) from across Canada will be identified through both regional and national professional and brain injury or concussion organizations and networks. Members of these networks represent an accessible and meaningful sample that will include many practicing clinicians with concussion assessment experience. The survey will be sent through these networks and associations by including the survey link in a newsletter or by sending the survey link through email to all members of the networks and associations. To ensure 'experts' are completing the survey, respondents will be asked to rate their concussion expertise using a 5-point Likert scale ("strongly not competent" to "strongly competent"). Any responses from participants self-reporting their competency as below 3 or "neutral" will be excluded. When needed, targeted emails will be sent to expert clinicians with publicly available contact information to ensure representation (minimum of 2 responses) of each profession.

Sample Size for Delphi Survey

Our target sample size is 50 clinicians, which we consider adequate to reach saturation on the types of clinical measures used in practice. This sample size is feasible based on an anticipated 25% response rate and assuming that approximately 200 clinicians will view the survey [25,26]. Clinicians who complete the first-round survey will be sent the second-round

survey. It is expected that the second round of surveys will elicit a response rate of approximately 60% (~30 clinicians) [27].

Working Group Membership

A working group consisting of expert clinicians, including at least one neurologist, physiatrist, sports medicine physician, and physiotherapist, will meet to discuss the feasibility of virtual use of each measure identified in the survey. Members of the research team will be offered the opportunity to participate. Targeted emails to Canadian practicing clinicians will also be used to ensure representation from each clinical field. A final list of potentially feasible outcome measures will be identified in the working group, which will then be further explored in the focus groups.

Focus Group Membership

Focus groups consisting of 5 to 7 participants [28,29] will be conducted following the methodological framework outlined by Breen [30]. It is hypothesized that 6 to 10 focus groups will be adequate to reach saturation (2-3 groups consisting of people living with concussions who have experience with virtual assessment and 4-8 focus groups consisting of clinician-experts) [28,29]. Patient-participants who have attended a virtual concussion assessment will be identified and recruited from the Ottawa Hospital Rehabilitation Centre. The remaining focus groups will contain mixes of neurologists, physiatrists, sports medicine physicians, and physiotherapists. Participants who complete the Delphi surveys will have the option to express interest in participating in a focus group. Additional recruitment strategies include face-to-face recruitment at the Ottawa Hospital Rehabilitation Centre and through Ontario Workers Network

clinics. Targeted emails to Canadian practicing clinicians will also be used.

Procedures

Quantitative Delphi Survey Data Collection

The survey process will follow a Delphi method, which aims to seek consensus among the participants [31]. In round one, clinicians will receive a link for participation, which includes the implied consent form and a demographic questionnaire with open-ended questions; the questionnaire will have free-text boxes asking participants to identify multiple outcome measures they currently use to assess each 5 domains of interest (Figure 2). The invitation to participate in the surveys will be undersigned by a physiatrist (SM), including the affiliation, to secure buy-in and encourage responses. Measures identified by at least 15% of all participants (eg, 8/50 participants) or at least 60% of participants from one profession will be retained for the survey in round two.

Figure 2. Clinical domains of interest for identification of assessment measures and sample questions for the vestibular domain for round one and two surveys. Similar questions were provided for each domain.
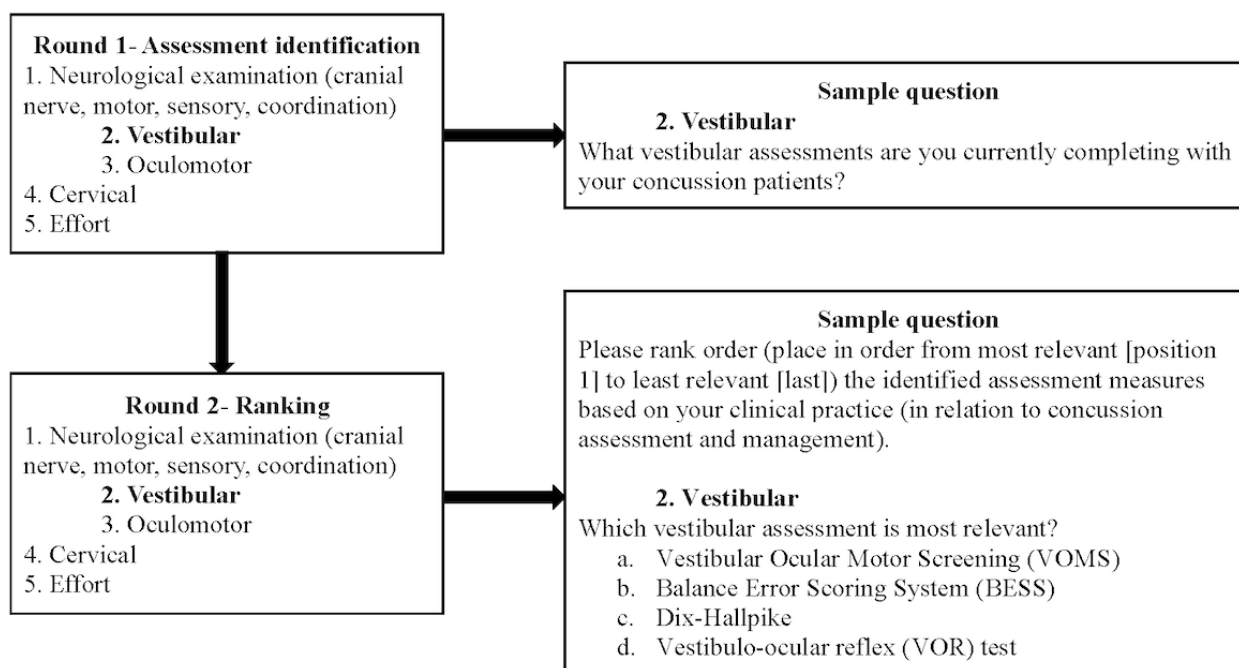
In round two, all participants from round one will be asked to rank order, according to perceived usefulness for their practice, the concussion assessment measures from each domain (ie, neurological exam, cervical spine, oculomotor, vestibular, and effort) retained from the first round (Figure 2). Prior to completing the second-round survey, participants will be invited to review reading materials with information on the retained measures, including information on sensitivity, specificity, and feasibility from the literature, when available.

Delphi Survey Questionnaire Administration

To increase response rates, reminder emails will be sent at 7-day and 14-day time points following the initial emails in the first and second rounds [25,30]. A universal level of consensus does not yet exist for the Delphi survey approach; however, various works have suggested a range of 51%-80% agreement [27]. For the purposes of this study, an above 51% agreement level for rankings of assessments has been set for the second round. Assessments that reach 15% in round one will be considered for clinical feasibility by the expert clinician working group.

Working Group to Derive Consensus on the List of Feasible Measures

A working group consisting of expert clinicians will meet over a videoconferencing platform, which involves bidirectional visual and audio communication technology, to discuss the current feasibility of the identified measures in a virtual context. Any measures deemed not feasible in the working group will be eliminated from further discussion in the focus groups. The final list of measures will be further explored in the clinician focus groups.

Qualitative Focus Group Data Collection

Focus groups with both clinician and patient-participants will be conducted. An interview guide with broad open-ended questions will be used as a prompt for the conduct of the focus groups. All focus groups will occur over a videoconferencing platform and will be audio and video recorded for later transcription. Multimedia Appendix 1 includes the semistructured interview guide for both patient-participants and clinician-participants.

Clinician-Participant Focus Groups

Prior to conducting the focus group, clinician-participants will be provided with available psychometric properties documented in the literature of the in-person measures that were identified from the second round of the surveys as well as descriptions of the assessments and instructions on how to complete the assessments. Clinician-participants in the focus groups will be prompted about the practical and technical issues associated with using each of the final measures. Barriers and facilitators associated with the assessments, including adverse events experienced or observed, will also be explored.

Patient-Participant Focus Groups

Patient-participants will be prompted to discuss the benefits and challenges associated with virtual concussion assessments based on their experiences.

Data Analysis

Quantitative Analysis of Delphi Surveys

Clinical measures identified in round one of the Delphi surveys will be categorized into the preestablished domains (ie, neurological examination, cervical spine, vestibular, oculomotor, and effort assessment). Frequency counts of the measures will be used to identify most commonly identified measures [32], and consistency of wording for the description of measures will be documented. For example, some clinicians may describe the measure rather than providing the name of the measure.

The quantitative data obtained in the second round of surveys (ie, rank order of measures) will be analyzed descriptively (ie, summary statistics to demonstrate patterns in the data). Measures of frequency and agreement percentages will be calculated.

Qualitative Analysis of Focus Groups

NVivo will be used to organize the qualitative data analysis. Recordings from the focus groups will be transcribed verbatim. Content analysis will be used to analyze the focus group data [33]. Two research assistants will independently identify codes related to barriers or challenges, benefits, and facilitators associated with using each of the identified measures. Codes will be sorted into 2 levels of categories: categories related to assessment of specific symptoms or domains and categories related to virtual assessment in general.

Ethics Approval

Ethics approval was obtained by the Ottawa Health Sciences Network Research Ethics Board (20210575-01H) in September 2021 followed by the Bruyère Research Institute Research Ethics Board (M16-22-006) and the University of Ottawa Board of Ethics (H-02-22-7611) in February 2022.

Results

Survey administration and the working group have been completed. Focus group recruitment is underway. The final results of the surveys, working group, and focus groups will lead to the identification of clinical measures to use in a virtual assessment tool kit, which will be tested in a future planned evaluation study.

Discussion

Expected Outcomes

We presented a protocol for a mixed methods study to identify the most appropriate clinical measures to include in a virtual assessment. We hypothesize that the measures identified in the surveys will vary based on clinical profession. We anticipate reliability properties of the identified measures to range from moderate to strong (intraclass correlation coefficients=0.41 to above 0.81). It is anticipated that the working group and focus group discussions will lead to an understanding of some of the real and perceived barriers and facilitators related to participating in or completing a virtual concussion assessment. We expect patient-perceived challenges to relate to the technical issues with technology and clinician-perceived challenges to relate to the challenges associated with engaging in hands-on approaches in virtual care.

A toolbox of concussion physical assessments has been proposed by Matuszak et al [14], which includes measures to assess domains that are frequently impacted by a concussion injury; however, many of the physical assessment measures used in the concussion population have limited psychometric data. The proposed toolbox includes evaluation of vital signs, mental status, neurological examination (ie, cranial nerves, manual muscle testing, and reflexes), head and cervicothoracic evaluation, balance or coordination assessment, and vestibulo-ocular evaluation [14]. This toolbox is proposed for the in-person examination. However, many of the virtual resources and guidelines include similar evaluations [19,20].

Although telehealth has existed for a long time, the COVID-19 global pandemic has increased both its need and its use in delivering health care services [34]. The COVID-19 pandemic has accelerated the need for telemedicine-supported remote assessments and has pushed both clinicians and researchers to determine what aspects of medical care could be feasible in a telehealth context [34,35]. A scoping review by O'Neil et al [36] noted that videoconferencing could be a valid means to remotely assess patients with moderate to severe traumatic brain injury. In addition, according to Fjeldstad-Pardo et al [37], no adverse events have been identified during participation in telerehabilitation, indicating that it is a safe approach to deliver services. Specifically, telerehabilitation has been reported to be feasible and effective for the intervention and management of neurological patients [38]. There has been a significant increase in the use of virtual assessments, with a rapid transition due to the pandemic. This transition limited the ability to implement virtual care using a planned and organized approach. The transition was a reaction to the pandemic rather than a planned response [39]. Due to this reactionary response, clinicians have been forced to complete remote assessments with limited information on the accuracy and reliability of the measures used in these assessments.

It is, therefore, important to understand which assessments clinicians are completing both in person and virtually in the context of the concussion examination. A study by Tobler-Amman et al [40] found that correlation values were low when measures assessing similar constructs in people living

with stroke were administered in person and virtually. Although clinicians thought the measures were assessing the same construct, the low correlation values indicate that administering the measures in the two different contexts may not provide the same information. Similarly, a study by Wang et al [41] on people living with Parkinson disease found that participants elicited a weaker reach when an assessment was completed virtually compared to in person. In the context of the concussion examination, understanding which assessments are being conducted and how the assessments are being conducted both in person and virtually is necessary to determine the equivalence of the assessments when administered in both contexts. Psychometric properties should be established in both in-person and virtual contexts of use to ensure accurate and reliable implementation in both contexts [23]. If the outcome measures used in person have poor documented psychometric properties or no documented psychometric properties, there may be additional challenges to validity and reliability when using the measure in a virtual context. It is important to gain an understanding of the properties of the clinical measures and their ability to produce equivalent results to the in-person assessment to inform decision-making in terms of their use in practice and their potential use in the virtual context [42].

With the increase in need for the uptake of telehealth in rural and remote areas, and now globally due to the COVID-19 pandemic, standardization of a feasible virtual concussion assessment is needed. The identification of the clinical measures that are most relevant and contribute the most reliable information in an adult concussion examination and the identification of the barriers and facilitators associated with using these specific measures in a telehealth context is an important first step to lead to this standardization. The results of this study and the future planned prospective evaluation study will be published and disseminated to targeted end users and networks.

Strengths and Limitations of Methodological Approaches

An important strength of the Delphi method is that it is a useful approach when lack of clarity exists, which is likely the case in the concussion assessment field [43]. It is apparent that although the Delphi approach has many strengths, it also has some limitations. Generally, the Delphi approach lacks agreed-upon standards or consensus [43].

Focus groups have been reported to be beneficial when participants are in different geographical locations [30], which will occur in this project due to the need to gain input from various clinicians and from people living with concussions to inform the follow-up studies. Some important limitations of focus groups include the following: the group setting nature of the focus groups may discourage participants from sharing their input; similarly, one single participant may dominate the focus group discussion (ie, overpower other participants) [30].

Conclusions

This mixed methods study will identify the assessment measures that are currently being used in person to evaluate people living with concussions. This study will further identify the barriers and facilitators as well as the challenges and benefits associated with using the identified measures, virtually. Psychometric properties documented in the literature of the in-person measures that will be discussed in the focus groups will be described. Results from this study will inform the selection of measures to include in a virtual assessment tool kit, which will be tested in follow-up studies. It is apparent that there are multiple gaps in the clinical assessment of concussion. There appears to be a need to further explore and expand on the understanding of the measures used to assess individuals experiencing prolonged symptoms in person; however, there is currently a need to explore the use of these measures in a virtual context. The limitations of the COVID-19 pandemic have highlighted the need for a rapid change in service delivery to virtual means, and although limited information exists regarding concussion assessment in a virtual context, remote assessments are currently being conducted in clinical practice, and therefore, need to be better understood.

Data Availability

Data sharing is not applicable to this study, as no data sets were analyzed during the study.

Authors' Contributions

All authors have made substantial contribution to the work presented in this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide.
[DOCX File , 14 KB - resprot_v11i12e40446_app1.docx]

Multimedia Appendix 2
Peer reviewed by Workplace Safety & Insurance Board (WSIB) Grants Program (Toronto, Ontario, Canada).
[PDF File (Adobe PDF File), 164 KB - resprot_v11i12e40446_app2.pdf]

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Protocol

The Role of Dysfunctional Sleep Beliefs in Mediating the Outcomes of Web-Based Cognitive Behavioral Therapy for Insomnia in Community-Dwelling Older Adults: Protocol for a Single-Group, Nonrandomized Trial

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Abstract

Background: Sleeping well is an essential part of good health. Older adult populations report a high rate of sleep problems, with recent studies suggesting that cognitive processes as well as behavioral and hyperarousal-related mechanisms could be important factors in the development and maintenance of insomnia. Individuals who have an asynchronous or uncoupled sleep pattern and sleep appraisal—those who complain about their sleep but do not have poor sleep quality, and vice versa—might show differences in subjective sleep and sleep perceptions and other characteristics that could impact their treatment outcomes following cognitive behavioral therapy for insomnia (CBT-I).

Objective: The purpose of this protocol is to describe the rationale and methods for a nonrandomized, single-arm trial assessing objective and subjective sleep quality in community-dwelling older adults aged 60-80 years with synchronous sleep patterns and sleep appraisal compared to those in older adults with asynchronous sleep patterns and sleep appraisal. The trial will further examine the role of cognitive, behavioral, and hyperarousal processes in mediating the treatment outcomes of web-based CBT-I.

Methods: This trial aims to recruit a sample of 60 participants, who will be assigned to 1 of 4 sleep groups based on their sleep pattern and sleep appraisal status: complaining good sleepers, complaining poor sleepers, noncomplaining good sleepers, and noncomplaining poor sleepers, respectively. The trial will be completed in 2 phases: phase 1 will assess objective sleep (measured via wrist actigraphy) and subjective (self-reported) sleep. Phase 2 will investigate the impact of a web-based CBT-I program on the sleep outcomes of individuals with uncoupled sleep compared to that of individuals without uncoupled sleep, as well as the mediators of CBT-I.

Results: Recruitment began in March 2020, and the last participants were recruited by March 2021. A total of 65 participants completed phases 1 and 2. Data analysis for phase 1 was finished in December 2021, and data analysis for phase 2 was finalized in July 2022. The results for phase 1 were submitted for publication in March 2022, and those for phase 2 will be submitted by the end of December 2022.

Conclusions: This trial will provide guidance on factors that contribute to the variability of sleep in older adults and their sleep outcomes following CBT-I. The outcomes of this study could be valuable for future research attempting to tailor CBT-I to individual needs.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12619001509156; https://tinyurl.com/69hhdu2w

International Registered Report Identifier (IRRID): DERR1-10.2196/32705

KEYWORDS

Introduction

Sleep problems, such as insomnia, are highly prevalent in those older than 60 years of age [1], with age-related changes in sleep architecture appearing from middle age and continuing to remain relatively constant past the age of 60 years [2]. Insomnia is characterized by difficulties with sleep initiation, duration, or quality that are not due to a lack of opportunity to sleep and which results in daytime impairment [3]. It is classified as chronic when it occurs at least 3 times per week and persists for more than 3 months [4]. Furthermore, a diagnosis of insomnia consists of 2 components: sleep quality and sleep appraisal. Sleep quality can be good or poor and sleep appraisal can be characterized by the presence or absence of a sleep complaint. These 2 factors have been described as being independent of each other [5], and in about 25%-35% of individuals, sleep quality and sleep appraisal are asynchronous and uncoupled [6]. It has been proposed that such uncoupling of sleep quality and sleep complaints may be prevalent among older adults [7,8]. In their seminal study examining poor sleepers that do not complain of insomnia, Fichten et al [9] first observed the asynchrony of sleep complaints and sleep patterns in older individuals. They reported that daytime impairment, assessed as sleepiness and daytime fatigue was higher in high-distress poor sleepers than in low-distress poor sleepers, and that low-distress poor sleepers experienced the same levels of daytime impairment as good sleepers.

The distinction between high- and low-distress, or asynchronous, good and poor sleepers could also be relevant for the treatment of sleep problems, as it could signify differences in how individuals respond to insomnia treatment. Cognitive behavioral therapy for insomnia (CBT-I) is the recommended first-line treatment method to address insomnia in any age group [10]. It contains several core components such as psychoeducation, cognitive therapy, and behavior therapy [11,12]. However, despite a widespread recommendation for the use of CBT in the treatment of insomnia, the provision of pharmacotherapy remains the dominant approach to address sleep problems in older adults. This is in part due to a lack of trained clinicians [13]. The pharmaceutical treatment of insomnia can lead to polypharmacy, the concurrent use of multiple medicines, which is an identified issue for older individuals [14]. Polypharmacy can result in interaction effects or side effects, for example, an increased fall risk, in older adults [15,16]. CBT-I's effectiveness and safety on the other hand have been well established, demonstrating moderate to large effects on improving sleep continuity [17]. CBT-I is also an effective treatment option for older adults, with recent research suggesting that even brief interventions can improve sleep onset latency, wake-after-sleep onset, sleep efficiency, and sleep quality [18,19], making it a viable alternative for older individuals at risk of polypharmacy.

The exact mechanisms by which such improvements are achieved remain unknown, and it is not fully understood why some individuals respond to CBT-I and others do not. It is estimated that 20%-30% of individuals with insomnia do not have a treatment response to CBT-I [20]. Cognitive processes are important factors in the development and maintenance of insomnia [5,20-27], particularly in older adults [28-30]. Discrepancies in subjective sleep perception and objectively measured sleep are also common [31]. In order to scrutinize sleep quality in older adults and the role that dysfunctional beliefs and other cognitive or behavioral factors play in mediating the outcomes of CBT-I, this study will examine both subjective and objective sleep quality in older adults aged 60-80 years in Western Australia. The age category of 60 years and older has been selected as it is the United Nations' agreed cutoff for the classification of older persons in high-income nations [32]. The upper cutoff of 80 years was chosen based on an American Academy of Sleep Medicine report highlighting that the sleep variability in adults aged 80 years and older is either significantly higher or significantly lower than that in adults under 65 years [33,34]. Consequently, adults aged older than 80 years will be excluded.

The concurrent measurement of objective and subjective sleep quality will be used to determine the prevalence of individuals with asynchronous sleep patterns and sleep appraisal in this sample (phase 1). Phase 2 will assess the impact of a web-based CBT-I program on the sleep outcomes of individuals with synchronous sleep patterns and sleep appraisal and those with asynchronous sleep patterns and sleep appraisal. It is anticipated that complaining good sleepers and complaining poor sleepers will show improved sleep outcomes following CBT-I, compared with noncomplaining good and poor sleepers. We further hypothesize that individuals with a sleep complaint but without poor sleep quality (complaining good sleepers) experience higher levels of dysfunctional sleep cognitions and distress than persons with poor sleep in the absence of a sleep complaint (noncomplaining poor sleepers). We expect that additional factors such as hyperarousal [35], sleep effort [36], sleep-related self-efficacy [37], sleep locus of control [38], sleep-related behaviors [39], and chronotype [40] mediate the relationship between web-based CBT-I and sleep outcomes in older adults; therefore, these processes will also be examined.

Since our planned study is likely to generate a considerable amount of data, we aim to reduce publication bias and improve the reproducibility of our research by publishing this research protocol.

Methods

Ethics Approval

Ethical approval for this study has been granted by the Edith Cowan University Human Research Ethics Committee (reference STREAM 22000). All participants will provide written informed consent.

Recruitment

Older adults with and those without self-reported poor sleep will be recruited from the community in Western Australia, with advertisements being displayed on the Sleep Health Foundation website and social media sites such as Facebook, as well as in community centers and senior citizen organizations. Participants are eligible to take part if they are aged 60-80 years and ordinarily reside in Western Australia, if they have not been diagnosed with an existing sleep disorder other than insomnia, if they have not been diagnosed with a severe psychiatric or cognitive disorder, if they have not engaged in regular shift work in the past year, and if they have not been diagnosed with epilepsy or are at high risk of falling.

Screening for the presence of obstructive sleep apnea, which is common among older adults, will be conducted using the STOP-Bang (snoring, tiredness, observed apnea, high BP, BMI, age, neck circumference, and male gender) questionnaire, a brief self-report instrument [41]. The STOP-Bang questionnaire has demonstrated a high sensitivity of 84% in detecting obstructive sleep apnea [41]. Participants that score 0 to 2 on the instrument are considered unlikely to present with moderate to severe sleep apnea. Participants who took sleep medication were not excluded, as CBT-I has shown to be effective in those who take sleep medication [12]. However, the type, dosage, and frequency of any medication taken by participants were recorded as part of the demographic assessment.

Design

Study participants will be required to complete a web-based questionnaire battery at baseline and following the intervention. It is estimated that it will take approximately 20-25 minutes to complete the questionnaire battery. Sleep-related dysfunctional beliefs will be assessed using the Dysfunctional Beliefs and Attitudes about Sleep (DBAS-16) scale [42]. The DBAS-16 was developed to examine sleep-related cognitions and dysfunctional beliefs. Items such as "I am worried that I may lose control over my abilities to sleep" are scored on a 10-point Likert scale ranging from 0 to 10. Like the original 30-item version, the DBAS-16 has been found to reliably discriminate between self-reported good and poor sleepers in older adult populations with adequate internal consistency (Cronbach α=.79 for research samples). A DBAS score of 4 or above is indicative of a clinically significant level of dysfunctional beliefs around sleep [21].

The Pittsburgh Sleep Quality Index [43] consists of 19 items and examines sleep quality and disturbances over the past month. The first 4 questions are open, whereas items 5 to 19 are rated on a 4-point Likert scale. Individual item scores from the 7 sections are calculated first, and those 7 component scores are subsequently added up to calculate the global score ranging from 0 to 21. A sleep score of >5 is indicative of poor sleep quality. The Pittsburgh Sleep Quality Index measures sleep quality in a broader sense than just insomnia severity and has good internal consistency (Cronbach α=.83).

The Insomnia Severity Index [44,45] is a brief self-report questionnaire used to measure the severity of insomnia, impairment of daytime functioning, and worry about sleep over the past 2 weeks. It examines both nighttime and daytime components of insomnia and is increasingly used in research as an instrument to examine treatment response. The Insomnia Severity Index has been shown to have excellent internal consistency in community samples (Cronbach α=.90).

The Glasgow Sleep Effort Scale [36] reviews sleep effort. Sleep effort is a concept that explains a person's voluntary effort to control a partially involuntary process, namely falling asleep. The Glasgow Sleep Effort Scale consists of 7 items, for example, "I put too much effort into sleeping when it should come naturally," rated on a 3-point scale ("very much", "to some extent", and "not at all"). Internal consistency was reported as fair, with Cronbach α=.77 [36].

The Self-Efficacy for Sleep Scale [37] assesses the "belief people have in their ability to participate in certain behaviors needed to promote their health" [46,47]. The Self-Efficacy for Sleep Scale is a 9-item measure of how confident an individual is to carry out a variety of behaviors related to sleep, for example, "fall asleep at night in less than 30 minutes." Items are scored on a 5-point scale, with higher scores being indicative of increased sleep self-efficacy. The SES has fair internal consistency (Cronbach α=.71) [48].

The Sleep Locus of Control Scale [38] is an 8-item measure that examines the internal sleep locus of control, the belief that sleep outcomes are dependent on one's behavior on a 6-point Likert scale. The Sleep Locus of Control Scale contains 2 subscales, internal locus of control and chance sleep locus, and is reported to have internal consistency of Cronbach α=.72 (internal locus of control) and .59 (chance sleep locus) [38].

Hyperarousal will be assessed using the Pre-Sleep Arousal Scale (PSAS) [35]. The PSAS measures cognitive and somatic symptoms of arousal before falling asleep using 2 subscales. The 2 subscales each consist of 8 items. The items are rated using a 5-point Likert scale, with scores ranging from 1 to 5. The internal consistency of the PSAS has been reported as Cronbach α=.67 for the cognitive and .84 for the somatic subscales in normal sleepers and .76 and .81, respectively, for individuals with insomnia.

The Morningness-Eveningness Questionnaire [40] assesses chronotype. The 19-item scale was developed to examine individuals' alertness at specific times of the day. The 19-item scale examines preferences in sleep and wake times and what times of the day subjects feel most alert. The Morningness-Eveningness Questionnaire has shown sufficient internal consistency for the original (Cronbach α=.82) as well as for the reduced version [49].

The Sleep-Related Behaviors Questionnaire [39] is a 32-item instrument that assesses safety behaviors relating to sleep; for example, "I miss or cancel appointments (daytime or evening)." Items are rated on a 5-point scale ranging from 0 (meaning "almost never") to 4 (meaning almost always"). The questionnaire has high internal consistency (Cronbach α=.92).

Participants will wear an actigraph and complete a sleep diary over 96 hours (72 hours plus an additional 24 hours to account for nonadherence wear time). Actigraphic sleep assessment will assess sleep onset latency, wake-after-sleep onset, total sleep

time, and the number of nighttime awakenings. The Actigraph model wGT3X-BT activity monitor (ActiGraph) will be used. Actigraphy has been recognized by the American Academy of Sleep Medicine as an appropriate method for assessing sleep. However, when compared with polysomnography, actigraphy has lower accuracy in detecting wake periods; especially in individuals with poor sleep quality [50]. The actigraphy data will be manually scored along with a sleep diary. This process was recommended by Boyne et al [51] to optimize agreement with polysomnography-measured sleep-wake. Additionally, the Choi algorithm will be used to differentiate between wear and nonwear times, which more accurately estimates time spent sedentary than other algorithms [52]. The sleep diary is a modified version of the Consensus Sleep Diary [53], which, in addition to the questions covered by the Consensus Sleep Diary, records the total duration of all daytime naps, how many times the study participant got up during the night, what time they had planned to wake up at, and whether they took any sleep medication.

Participants will be grouped into 4 sleep groups: noncomplaining good sleepers, complaining good sleepers, noncomplaining poor sleepers, and complaining poor sleepers. Participants will be grouped based on their actigraphy results and sleep complaint status (complaining versus noncomplaining sleepers), with participants appraised as poor sleepers if their sleep onset latency or wake-after-sleep onset is ≥31 minutes, 3 times or more during the recording period (as per actigraph recording). A participant will be considered a complaining sleeper if they report having had a sleep problem (eg, trouble falling asleep) for a minimum of 6 months at baseline data collection [5,54].

Procedure

Participants who express an interest in participating will be contacted to make an appointment for a screening call. During the screening call, potential participants will be provided with information about the study and will be assessed against the eligibility criteria. Once a potential participant is confirmed to be eligible, they will complete, sign, and return the consent form. Upon study commencement, potential participants will be provided with an individual web-based link to the Qualtrics questionnaire battery (Qualtrics XM Platform software, Qualtrics). Once the questionnaire has been completed, actigraphs will be posted to participants using a courier service. Delivery and collection times will be arranged before dispatch at a time convenient for the participant. Where courier services are not available, the sleep watches will be posted by registered express mail, including a prepaid self-addressed return envelope. Study participants will be required to wear an actigraph on their nondominant wrist for 96 hours, except when they take a bath, have a shower, go swimming, or undergo any other activity that would result in them submerging the actigraph in water. They will also be instructed to record the exact time when they remove the actigraph and, subsequently, when they reattach the actigraph to their wrist in their sleep diary. This allows for accurate matching of the actigraph-estimated wear and nonwear times with the sleep diary. The sleep diary will be completed concurrently to record bedtimes, sleep and wake times, frequency and duration of nocturnal awakenings, rise times, daytime naps, and nonwear times, and will be returned with the actigraph after the measurement has been completed. A printed copy of the sleep diary will allow the participant to keep the diary on their bedside table so the relevant sections can be completed upon going to bed and waking up in the morning.

Following the baseline assessment, including the recording of demographic information and sleep complaints, the administration of the questionnaires, and actigraphy measurement, all groups will receive identical instructions for the web-based CBT-I program. Participants will be required to complete the 4 sessions plus homework of the program within 4 weeks. Participants will receive weekly email reminders from the principal investigator to confirm the completion of each of the 4 CBT-I modules. Once the completion of the CBT-I program has been confirmed with the participant, actigraphy, sleep diary, and questionnaire measurements will be repeated posttreatment. The study process is shown in Figure 1.

Figure 1. Study process flowchart. CBT: cognitive behavioral therapy; CG: complaining good; CP: complaining poor; NG: noncomplaining good; NP: noncomplaining poor; SOL: sleep onset latency; WASO: wake-after-sleep onset.

Study process flow chart

```
┌─────────────────────────┐
│ Consumer involvement –   │──────────────────────┐
│ study review            │                      │
└─────────────────────────┘                      ▼
             │                          ┌──────────────────────┐
             ▼                          │ Not eligible         │
┌─────────────────────────┐            │                      │
│ Recruitment: Older adults│            │ Thank you email      │
│ with and without self-   │            └──────────────────────┘
│ reported poor sleep      │
└─────────────────────────┘
             │
             ▼
┌──────────────────────────────────────────────┐
│ Eligible                                       │
│  • Aged 60-80 years or over                    │
│  • No severe psychiatric/ cognitive disorder   │
│  • No sleep disorder other than insomnia       │
│  • No regular shift work in the past year      │
│  • No epilepsy or high fall risk               │
└──────────────────────────────────────────────┘
             │
             ▼
┌──────────────────────────────────────────────┐
│ Phase 1:                                       │
│  ➤ Demographics, including assessment of sleep │
│    complaint                                   │
│  ➤ Actigraphy and sleep diary over 72 (96)    │
│    hours                                       │
│  ➤ Complete questionnaires via Qualtrics       │
└──────────────────────────────────────────────┘
             │
             ▼
┌──────────────────────────────────────────────┐
│ SOL or WASO of ≥31min, for ≥3x week = poor    │
│ sleeper (actigraphy)                           │
│ Self-reported sleep problem ≥6 months =        │
│ complaining sleeper (demographic               │
│ questionnaire)                                 │
│                                                │
│ Participants divided into 4 sleep groups based │
│ on objective sleep (good vs poor) and          │
│ complaint status (complaining vs               │
│ noncomplaining)                                │
└──────────────────────────────────────────────┘
```

NG	CG	NP	CP
- Complaint	+ Complaint	- Complaint	+ Complaint
- Objective poor sleep	- Objective poor sleep	+ Objective poor sleep	+ Objective poor sleep

```
┌──────────────────────────────────────────────┐
│ Phase 2: 4-week online CBT sleep intervention  │
│ (This Way Up). Participants will receive       │
│ weekly reminders.                              │
└──────────────────────────────────────────────┘
             │
             ▼
┌──────────────────────────────────────────────┐
│ Post treatment                                 │
│  ➤ Actigraphy and sleep diary over 72 (96)    │
│    hours                                       │
│  ➤ Participants will be asked to complete      │
│    questionnaires via Qualtrics                │
└──────────────────────────────────────────────┘
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Description of Intervention

There are a variety of web-based CBT-I courses, mostly developed in the United Kingdom or the United States. One exception is the "This Way Up—Managing Insomnia" program [55,56]. This treatment course was created by a team of clinical psychologists and psychiatrists at the Clinical Research Unit for Anxiety and Depression, which is run by the University of New South Wales and St Vincent's Hospital in Sydney. The free self-help program consists of 4 lessons in a comic-based format. Lesson 1 provides background knowledge about sleep and insomnia and which factors are conducive to good sleep and which ones are related to insomnia (sleep hygiene). Lessons 2 and 3 address the management of thoughts and behaviors that interfere with sleep (sleep restriction, stimulus control, and cognitive therapy). The sleep restriction protocol aims at

decreasing nighttime awakenings by limiting the time a person spends in bed [57]. Initially, the prescribed time in bed corresponds with the average total sleep time as measured in the week prior to initiating the sleep restriction protocol, with a minimum time in bed of 5.5 hours. Time in bed is then gradually increased until the amount of nighttime sleep achieved is sufficient for individual requirements. Lesson 4 focuses on relaxation techniques. The program cannot be individually tailored to the patient's specific sleep difficulties but provides broad topic coverage of the most common factors present in insomnia (eg, waking too early), and program participants are advised that not all themes covered may be relevant to their circumstances.

Each lesson takes about 20 minutes to complete, with additional compulsory homework. A unit only registers as completed once the homework has been downloaded. It is recommended that a user completes 1 lesson every 1-2 weeks. However, the system will not grant access for less than 5 days between modules. Reminders are emailed or sent by text message automatically once a new session becomes available, and there is also the option to set a web-based appointment for the next course module. In addition to the course unit and homework, participants are required to complete a sleep diary. Upon completion of the course, an extra 12 months' access is made available for additional practice. The program is available only to individuals who live in Australia.

The program's easy-to-access platform makes it suitable even for individuals with low eHealth literacy. This could be important when providing web-based CBT-I to older populations, even though older adults are increasingly familiar with using the internet and social media. A recent report exploring the attitudes and behaviors of adults aged 70 years and older pointed out that 99% of individuals have searched for information on the internet, 65% of them post on or read from social media, and 82% of them who are on social media use Facebook [46].

Participants with moderate to extremely severe total scores on any scale of the DASS-21 (Depression, Anxiety, and Stress Scale-21) will receive a letter outlining the results and will be encouraged to discuss these with their health care professionals. This is considered an advisable measure of duty of care. However, while the DASS-21 measures the emotional states of anxiety, stress, and depression over the previous week, it is based on a dimensional rather than a categorical conception of disorder and should not be used as a diagnostic tool [58]. Participants with ongoing or severe insomnia, stress, anxiety, or depression symptoms will be advised to contact the university's Psychological Services Centre or community services such as Lifeline.

Consideration will also be given to the delivery of a sleep restriction module as part of the web-based CBT-I. Any contraindications to CBT-I usually arise from the use of the sleep restriction element and occur when an individual has epilepsy, bipolar disorder, or is at high risk of falling, and can also exacerbate symptoms in those with excessive daytime sleepiness, for example, in individuals with sleep apnea [59]. Participants will be screened for obstructive sleep apnea risk

using the STOP-Bang questionnaire and will be asked if they have ever been diagnosed with epilepsy or severe psychiatric (eg, bipolar disorder) or cognitive impairment (eg, mild cognitive impairment). Participants will also be questioned about their fall risk, including queries about whether they have had a fall in the past year, feel unsteady when standing or walking, or if they are worried about falling. Participants with epilepsy, bipolar disorder, cognitive impairment, a sleep apnea diagnosis, or a high fall risk will be excluded from the study. Individuals with any other psychiatric disorder (eg, borderline personality disorder) will be excluded depending on their active symptomatology and current management of the condition, following consultation with the clinical psychologist on the research team. Cognitive disorders and personality disorders will be assessed through self-report.

Statistical Analysis

An a priori power analysis using the program G*Power was performed to assess whether the study will have enough power to detect significant differences in sleep outcomes between the study groups [60]. We calculated that a sample size of 40 would be sufficient to detect this size effect. In order to account for attrition rates and missing data, a minimum of 60 participants will be recruited for the study.

Since sleep complaint status (sleep problem, eg, initial insomnia, for a minimum of 6 months) is used to classify participants as complaining or noncomplaining sleepers, multivariate ANOVA will be conducted separately to examine subjective and objective sleep quality for the 4 sleep groups. The multivariate ANOVA enables the analysis of multiple continuous dependent variables simultaneously (eg, sleep onset latency, wake-after-sleep onset, total sleep time, and the number of nighttime awakenings). In addition, a mediation analysis will be performed to determine whether sleep improvements following web-based CBT-I are the result of changes in sleep-related beliefs or other factors in older adults living in the community. Mediation analysis will be carried out using the bootstrapping method in the Hayes Process Macro for mediation, moderation, and conditional analysis for SPSS (version 28.0; IBM Corp) [61,62].

Actigraphy measures will be scored using the Cole-Kripke algorithm, which is suitable for use with older populations [63] and using ActiLife software (ActiLife 6 software, Version 6.13.1, ActiGraph). The autoscored data will be manually compared with the sleep diary to determine any incongruence between the actigraph measurements and the sleep diary.

Results

Study recruitment was completed in March 2021, with a total of 65 participants. In addition, a feasibility study to assess whether the study format was acceptable for participants aged 60-80 years was conducted from October 2019 to 2020.

Data analysis for phase 1 was finished in December 2021, and data analysis for phase 2 was finalized in July 2022. The results for phase 1 have been submitted for publication in March 2022, and those for phase 2 will be submitted by the end of December 2022.

Discussion

Expected Findings

We anticipate that our study will highlight the variability of sleep patterns in older adults and the factors that impact their sleep outcomes following CBT-I. Since the mid-1990s, the need to examine the asynchronous sleep pattern characterized by a mismatch between objective sleep quality and subjective sleep complaint has been highlighted in the literature [7-9,64]. Research to date has indicated that higher levels of distress and maladaptive cognitions, particularly as displayed by complaining sleepers with a subjective sleep complaint, show a stronger correlation with daytime impairment than with objective sleep disruption, and that individuals with subjectively poor sleep report lower sleep quality even if their objective sleep is within acceptable parameters [65]. In addition, the prevalence of complaining good sleepers appears to be high in older adults [26].

The COVID-19 pandemic and its associated impact on mental and physical health outcomes add an additional dimension to the need to investigate sleep health and the role sleep perceptions play in insomnia. Sella et al [66] stressed in their recent paper that during the COVID-19 pandemic, changes in self-reported sleep quality in older adults were predominantly associated with changes in dysfunctional sleep beliefs. Furthermore, the pandemic has brought the need for web-based health services, such as digital CBT-I, to the forefront. Recent systematic reviews suggest that CBT-I reduces dysfunctional sleep beliefs, which contributes to the improvement of insomnia symptoms [27,67].

In our study, we will use actigraphy to measure objective sleep outcomes. Actigraphic sleep assessment can provide an accurate estimate of sleep and wake patterns, even when compared with the gold standard of sleep measurement, polysomnography. It has been recommended for the estimation of sleep parameters in adults with insomnia [68], but the limitation of actigraphy is that it underestimates total sleep time [69]. However, research has also indicated that actigraphy is sensitive in detecting treatment effects [70], making it suitable for assessing the sleep outcomes following CBT-I.

This study will add to the knowledge base regarding CBT-I outcomes in an older adult population and will help ascertain whether asynchronous sleep patterns and sleep appraisal as well as associated maladaptive sleep beliefs, high arousal, and other cognitive factors play a role in this process.

Conclusions

It is crucial to examine sleep quality in older adults as this age group shows a high rate of sleep disturbances. The relatively high prevalence of older adults who are complaining good sleepers is of particular concern. Individuals with a subjective sleep complaint often report worse outcomes regardless of how well they sleep, which suggests that insomnia might not arise from sleep deprivation but could be associated with how sleep quality is perceived by the individual.

To address these concerns and examine the prevalence of uncoupled sleepers specifically in the Western Australian context, this study will assess subjective and objective sleep quality in community-dwelling older adults aged 60-80 years and examine the role of cognitive processes, such as dysfunctional sleep beliefs, in mediating the treatment outcomes of a digital cognitive behavioral therapy program for insomnia.

Authors' Contributions

YK designed the study protocol and wrote the initial manuscript draft. MS, LW, and EQ contributed to the study design. All authors made substantial contributions to revising the initial manuscript and read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CBT-I: cognitive behavioral therapy for insomnia
DASS-21: Depression, Anxiety and Stress Scale-21
DBAS-16: Dysfunctional Beliefs and Attitudes about Sleep
PSAS: Pre-Sleep Arousal Scale
STOP-Bang: snoring, tiredness, observed apnea, high BP, BMI, age, neck circumference, and male gender

Protocol

Treatment of Infected Tibial Metaphyseal Nonunions Using the Ilizarov Method: Protocol for a Prospective Nonrandomized Study

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Abstract

Background: The management of infected metaphyseal nonunion of the tibia is devastating, especially when associated with significant bone loss, poor soft tissues, draining sinuses, axial deformity, knee or ankle joint stiffness, limb discrepancy, and multiresisted pathogens. A systematic review, performed recently by the primary investigators but not yet published, yielded the lack of studies in the field and the huge heterogeneity of the presented results. We found several bias and controversies such as no clear definition of the exact part of the tibia where the nonunion was located, the pathogen causing the fracture-related infection, the number of previous interventions and time to presentation, and the exact type of treatment methods including the use of muscle flaps or bone grafting. Time to final union as a functional score is another important but missing data.

Objective: The proposed study is designed to evaluate a sufficient number of patients with infected metaphyseal tibial nonunions using various general health, functional, and bone scores.

Methods: This prospective clinical trial study, with a minimum follow-up period of 36 months, focuses on the effectiveness of the Ilizarov method after radical nonunion debridement and targeted antibiotic therapy in patients with infected metaphyseal tibial nonunions. The primary outcomes would be the definite healing of nonunion and infection-free results. Secondary outcomes would be limb alignment and discrepancy, alteration in the patient's quality of life, and functional results. A power analysis calculated a minimum of 11 patients to obtain statistical power, but we aim to include at least 25 patients. Limb discrepancy, clinical validation of infection eradication and fracture healing, radiographic validation, and patient-reported outcome measures will be highlighted and correlated. Statistical analysis of the results will offer data missing from the literature so far. Measurements are scheduled at specific times for each patient: preoperatively, 3 and 6 months postoperatively, 1 month after Ilizarov frame removal, and once per semester afterward until the end of the follow-up period (minimum 36 months). Laboratory evaluation will be assessed once per month. Any complication will be reported and treated when it occurs.

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Results: The trial has already started. It was funded in June 2020. As of May 2022, 19 participants have been recruited and no major complications have been noticed yet. Data analysis will be performed after data collection ends, and results will be published afterward.

Conclusions: An infected metaphyseal tibial nonunion is a rare condition with limited treatment options and many controversies. There is no consensus in the literature about the best treatment strategy, and this lack of evidence should be fulfilled.

Trial Registration: International Standard Randomized Controlled Trial Number (ISRCTN) 30905788; https://www.isrctn.com/ISRCTN30905788

International Registered Report Identifier (IRRID): DERR1-10.2196/39319

Introduction

Background

The infected nonunion of the tibia is always a challenging problem for the orthopedic surgeon and can pose a substantial burden on both patients and their families [1,2]. According to Schade et al [3], who performed a systematic review on 17,073 patients with open tibia fractures, the rates of infection, nonunion, and subsequent amputation were 22%, 11%, and 16%, respectively, with a total hospitalization cost between £356 (US $440) to £126,479 (US $156,313) and an average length of hospital stay of 56 days. Hendrickx et al [4], in their systematic review of 8110 patients treated with intramedullary nailing for a tibial shaft fracture, reported a nonunion rate of 11% and an incidence of early deep infection of 3%.

In a recent systematic review of 41,429 patients with tibial fractures, Tian et al [5] defined the main predisposing factors to nonunion: aged >60 years, male gender, BMI >40, smoking, diabetes, nonsteroidal anti-inflammatory drug or opioid use, fracture of the middle and distal tibia, high-energy fracture, open fracture, Gustilo-Anderson grade IIIB and IIIC, Müller AO type C, open reduction, fixation model, and infection. The authors found also that the prevalence of nonunion was 6.8% and that closed reduction and minimally invasive percutaneous plate osteosynthesis had the lowest risks of nonunion. Regarding the infection rates, a machine learning algorithm to identify patients with tibial shaft fractures at risk for infection after operative treatment was published recently, which identified seven stratified risks for infection: (1) Gustilo-Anderson or Tscherne classification, (2) bone loss, (3) mechanism of injury, (4) multitrauma, (5) AO Foundation/Orthopaedic Trauma Association (AO/OTA) fracture classification, (6) age, and (7) fracture location [6]. Metsemakers et al [7] tried to identify individual risk factors for both deep infection and nonunion or malunion after intramedullary nailing in the tibia and failed to identify any specific multifactorial model; polytrauma and primary external fixation were the only risk factors for nonunion and deep infection, respectively.

The incidence of infection and associated risk factors, especially for the fractured distal and proximal tibia metaphysis, are scarce in the literature. Parkkinen et al [8] reported a 5.2% incidence of deep infection (82% acute) on 655 proximal tibial fractures treated with open reduction and plate fixation; 50% required muscle flap coverage, and 5 patients (15%) eventually underwent above-the-knee amputation. The main risk factors included aged ≥50 years, obesity, alcohol abuse, AO/OTA–type-C fracture, and a previous fasciotomy. Bleeker et al [9] performed a systematic review on how we should personalize surgical treatment for the treatment of distal tibial fractures using either intramedullary nailing or plate fixation; 1332 patients were analyzed, including 10 randomized clinical trials (n=873) and 5 observational studies (n=459). Plating led to a lower risk for malunion but higher risk for infection (8%). No differences were detected regarding nonunion, subsequent reinterventions, and functional outcomes.

A narrative systematic review, registered on International Prospective Register of Systematic Reviews (PROSPERO; CRD42020205781) but not yet published, regarding septic metaphyseal tibial nonunion and their treatment strategy in adult populations, yielded the lack of studies in this field and the huge heterogeneity of the results. Moreover, through these studies, there was no clear definition of the exact part of the tibia where the nonunion was located, the pathogen causing the fracture-related infection (FRI) and nonunion, the number of previous surgeries and time to presentation, the exact type of treatment method, the use of muscle flaps or bone grafting, time to final union and eradication of infection, and finally, the report and management of complications. Above all, the absence of preoperative and postoperative functional and bone scores was the main cause that prevented us to extract safe conclusions about safety and efficacy. The limited number of patients (<100) with infected metaphyseal nonunions that were finally included in this review reflects the rarity and predicament of this condition.

Aims of the Study

The proposed prospective study—Treatment of Septic Metaphyseal Nonunion of Tibia Using the Ilizarov Method (SePseT Ilizarov)—is designed to evaluate multiple clinical, radiological, and quality-of-life parameters in patients with infected tibial metaphyseal nonunions managed with the Ilizarov method and proper antibiotic treatment.

The *primary outcomes* of the study are bifold: (1) definite bone healing of the nonunion and (2) the absence of recurrent infection. The course of bony treatment will be further analyzed regarding complications and additional surgical interventions (before frame removal) until the end point, namely, healing or

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definite failure (amputation or death). The course of infection treatment will ascertain through the normalization of specific markers (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], and white blood cell count [WBC]), and the failure of antibiotic therapy will be defined as (1) recurrent infection with new positive cultures, (2) new sinus formation, (3) further surgical debridement, or (4) need for long-term antibiotic treatment for persistent symptoms.

Secondary outcomes will be the final limb length discrepancy (LLD), external fixation index (EFI), the Association for the Advancement of Methods of Ilizarov (ASAMI) bone and functional classification scores [10], and several patient-reported outcome measures including the American Orthopaedic Foot and Ankle Society (AOFAS) ankle-hindfoot score [11], the Knee Outcome Survey–Activity of Daily Living Scale (KOS-ADSL) score [12], the American Academy of Orthopaedic Surgeons (AAOS) Lower Limb Scale [13], the EQ-5D-3L [14], the quality-adjusted life year (QALY) Time Trade-Off [15], the Short-Form (SF) 12 and SF-6D [16,17], and finally, the 11-point Pain Numerical Rating Scale (PNRS) [18].

Methods

Trial Registration

The proposed study has been registered in International Standard Randomized Controlled Trial Number (ISRCTN; 30905788).

Ethics Approval

This study was approved by the Ethics Committee of General Hospital of Serres (No 09/21-09-2020), General Hospital of Drama (No 336/2020, 04/09/2020), and University of Patras (No 5141/38886, 20-11-2020).

Patient Consent

Informed consent will be taken from all the patients. We will obtain written consent to publish from the participants to report individual patient data.

Design

We will enroll patients aged >18 years with infected metaphyseal nonunion of the proximal or distal tibia demonstrating the absence of healing for longer than 9 months and no observation of healing during the previous 3 months. Consent forms will be freely signed by the participants after a thorough explanation provided by lead investigators, and confidentiality is guaranteed according to General Data Protection Regulation rules. Patients will be excluded if (1) there is adjacent knee or ankle joint infection, (2) the bony defect once debrided exceeds 7 cm, (3) the foot is insensate, (4) there is a pathological fracture, and (5) there is evidence of hormonal disorders or diseases that affect bone healing.

Evaluation

At presentation, the details and type of initial injury; previous surgical interventions and medical treatments; associated illnesses; other injuries; nicotine, alcohol, and drug abuse; and the affirmation of infection according to FRI criteria [19,20] will be documented. These FRI criteria can be either *confirmatory*—(1) fistula, sinus or wound breakdown; (2)

purulent drainage from the wound or presence of pus intraoperatively; (3) phenotypic confirmation of the existence of the germ in at least two different deep tissue cultures; or (4) presence of microbes in deep tissue taken intraoperatively, as confirmed by histopathology—or *suggestive*, such as (1) clinical signs (pain, local redness, local swelling, increased local temperature, and fever >38.3 °C); (2) radiological signs (osteolysis, implant loosening, sequestration, bone healing arrest, and periosteal bone formation); (3) presence of pathogenic microorganism in a culture from the deep layer; (4) elevated inflammatory markers (ESR, WBC, and CRP); (5) persistent wound drainage after the first days, increasing or new onset; and (6) new onset of joint effusion in patients with fractures.

During physical examination, the patients will be screened for LLD, ankle and knee range of motion, pathological motion at the fracture site, neurovascular deficiency, and the condition of soft tissues. Long leg standing radiological views, computed tomography or magnetic resonance imaging if indicated, and 3-phase bone scintigraphy will be ordered to establish nonunion, bone defect, and osteomyelitis. Regarding bone deficit, the nonunion would be classified using the criteria of Paley [10] into type A when the defect is <1 cm (A1: atrophic flexible; A2-1: hypertrophic stiff, without deformity; and A2-2: hypertrophic stiff, with deformity) or type B when the defect is >1 cm (B1: bone deficit without shortening; B2: bone deficit and shortening without the dimension of the descendants; and B3: bone deficit and shortening).

Intervention

After careful preoperative planning, the patients will be informed about the scheduled treatment plan and give their informed consent. Intraoperatively, all previous implants will be removed, and a radical debridement of avascular or infected bone and adjacent necrotic soft tissues will be performed such that bleeding bone ends will remain. The application of the frame will follow the well-established principles of Ilizarov with various ways depending on the degree of deformity: monofocal compression, monofocal distraction, bifocal acute compression, and gradual distraction or bone transport. Corticotomy will be performed proximally or distally, as indicated by the location of nonunion. A healthy soft tissue envelope will be achieved either with direct skin closure or using local muscle flaps; at least 5 samples of deep tissues will be obtained for culture and histopathology. The Cierny classification [21] will be used to classify the type of osteomyelitis: Type I (medullary), Type II (superficial), Type III (localized full-thickness cortical involvement), and Type IV (diffusely involves the entire circumference of a segment of the bone). All patients will discontinue any previous antibiotic therapy for at least 14 days before surgery to aid microbiologic diagnosis. Broad spectrum antibiotics (vancomycin-meropenem) will be administered intraoperatively followed by culture-specific antimicrobial therapy for at least 6-8 weeks. After the application of the Ilizarov frame, patients will be closely monitored every week and gradually every month in the outpatient clinic of the mentioned hospital. Distraction will be started on the seventh day at the rate of 1 mm/day, with 4 increments of 0.25 mm each day. Patients will be allowed to have full weight bearing with crutches for the first postoperative day, and early range of

Power Analysis and Statistical Methods

To calculate the sample size of this study, we obtained information from the study of Jayadevappa et al [22] who assessed the usability of minimal important difference (MID) and minimal clinically important difference for measuring meaningful changes in disease-specific and generic health-related quality-of-life outcomes. Our primary outcomes, fractures healing and infection eradication, are not countable. As our patients will have different sites of nonunion (proximal or distal), the joint-specific outcome instruments (AOFAS and KOS-ADSL) will be not feasible. Instead, generic health-related quality-of-life outcomes will be more appropriate, namely, SF-6D and EQ-5D; the SF-6D is scored on a 0.29 to 1.00 scale and the EQ-5D on a –0.59 to 1.00 scale, with a score of 1.00 on both indicating "full health." In the study of Jayadevappa et al [22], the mean MID for the SF-6D was 0.041 (range 0.011-0.097) and the mean MID for the EQ-5D was 0.074 (range –0.011 to 0.140). We assume that the continuous data are parametric—that is, all scores (questionnaire response) will follow a normal distribution; thus, Student 2-tailed t test can be applied. According to Walters et al [23], the scores are mainly in the "small to moderate" range using the criteria of Cohen [24] regarding the standardized response means (SRMs) of the questionnaire responses. Cohen's criteria (in context of the one-sample t test) defines a small effect size at around d=0.2 and a medium effect size at around d=0.5, with d being the standardized difference of the means. We are mainly concerned with the comparison of the actual SRMs to the value 1, denoting "full health." We call this concept "distance to health," and in terms of statistical power analysis, we approach it with a one-sample t test, which compares an SRM to 1. Statistical significance was taken at <.05 by default, and the results are summarized in Figure 1. The implementation was held with the R software (package *pwr*; R Foundation for Statistical Computing) and the RStudio integrated development environment; both are open-source products. The required number of patients is from 20 to 30 for a power of 90% (Figure 1 and Table 1).

Figure 1. Power analysis—"distance to health" SRM: the statistical power of the study and number of the requiring patients for inclusion in the study. SF: Short-Form; SRM: standardized response mean.
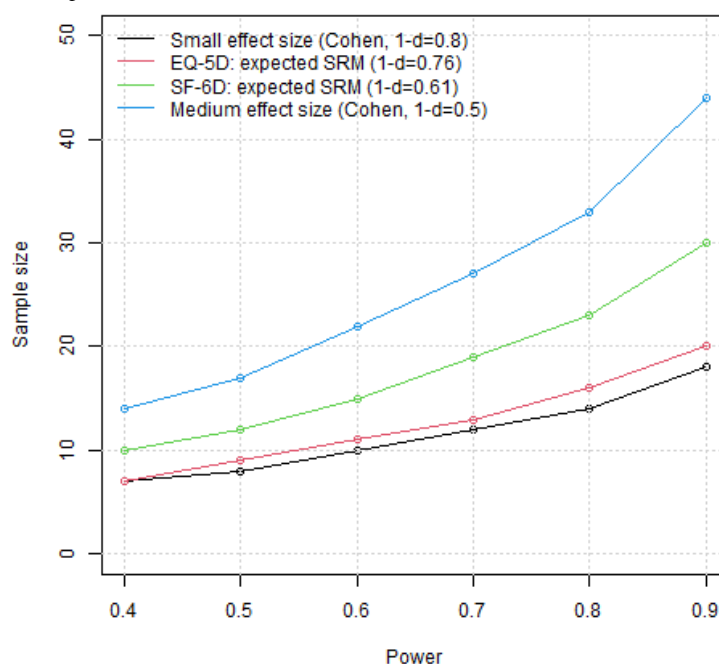
Table 1. Power analysis—table of data.

	Power (%), number of patients					
	40	50	60	70	80	90
Small effect size (Cohen, $1 - d = 0.8$)	7	8	10	12	14	18
EQ-5D: expected SRM[a] ($1 - d = 0.76$)	7	9	11	13	16	20
SF-6D[b]: expected SRM ($1 - d = 0.61$)	10	12	15	19	23	30
Medium effect size (Cohen, $1 - d = 0.5$)	14	17	22	27	33	44

[a]SRM: standardized response mean.

[b]SF: Short-Form.

Values for subjective and objective outcomes will be presented as means with SDs or ranges. The outcome variables are union versus nonunion, the recurrence of infection or not, PNRS, ASAMI criteria, LLD, time to fracture healing, EFI, and the comparison between preoperative and final outcome scores (joint specific and generic). To deal with a set of scores (questionnaire responses) measured longitudinally, assuming normality, repeated measures ANOVA will be used to assess a comparison among the consecutive (paired) distributions. Bivariate comparisons will need to use Student paired 2-tailed *t* test. Prospective factors that have an effect on the aforementioned trajectories will be assessed with analysis of covariance; an alternative solution of the latter will be to use ANOVA on the differences of the scores (after – before).

Outcome Assessment

The patient's clinical, radiological, and functional outcomes at the end of the study period (minimum 3 years after the frame application) will be compared to the preoperative values. The main outcomes would be the definite healing of the nonunion and the eradication of infection. Inability to control the infection, joint arthrodesis, amputation, and death would be recorded as failures.

Various patient-reported outcome scores will be assessed preoperatively and at predetermined time intervals until the final outcome (Table 2). For the subjective clinical outcome, we intent to use 2 joint-specific scores, the AOFAS ankle-hindfoot score [11] and the KOS-ADSL score [12], and several general health questionnaires including the AAOS Lower Limb Scale [13], the EQ-5D-3L [14], the QALY Time Trade-Off [15], the SF-12 (physical and mental component scores) and SF-6D [16,17], and the PNRS [18]. For the functional outcome, we will use the LLD, EFI, and ASAMI bone and functional classification scores [10]. The latter is scored as excellent, good, fair, and poor. An excellent *bone result* equals to union, no infection, deformity of less than 7°, and tibia discrepancy <2.5 cm, whereas an excellent *functional result* means an active individual without limp, equinus rigidity, soft-tissue dystrophy, and pain. Finally, a detailed laboratory testing of kidney and liver function will be performed tactically in cases with prolonged antibiotic therapy. Protentional subgroups could be formed according to demographics, anatomic location, and functional scores. Trial results will be published after the end of the trial to enrich literature about this topic.

Table 2. Timetable and description of the preoperative and follow-up evaluation.

Outcome measure	Definition	Score	Preoperative evaluation	3-month follow-up	6-month follow-up	1 month after Ilizarov removal	Every 6 months up to the end of follow-up period (minimum 3 years)
Patient-reported							
PNRS[a]	Pain Numerical Rating Scale	0-10	✓	✓	✓	✓	✓
AOFAS[b] ankle-hindfoot score	Foot and ankle–specific score	0-100	✓			✓	✓
KOS-ADLS[c]	Knee-specific score	0-70 and 0-55	✓			✓	✓
AAOS[d] Lower Limb Scale	General lower limb condition	0-80	✓			✓	✓
EQ-5D-3L	Health-related quality of life	5-15 (less the better)	✓	✓	✓	✓	✓
QALY[e] Time Trade-Off	Quality of life	N/A[f]	✓			✓	6 months after Ilizarov removal
SF-12[g] and SF-6D	General health questionnaire and QALY from the SF-12	Physical and mental component scores	✓	✓	✓	✓	6 months after Ilizarov removal
Objective measures							
Limb discrepancy	Limb length normalization is one of the goals (fracture healing and infection eradication are the others)	N/A	✓	✓	✓	✓	✓
Radiographic evaluation of bone healing	Fracture union and restoration of bone axis	N/A	✓	Every month	Every month	Every month	✓
External fixation index	Time in external fixation / length of bone regenerated (months/cm)	N/A		After Ilizarov removal	After Ilizarov removal	After Ilizarov removal	
Laboratory infection markers (CRP[h], WBC[i], ESR[j], liver and kidney function)	Comorbidities and side effects due to the antibiotic therapy	N/A	✓	Every month	Every month	Every month	✓
ASAMI[k] scoring system (bone and functional)	Bone quality and functional results	Excellent, good, fair, or poor	✓			✓	✓
Complications	N/A	N/A	Intraoperative	Reported each and any time they appeared	Reported each and any time they appeared	Reported each and any time they appeared	Reported each and any time they appeared

[a]PNRS: Pain Numerical Rating Scale.

[b]AOFAS: American Orthopaedic Foot and Ankle Society.

[c]KOS-ADLS: Knee Outcome Survey- Activity of Daily Living Scale.

[d]AAOS: American Academy of Orthopaedic Surgeons.

[e]QALY: Quality Adjust Life Year.

[f]N/A: not applicable.

[g]SF: Short-Form.

[h]ASAMI: Association for the Study and Application of the Methods of Ilizarov.

[i]CRP: C-reactive protein.

[j]WBC: white blood cell count.

[k]ESR: erythrocyte sedimentation rate.

Complications

Throughout the study period (3 years), all type of complications would be recorded and treated accordingly. These might include superficial pin tract infection, broken pins, transient knee or ankle flexion contracture, skin invagination or necrosis, equinus requiring Achilles tendon lengthening, ring fixator intolerance, nonunion of the docking site, refracture, late deformity of the regenerate callus, residual angular deformity, and residual LLD >2.5 cm. Any of these complications will be treated and reported accordingly. Due to the short period of the trial and the common risks of this intervention being established conditions, a data monitoring committee is not mandatory.

Results

The trial has already started. It was funded June 2020. As of May 2022, 19 participants have been recruited. Data are collected on prescheduled dates according to the protocol's timeline (Table 2), with the exception of complications, which are dealt with and recorded when encountered (no major complications have been noticed yet as of May 2022). Data analysis will be performed after data collection ends (ending time point is a minimum follow-up period of 36 months for all participants), and results will be published afterward.

Discussion

Overview

At least 25 patients will be recruited in this trial. These individuals will be followed up for a period of at least 36 months regarding not only fracture healing and infection eradication but also some other secondary outcomes; AOFAS ankle-hindfoot score, KOS-ADSL, AAOS Lower Limb scale, EQ-5D-3L, SF-12, and QALY Time Trade-Off will be assessed as patient-reported parameters. Objective measures, namely, limb discrepancy and its pre- and postoperative difference; laboratory infection makers (CRP, WBC, ESR, and liver and kidney function) and their alterations; and ASAMI (bone and functional), clinical (weight-bearing ability), and radiographic evaluation of fracture healing will be also assessed according to a preformed timetable (Table 2). As mentioned before, with any complication will be dealt with when they occur.

The statistical analysis of these parameters will provide valuable conclusions and proofs about the effectiveness and usefulness of the Ilizarov method during the treatment of septic tibial metaphyseal nonunions.

Expected Findings

At the end of this trial, we hope to see fracture healing and infection eradication for all participants. Furthermore, a significant improvement of all patient-reported outcome measures is expected. ASAMI scores, both functional and bone, should be for the vast majority at least good, and LLD should ideally be absent or close to zero. In other words, our objective is patients returning to their work and social life with a healed, infection-free tibia.

The treatment of an infected tibial nonunion entails a substantial amount of time and patient discomfort. The first step in the work-up of these cases is a well-established diagnosis. An internationally accepted definition of FRI has been recently adapted [19,20], including 2 levels of certainty around diagnostic criteria: confirmatory (infection is definitely present) and suggestive (further investigation is required to exclude the possibility of an FRI) as previously described. Except for proper antibiotic treatment, the key aspects of surgical management are a thorough debridement, irrigation, fracture stability (usually with Ilizarov frames), dead space management, and adequate soft tissue coverage, but these approaches are usually compromised by the poor soft tissue status, active draining sinuses, osteomyelitis, osteopenia, LLD, and stiffness and contractures of the adjacent joints [25-29].

The problem is even more difficult when the infected nonunion is located to the proximal or distal metaphysis. The porosity of the cancellous bone differs from that of the cortical one because of the differences in cellularity, rich blood flow, and increased contact area. Therefore, the occurrence of metaphyseal nonunion is much more uncommon but more troublesome to treat, as it is often accompanied by poor bone stock (osteoporosis), small metaphyseal bone segment, deformity, bone deficit, soft tissue lesions, and posttraumatic arthritis [30-32].

The literature is scarce regarding infected metaphyseal tibial nonunions. For example, Eralp et al [33] and Brinker and O'Connor [34] used Ilizarov frames in infected distal metaphyseal nonunions of the tibia in compression or bone transport mode in combination with antibiotic therapy and reported good results. Siboni et al [35] and Yoon et al [36] reported very good results using the induced membrane (Masquelet) technique in combination with internal or external fixation and antibiotic therapy. A narrative systematic review, performed by the primary investigators but not yet published, yielded the lack of studies in the field and the huge heterogeneity of the presented results. We found several bias and controversies, such as no clear definition of the exact part of the tibia where the nonunion was located, the pathogen causing the FRI, the number of previous interventions and time to presentation, the exact type of treatment methods including the use of muscle flaps or bone grafting, the time to final union and eradication of infection, and finally, the report and management of complications. Above all, the absence of preoperative and postoperative functional and bone scores was the main cause preventing us to extract safe conclusions about the preferable treatment method.

Limitations

The lack of control group, the location of the nonunion (proximal or distal), the size of bone defect, the condition of

soft tissues, the heterogeneity of previous surgeries and implants, the different pathogens causing the infection, the length of the antibiotic therapy and frame application, as well as the different socioeconomic and psychological status of the included patients are some of the limitations of this study. However, its strongest advantage is the prospective design with the adequate number of participants and the multimodal evaluation with joint-specific and general health scores, including QALY (Time Trade-Off and SF-6D), as opposed to what already exists in literature.

Conclusion

An infected metaphyseal tibial nonunion is a rare condition with limited treatment options and many controversies. There is no consensus in the literature about the best treatment strategy, and this lack of evidence should be fulfilled.

Data Availability

All data generated or analyzed during this study are included in the published article (and its additional files). Investigators will have limitless access to the final trial data set.

Trial results will be published after the end of the trial to enrich literature about this topic. All data will be available afterward.

Authors' Contributions

All authors contribute equally to the design of the study, analysis of the data, and methodology. AP wrote the manuscript. JL was responsible for the statistics. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AAOS: American Academy of Orthopaedic Surgeons
AO/OTA: AO Foundation/Orthopaedic Trauma Association
AOFAS: American Orthopaedic Foot and Ankle Society
ASAMI: Association for the Study and Application of the Methods of Ilizarov
CRP: C-reactive protein
EFI: external fixation index
ESR: erythrocyte sedimentation rate
FRI: fracture-related infection
ISRCTN: International Standard Randomized Controlled Trial Number
KOS-ADLS: Knee Outcome Survey–Activity of Daily Living Scale
LLD: limb length discrepancy
MID: minimal important difference
PNRS: Pain Numerical Rating Scale
PROSPERO: International Prospective Register of Systematic Reviews
SePseT Ilizarov: Treatment of Septic Metaphyseal Nonunion of Tibia Using the Ilizarov Method
SF: Short-Form
SRM: standardized response mean
QALY: quality-adjusted life year
WBC: white blood cell count

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Protocol

General Practice Patients' Experiences and Perceptions of the WiserAD Structured Web-Based Support Tool for Antidepressant Deprescribing: Protocol for a Mixed Methods Case Study With Realist Evaluation

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Abstract

Background: Research suggests that the rapid increase in worldwide antidepressant use is mainly due to a rise in long-term and potentially inappropriate use. It has been suggested that 1 in 3 antidepressant users among general practice patients are no longer experiencing clinical benefits from their medication and should commence deprescribing. However there are many barriers to antidepressant deprescribing for both patients and clinicians, which adds to the complex nature of reducing or ceasing the medication. As such, antidepressant deprescribing does not routinely occur in clinical practice. Evidence-based supports and interventions for safe and successful antidepressant deprescribing are needed to assist patients and their doctors. Interventions should also include an understanding of how an intervention works, why it works, and whom it is for.

Objective: This study aims to evaluate how the WiserAD approach to antidepressant deprescribing works, whom it is for, and the underlying circumstances by (1) examining the experiences and perceptions of WiserAD among antidepressant users, (2) identifying the underlying mechanisms of the WiserAD approach to antidepressant deprescribing, and (3) describing in what contexts and to what extent the underlying mechanisms of WiserAD are suited for antidepressant users.

Methods: A mixed methods case study with realist evaluation will be conducted among participants in the WiserAD randomized controlled trial for antidepressant deprescribing. Quantitative data will be obtained from up to 12 participants from the intervention and control arms at baseline and 3-month follow-up. Baseline data will be used to characterize the sample using descriptive statistics. Paired samples t tests will also be performed to compare responses between baseline and 3-month follow-up for participant self-management, skills, confidence and knowledge, beliefs about medicines, current emotional health, and well-being symptoms. Qualitative data from the same participants will be collected via narrative interview at 3-month follow-up. Quantitative and qualitative data will be converged to form a "case," and analysis will be conducted within each case with comparisons made across multiple cases.

Results: Recruitment of participants commenced in October 2022 and will be completed by March 2023. Analysis will be completed by June 2023.

Conclusions: To our knowledge, this will be the first realist evaluation of an antidepressant deprescribing intervention in general practice. Findings from this evaluation may assist in the implementation of the WiserAD approach to antidepressant deprescribing in routine clinical practice.

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Introduction

Background

Antidepressant use is rapidly increasing with the rate of antidepressant prescriptions doubling in western countries, such as Australia, Canada, the United Kingdom, and Iceland, over the past 10 years [1,2]. Antidepressants are the first-line treatment for depression that is considered as "more severe" (or moderate to severe depression), for which they have been shown to be effective [3-5]. Current guidelines advise that antidepressant treatment should continue for 6-12 months after remission of symptoms; however, research indicates that there has been an increase in long-term use (≥12 months) [6]. For example, in the Netherlands, long-term use increased from 30% in the period of 1995-2005 to 44% in the period between 2005 and 2015 [7] and from 45.6% to 67.4% between 2009 and 2010 in the United States [8]. Other studies have shown that the prevalence of long-term use among antidepressant users is approximately 36% and 42% in the United Kingdom [9] and the Netherlands [10], respectively.

Antidepressants are associated with common side effects such as gastrointestinal upset (for example nausea and constipation), dry mouth, and fatigue [11,12]. Research suggests that these initial side effects persist with long-term use [13], which also increases the risk of gastrointestinal bleeding [14], cardiovascular disease [15], weight gain [16], and feelings of emotional numbness [17]. Studies have shown that 1 in 3 people may be taking antidepressants without any clinical benefit [18,19], which suggests that prolonged use may place some people at unnecessary risk of adverse side effects.

The majority (86%) of antidepressants are prescribed in primary care [20], placing general practitioners (GPs) in a unique position to also deprescribe (the planned and supervised process of dose reduction or cessation [21]). However, antidepressant deprescribing can be complex and does not routinely occur in clinical practice [22,23] with reported barriers by both GPs and patients, including fear of relapse or recurrence and a lack of quality guidelines for deprescribing [24-27]. Discontinuation symptoms such as tremors, sweating, anxiety, mood swings, and electric shock sensations are also associated with stopping antidepressants [28-30] and can be confused with relapse or recurrence. As such, there is a need to support GPs and patients through the complexities of antidepressant deprescribing.

Patients have become increasingly responsible for managing the demands of their own health care [31,32] but are rarely being given the right support or information for how to do so effectively and confidently [31]. For deprescribing, GPs report only providing advice and support upon patient request [24,33]; hence, initiation of the deprescribing process is often left to the patient. However, patients who have approached their GP for antidepressant deprescribing often report becoming disillusioned with their clinician owing to a perceived lack of clinical skills and knowledge, causing them to turn to informal sources for deprescribing advice [34]. Stopping antidepressant medication without proficient GP support can increase the risk of withdrawal effects, relapse, and recommencement of medication [35,36]. As such, there is a need to determine how to best assist patients to make supported and evidenced-based decisions when stopping their antidepressant treatment in conjunction with their GP.

A web-based support tool called "WiserAD" has been developed to support patients and their GPs to safely and successfully deprescribe unnecessary antidepressant medication. WiserAD is currently being tested in a randomized controlled trial (RCT; see Textbox 1) and offers an opportunity to investigate the mechanisms and contextual factors that may influence the utility of the antidepressant deprescribing activities embedded in WiserAD. Determining how and why WiserAD works and for whom may assist in the implementation and sustainability of antidepressant deprescribing in clinical practice.

Textbox 1. Details about the WiserAD trial.

WiserAD (Kaylor-Hughes et al, unpublished data, 2022) is a patient-centered, web-based structured support tool for patients and general practitioners (GPs) to safely deprescribe antidepressants while maintaining patients' mental and physical well-being. WiserAD is based on the "5As" approach (ask, assess, advise, assist and arrange follow-up) to quitting smoking endorsed by the World Health Organization and the Royal Australian College of General Practitioners. Potential participants will be invited to consider taking part in the WiserAD randomized controlled trial by their GP clinic and will receive a follow-up call by a WiserAD team member who will provide more information about the study and check participant eligibility. Patients will be aged 18-75 years, stable on their selective serotonin reuptake inhibitor (SSRI) or serotonin–norepinephrine reuptake inhibitor (SNRI) for at least 12 months, have no or mild depressive symptoms, and have sufficient English to provide informed consent. Antidepressant users who are currently experiencing or expect to be experiencing a major life event in the next 3 months, are taking an SSRI or SNRI for a reason other than depression, are currently taking a non-SSRI or antipsychotic or another mood stabilizer, or do not have daily access to the internet will be excluded from participation. Once enrolled, participants will be randomly allocated to the WiserAD intervention or attention control group. Participants allocated to receive access to WiserAD will receive a login to the WiserAD portal, which will house their personalized tapering schedule and action plan for the management of any withdrawal symptoms, a daily mood tracker to monitor for changes in mental well-being and education about their antidepressant medication. Participants will only begin deprescribing once the tapering plan has been approved and discussed with their GP. Attention control participants will also be given a login to the WiserAD portal where they will only be able to view an antidepressant medication fact sheet. The WiserAD trial aims to recruit 312 antidepressant users from up to 30 GP clinics in Victoria, Australia.

Objectives

The aim of this study is to understand how the WiserAD approach to antidepressant deprescribing works, for whom it is, and in what circumstances can it be implemented. To realize this aim, the following research questions will be answered: What are the experiences and perceptions of WiserAD by antidepressant users? What are the key underlying mechanisms of the WiserAD approach to antidepressant deprescribing? In what contexts and to what extent do the underlying mechanisms work for antidepressant users enrolled in WiserAD?

Methods

Theoretical Approach

A pragmatic, mixed methods case study with a core convergent design that draws upon the realist evaluation principles of Pawson and Tilley [37] will be used. Realist evaluation and case study designs are complimentary as both approaches aim to investigate how and why complex interventions work, not whether they work [38,39]. Mixed methods case studies can be used to examine a phenomenon from multiple perspectives in a real-life context [39], which allows for more in-depth understanding of a research problem [40]. For example, the exploration of qualitative and quantitative responses across patients who may have different levels of exposure to WiserAD will help to determine how the intervention may be working differently in different contexts and for different people [37]. In convergent mixed method designs, qualitative and quantitative data are collected concurrently and then merged together to enable comparison across and within multiple cases [40].

Realist evaluations are theory-driven evaluations that are based on an underlying theory of how an intervention (or program) works to trigger an outcome. In a realist evaluation, an initial theory is firstly elicited, and then it is tested and refined [37]. During the elicitation phase, a set of hypotheses (or initial program theories) are articulated using the formula "C + M = O," where C refers to context, M to mechanism, and O to outcomes [37,38]. Mechanisms are underlying interactions between the resources of a program and the ways in which a participant interprets and responds to them. Mechanisms are central to realist evaluation as they provide an explanation for how and why programs produce outcomes [37,38,41]. Contexts are factors in situations that are not part of a program but interact, modify, and influence the program and how mechanisms may operate [37,38,41]. Outcomes are the intended and unintended consequences of a program and are generated by the activation of mechanisms and contexts [37].

Realist evaluations are conducted across three phases: (1) eliciting and formulating the initial program theory, (2) testing the initial program theory, and (3) building a refined program theory [37,42]. An initial program theory has already been formulated and is ready for testing in the current study. As such, phase 1 has been completed, and the focus of this protocol is how we propose to test the initial theory in phase 2 and present the results in phase 3 (see Figure 1). The RAMESES (Realist And Meta-narrative Evidence Syntheses–Evolving Standards) II reporting standards for realist evaluations [41,43] also informed the design of the 3 phases.

Figure 1. The 3 phases of a mixed methods case study with realist evaluation of the WiserAD approach to antidepressant deprescribing. GP: general practitioner.
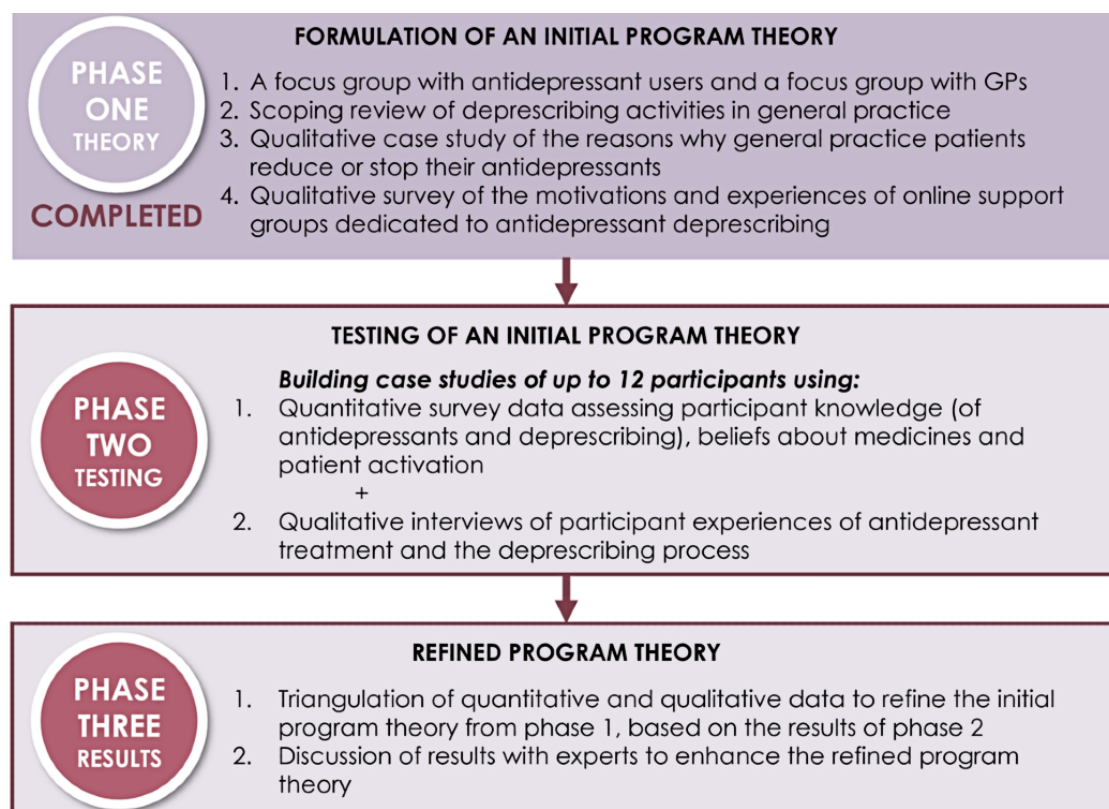
Phase 1: Eliciting and Formulating the Initial Program Theory

Phase 1 has been completed. Briefly, 4 data sources were used to develop the initial program theory. First, separate focus groups with GPs (n=8) and individuals with a history of long-term AD use (current or past; n=9) were conducted in 2019 at the Department of General Practice, University of Melbourne (Kaylor-Hughes et al, unpublished data, 2022). The focus groups were analyzed thematically to identify barriers and facilitators to antidepressant deprescribing and inform the development of the first prototype of the WiserAD intervention. Second, a scoping review of 50 deprescribing interventions being used in general practice for any condition and medication was conducted in 2021 [44]. The scoping review identified key deprescribing activities and provided additional steps to create a self-sustaining deprescribing process loop for use in clinical practice. Third, a qualitative case study examined the reasons that 178 general practice patients with depressive symptoms gave for reducing or stopping their antidepressant medications (Coe et al, unpublished data, 2022). Thematic analysis was used to identify if the reasons why antidepressant users reduce or stop using antidepressants in a naturalistic setting could inform features of an antidepressant deprescribing intervention. Finally, a 2021 web-based qualitative survey was completed by 30 members of 2 web-based support groups for antidepressant deprescribing (Abid et al, unpublished data, 2022). This survey examined the motivations of participants for joining a web-based support group as well as their past and current experiences with deprescribing.

Initial Program Theory

The findings from the studies in phase 1 have informed the initial program theory for how WiserAD may work, which is presented in the subsequent section (see Figure 2). It is expected that antidepressant users will have minimal prior knowledge of antidepressant deprescribing [26] (Coe et al, unpublished data, 2022). Participants may have also had limited clinical advice when initially being prescribed antidepressant medications with subsequent unsuccessful deprescribing attempts in the past [26] (Abid et al, unpublished data, 2022; Kaylor-Hughes et al, unpublished data, 2022). Despite the anticipated lack of deprescribing knowledge, it is anticipated that participants will be interested in or express a desire and willingness to deprescribe when presented with the opportunity [45,46].

Figure 2. Conceptual context–mechanism–outcome framework for antidepressant deprescribing. AD: antidepressant; GP: general practitioner.
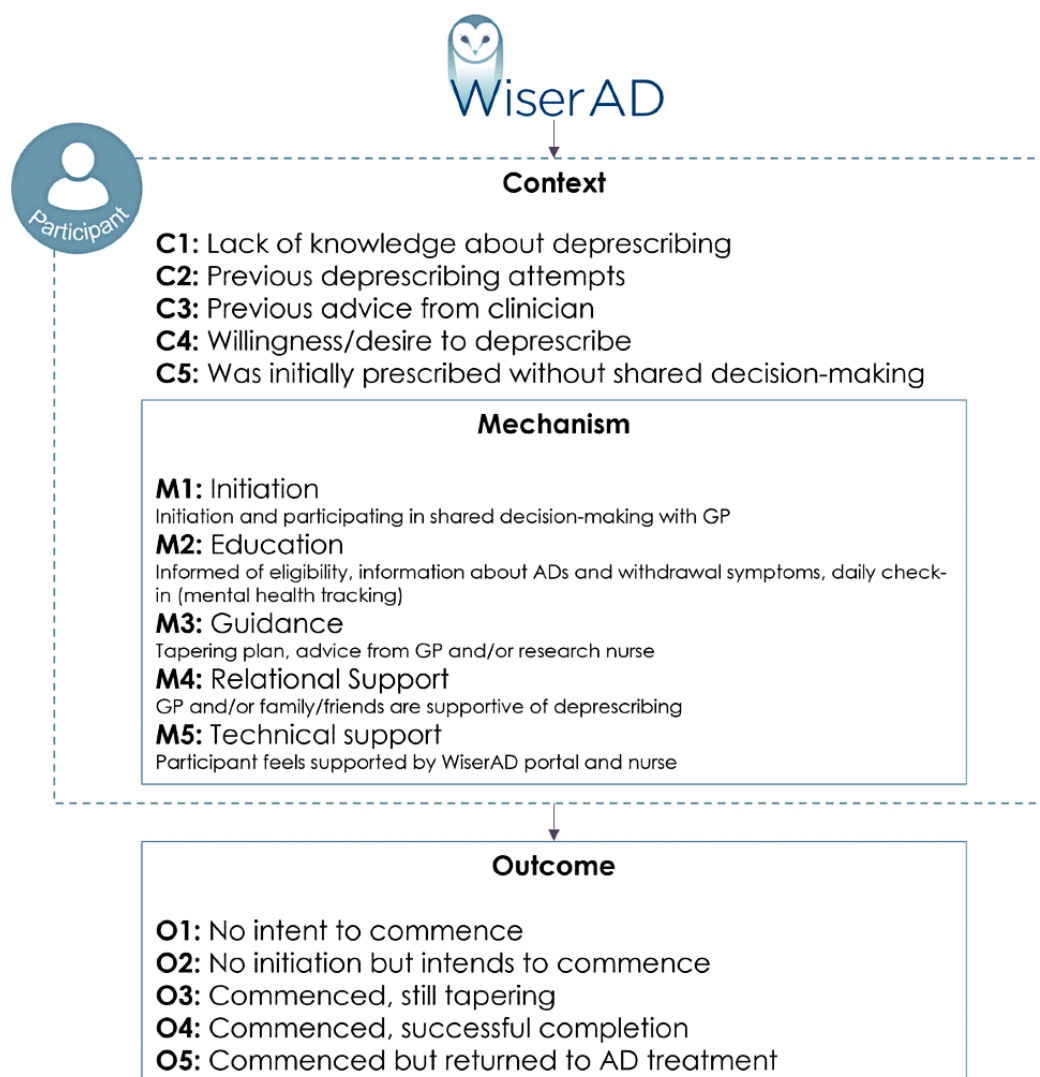
The following potential WiserAD mechanisms are expected to trigger deprescribing: (1) initiation of and participating in shared decision-making with GP regarding antidepressant deprescribing [26,35,44,47]; (2) patient education (participants will be assessed for, and informed of, their eligibility to deprescribe on the basis of the stability of their mental well-being, information about antidepressant medication, and withdrawal symptoms and daily check-ins of their depressive symptom status) [26,44,48] (Abid et al, unpublished data, 2022; Kaylor-Hughes et al, unpublished data, 2022); (3) guidance (provided with a tapering plan that is supported by a GP and a research nurse) [26,35,44,47], (Kaylor-Hughes et al, unpublished data, 2022); (4) relational support (GPs, family, and friends are supportive of deprescribing) [26]; and (5) technical support (patient feels supported by the WiserAD tool and processes; for example, the research nurse) [26,44]. These mechanisms will work by increasing participant empowerment, confidence, and self-management and by positively challenging participant beliefs about antidepressant medication, allowing participants to at least intend to or have commenced deprescribing or successfully complete deprescribing.

Phase 2: Testing the Initial Program Theory

Testing of the initial program theory will be conducted as a mixed methods case study realist evaluation. The realist evaluation will be carried out in the early stages (participant recruitment to 3-month follow-up) of the WiserAD trial and will form a multiple case study of up to 12 WiserAD participants from the intervention and control arms. Three-month follow-up has been chosen, as this will capture the context–mechanism–outcome configuration related to early decision-making by participants regarding the initiation of antidepressant deprescribing and the resulting outcome. The 5 outcomes presented in Figure 2 anticipate the different stages that participants may be in at 3-month follow-up. These outcomes acknowledge that participants may take longer or shorter periods of time to taper their medication. As this evaluation focuses on how, why, and who WiserAD works for, it will determine all possible outcomes of an approach to antidepressant deprescribing rather than showing if it works. The effectiveness of WiserAD on successful deprescribing will be shown at the completion of the WiserAD RCT where an additional evaluation may be carried out and presented in a future publication.

Recruitment and Consent

All participants will have been invited to complete an interview at the time of enrollment in the trial. Participants from the intervention and control arms who agreed to an interview will then be purposively selected on the basis of their age, gender, and level of use of the web-based WiserAD tool (ie, the number of logins to the website in the 3 months since enrollment into the trial) and their GP clinic to ensure diversity of experiences. When participants reach 3 months post commencing participation in the trial, author AC will send an email with a plain-language statement to reinvite them to an interview. AC will then follow up the email with a phone call within 7-10 days. Interested participants will then be booked in to complete the interview at a mutually convenient time.

Data Collection

Quantitative data from the WiserAD study collected at baseline and 3-month follow-up from interview participants will be used in this study. Surveys will be completed digitally, though, if required, the surveys can be completed via telephone or video call or in person at the participants GP clinic. The baseline survey will collect demographic information and both the baseline and 3-month follow-up surveys will ask questions about participant self-management, skills, confidence, and knowledge (Patient Activation Measure–Mental Health) [49], beliefs about their antidepressants (Beliefs About Medicines Questionnaire) [50], and current emotional health and well-being symptoms (Patient Health Questionnaire-9) [51], including those of generalized anxiety disorder; (7-item Generalized Anxiety Disorder scale [52]). WiserAD website usage data will be analyzed to determine the number of logins, number of times pages were looked at, and how much time was spent on each page. The survey has been tested and approved by antidepressant users with lived experience of depression.

Interviews with WiserAD participants will be conducted by a PhD researcher (AC) at 3-month follow-up to further identify and understand the mechanisms of impact that WiserAD has on antidepressant deprescribing. Interviews will be conducted via telephone, video call, or in person. Each interview will last approximately 60 minutes. A narrative interview approach will be taken to allow the participant to naturally report potential mechanisms, contexts, and outcomes without the risk of interviewer bias. The interview process will be guided by the narrative interviewing phases, as suggested by Jovchelovitch and Bauer [53], namely, preparation (formulation of questions), initiation (posing or formulating the topic for narration), main narration (allowing interviewee to talk without interruption), questioning phase (prompting interviewee to continue narration), and conclusion of talk [53]. The phases of narrative interviewing are designed to elicit rich narration rather than falling into a pattern of question-answer with the interviewee.

Sample Size

When conducting qualitative studies, a sample size is deemed adequate when no new information (or data saturation) has been reached [54]. However, for realist evaluations, reaching saturation occurs by exploring a combination of qualitative and quantitative data along with the information obtained when formulating the initial program theory [55]. Additionally, the descriptive statistics that will be generated in this study do not require a minimum sample size. This study will be guided by the case study design recommendation of a minimum sample size of 4-10 participants [40]. As this is a novel area of research, a target sample size of 10-12 participants will used to ensure thoroughness and depth.

Data Analysis

Quantitative Data

Quantitative data (numerical and closed-question data) will be coded and prepared for analysis in Stata (version 17; StataCorp) [56]. Summary statistics in the form of descriptives (means and SDs for continuous data and frequencies and percentages for categorical data) will be calculated, and repeated measures *t*

tests will be performed to compare survey data at baseline and 3-month follow-up. Data will be described and graphically represented. Identification of missing values will first be achieved through web-based assessment, and the Little Missing Completely at Random test [57] will be performed.

Qualitative Interview Data

Narrative interviews will be audio-recorded and transcribed verbatim. Anonymized transcripts will be uploaded to NVivo (version 12; QSR International) [58] for management, coding, and analysis. Data will be coded as a context, mechanism, or outcome. Coding, analysis, and interpretations will be conducted iteratively via discussion among study team members.

Figure 3. Concurrent triangulation of data.

Independent double-coding of the transcripts will be completed by 2 study team members.

Data Converging

In accordance with convergent mixed method designs, qualitative and quantitative data will be collected and analyzed concurrently to generate cases (the main subject of study in a case study) [39,40]. These cases will represent an individual participant in the WiserAD trial. Cases will be analyzed separately and then compared across cases to determine any similar or opposing evidence through data triangulation and theme matching (Figure 3).

Phase 3: Building a Refined Program Theory

In phase 3, triangulation of the quantitative and qualitative data from phase 2 will be used to check and, if necessary, adapt the initial program theory to create a refined program theory showing what works, for whom, and in what circumstances, for successful antidepressant deprescribing. The refined theory will be discussed in depth by the WiserAD research and investigator team that comprises experts in primary care, nursing, health economics, psychiatry, psychology, pharmacology, and business management. Experts will provide validation or disconfirmation of the program theory on the basis of their own experiences and knowledge. This feedback will be used to apply final refinements to the theory. The final refined theory will inform any necessary changes to the web-based WiserAD support tool prior to implementation into clinical practice.

Ethical Considerations

Ethical approval for this study has been granted by the University of Melbourne Human Ethics Committee (#20558). Participants will receive a plain-language statement that will detail the aims of the study, what participation involves and,

information regarding privacy and confidentiality of data. Confirmation of consent will be given verbally at the time of the interview, which will be audio-recorded with the participants' permission. Consent to take part in the interview will also be indicated by continued participation in the interview. Participants will be asked for permission to have their interview audio-recorded and will be informed that they are free to decline, and if they consent, they are free to discontinue the recording or interview at any time. No participant details will be stored with the audio recordings or transcripts, both of which will receive a study identification number. Participants will be informed that any names mentioned in the interviews will be anonymized in the transcript. All quantitative data will be deidentified prior to being provided to AC for analysis by the WiserAD data manager. After completing the interview, participants will receive an Aus $50 (US $33.5) gift card as reimbursement for their time.

Results

The WiserAD trial commenced in May 2022. Sample size requirements for the realist evaluation were reached by

November 2022 with the anticipated completion date for the current study being March 2023. Dissemination of the study findings will occur via peer-reviewed publications, public presentations, and a PhD thesis in 2023.

Discussion

Expected Findings

This protocol presents a mixed methods case study with realist evaluation of the web-based WiserAD support tool. This will be an evaluation of the first participants in the WiserAD RCT and aims to understand how the WiserAD approach to antidepressant deprescribing works, for whom it is intended, and in what circumstances can it be implemented. Quantitative survey data and qualitative interview data will provide information about participants' experiences and perceptions of WiserAD to confirm and refine an initial theory of how antidepressant deprescribing may work in general practice. It is anticipated that initiation of deprescribing, guidance, provision of education about deprescribing, relational support, and technical support will be drivers for patients to intend to or be actively deprescribing their antidepressant.

Only one realist evaluation of a deprescribing intervention has been conducted to date, which investigated the impact of providing an educational brochure about benzodiazepines to older adults in the community [46]. Martin and Tannenbaum [46] reported that by improving knowledge about medication, patients' self-efficacy to deprescribe also increased. As detailed earlier in this protocol, it is expected that education and increased self-efficacy will also impact patients' decision to deprescribe their antidepressants. To our knowledge, this will be the first realist evaluation of an antidepressant deprescribing intervention in general practice and will contribute empirical and theory-informed novel findings about the mechanisms underlying antidepressant deprescribing. It will advance knowledge of antidepressant user experiences of deprescribing in general practice and provide a theoretical contribution to the deprescribing literature. Specifically, it will help determine what general practice patients need in order to successfully and safely deprescribe their antidepressant. It will also enhance knowledge about how to support patients to make decisions about their own antidepressant treatment.

Strengths and Limitations

This study sample will satisfy the sample size requirements of a case study design; however, a sample of 12 participants is small. Additionally, the duration of antidepressant deprescribing may occur over a time period that is longer than 3 months. Therefore, future evaluation of the WiserAD approach to deprescribing should be conducted upon completion of the RCT. The use of mixed methods over a singular data collection method is a strength of this study and will allow for a better understanding of participants' experiences with the WiserAD approach to antidepressant deprescribing. Mixed methods designs are also used to provide in-depth, rigorous evidence of a phenomenon; thus, we can be confident that the findings of this study will make an important contribution to the literature.

Conclusions

This will be the first realist evaluation of an approach to antidepressant deprescribing in general practice. The findings from this study will provide insight into patients' experiences and perceptions of antidepressant deprescribing and thus increase the current understanding of the factors that influence the occurrence of deprescribing in clinical practice.

Data Availability

The data sets generated or analyzed in this study will not be publicly available as the proposed sample size is small and could compromise the privacy of research participants. Additionally, consent and ethical approval for this study does not include a provision for the sharing of data from this study.

Authors' Contributions

All authors contributed to the conceptualization and design of the study. AC drafted the manuscript. All authors revised all drafts.

Conflicts of Interest

None declared.

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Abbreviations

GP: general practitioner
RAMESES: Realist And Meta-narrative Evidence Syntheses–Evolving Standards
RCT: randomized controlled trial

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Protocol

Development of a Home-Based Stress Management Toolkit for Dementia Caring Dyads: Protocol for a Pilot Intervention Development and Feasibility Study

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Abstract

Background: People living with dementia (PLWD) and their care partners (dementia caring dyads) are at a heightened risk of experiencing stress-related symptoms and conditions. Yet, many dyadic stress management interventions have had limited uptake by health care systems and in the community. An intervention that combines simple, safe, easy-to-use, nonpharmacologic tools (eg, animatronic social pets, weighted blankets and garments, aromatherapy and bright light therapy devices, acupressure, and massage tools) that can be used in the home may be a promising approach to promote stress management among dementia caring dyads.

Objective: The proposed study aims to develop and user test a dyadic toolkit intervention composed of simple, tangible stress management tools for community-dwelling PLWD and their care partners. This study will also explore the feasibility of collecting several stress-related outcome measures to inform measurement selection for future studies.

Methods: A human-centered design (HCD) approach will be used to increase the likelihood of developing an intervention that will be translatable to real-world settings. This study consists of 2 phases. The first phase will address the discover, define, and design stages of HCD using qualitative focus groups with dementia caring dyads (N=12-16 dyads). Dyadic focus groups (3-4 groups anticipated) will be convened to understand participants' stress experiences and to co-design a stress management toolkit prototype. Rapid qualitative analysis will be used to analyze focus group data. In phase 2, the toolkit prototype will be user tested for 2 weeks in a new sample to address the validation step of HCD. A within-subjects (n=10 dyads), pre-post design will be used with measures of usability (frequency of toolkit use), feasibility (enrollment and withdrawal rates, adverse events/injuries), and acceptability (satisfaction, benefit) collected via questionnaires (at the end of weeks 1 and 2 of user testing) and focus groups (n=3-4 dyads/group at the end of week 2). The feasibility of collecting participant-reported, stress-related outcomes (neuropsychiatric symptoms of dementia, caregiver stress, dyadic relationship strain) and salivary cortisol as a physiologic measure of stress will be assessed at baseline and after user testing.

Results: This study will yield a working prototype of a stress management toolkit for dementia caring dyads, as well as preliminary data to support the feasibility and acceptability of the intervention. User testing will elucidate areas to refine the prototype and provide data to inform preliminary testing of the intervention. As of September 2022, this study has received institutional ethics board approval with phase 1 recruitment anticipated to begin January 2023.

Conclusions: Few interventions have focused on combining simple, safe, low burden tools to promote stress management among community-dwelling dementia caring dyads. By involving families and exploring feasibility and acceptability at the onset of development, this intervention will have greater potential to be implemented and sustained in the future.

Trial Registration: ClinicalTrials.gov NCT05465551; https://clinicaltrials.gov/ct2/show/NCT05465551

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Introduction

Background

Nearly 1 in 9 older Americans are living with dementia, a chronic, progressive disease that affects every aspect of a person's health and well-being [1]. People living with dementia (PLWD) often live in a heightened state of stress due to changes in how they perceive and respond to the world around them. When their stress threshold is exceeded, distressing behavioral and psychological symptoms (eg, agitation, anxiety, hallucinations, delusions, sleep disturbances) occur [2,3]. The stress process of PLWD is interdependently related to that of their caregivers and care partners [4]. Thus, changes in how PLWD experience and respond to stress can impact the mental and physical well-being of individuals diagnosed *and* their care partners [4-6]. Dyadic interventions focused on improving stress among PLWD and their care partners are paramount to promoting health and well-being among families living with dementia [4,6,7].

Dyadic stress management interventions for PLWD and their care partners often consist of several components and frequent interactions with health care professionals (eg, case management, advanced medical management, psychoeducation, cognitive behavioral training) [8,9]. While such interventions enable a variety of outcomes to be targeted, their complexity can increase burden on care partners who bear primary responsibility for engaging with the intervention. High degrees of burden and cost, exacerbated by the intensive nature of multilevel interventions, have led to limited real-world uptake by health care systems [10,11]. Simple, home-based, dyadic interventions that place minimal burden on care partners are thus needed to reduce stress-experienced families living with dementia.

Stress management tools such as dementia-friendly music devices, social robot pets and dolls, and acupressure and massage tools have been shown to significantly improve stress-related outcomes for PLWD and their care partners [12-15]. Although their effects on stress have not yet been determined, other tools have demonstrated high degrees of safety, feasibility, and acceptability in this population including weighted blankets and garments, prompted journals, aromatherapy, and bright light therapy devices [16-18]. These tools are designed to be used regularly to help the user remain in a healthy, low-stressed state. This is especially important for PLWD who are known to experience a heightened perception of stress and a decreased tolerance of stressful stimuli, which increases their potential for being in an unhealthy state of distress [2]. These tools are hypothesized to prevent distress by increasing social engagement, providing comfort and relaxation, engaging the senses, and connecting users to in-the-moment feelings and surroundings [19-21]. Importantly, all these tools are applicable to everyday situations and are relatively passive in nature, requiring limited supervision and minimal effort to use. By mitigating caregiver burden, such tool-based interventions are expected to have greater acceptability, uptake, and adherence in dyadic contexts compared with more complex interventions. Despite ongoing research on stress management tools, there is a significant knowledge gap in the delivery of *dyadic* stress management interventions to community-dwelling dementia caring dyads. Few studies have combined such tools to best meet the needs of PLWD and their care partners and few tool-based interventions have been designed with ongoing, iterative feedback from this population which will be essential for optimizing delivery and facilitating broad uptake [21,22].

Prior studies have primarily relied on participant-reported outcomes to measure outcomes of stress, and most have focused solely on care partner–specific outcomes. Participant-reported outcomes are useful indicators of psychosocial components of stress, but they can be difficult to collect among PLWD and are subject to inherent risk of bias when completed by proxy report [23,24]. Including biomarkers of stress as outcomes can mitigate limitations of self-report as physiologic stress reactivity is associated with self-reported stress levels among older adults [25]. Physiologic measures of stress may provide a nuanced understanding of intervention efficacy when supplemented with more traditional participant-reported stress outcomes [7]. A multipronged approach to measuring individual and dyadic stress that captures the biopsychosocial nature of the stress process is critical to examining the impact of interventions on dementia caring dyads [7]; however, the feasibility of collecting physiologic measures of stress in this population needs to be determined prior to use in efficacy trials.

The overarching goal of this study is to design a prototype of a dyadic, tangible stress management toolkit with *and* for PLWD and their families [19]. Using a human-centered design (HCD) approach that prioritizes stakeholder engagement at the outset, PLWD and care partners will collaborate with the research team to create the toolkit using 4 key design steps (discover, define, design, and validate) to optimize the intervention for future use (Table 1) [20,26,27].

The *specific aims* of this study are to:

- Aim 1: Develop a prototype of a dyadic stress management toolkit with and for PLWD and their care partners.
- Aim 2: User test the dyadic stress management toolkit intervention with 10 PLWD and their care partners.
- Aim 3: Explore the feasibility of collecting stress-related outcome measures in dyads participating in user testing, including participant-reported outcomes (ie, neuropsychiatric symptoms of dementia, caregiver stress, dyadic relationship strain) and salivary cortisol biospecimens as a physiologic measure of stress.

Table 1. Human-centered design steps addressed through study phases 1 and 2.

Phase and aim	Step and definition
Phase 1 (aim 1)	• Discover: gather data to understand perceptions, opinions, motivations, experiences, and insights of participants • Define: use insights and knowledge discovered to define problem • Design: brainstorm, identify, and co-develop potential solutions and protypes with stakeholders
Phase 2 (aims 2 and 3)	• Validate: user test developed solutions and prototypes on a small scale with end users to identify refinements and modifications needed to improve prototype

Preliminary Studies

The first author conducted a within-subjects, pre-post design study (n=21 dyads) to examine the feasibility and acceptability of a virtually delivered weighted blanket intervention for community-dwelling PLWD [28]. Findings showed high degrees of feasibility (enrollment rate=64%, 21 dyads recruited in <4 months, blankets used for the recommended duration 23.8/30 days, SD 6.4, withdrawal rate=5%, no injuries/adverse events) and acceptability (ie, tolerability, satisfaction, benefit) as reported by PLWD and their care partners. This study demonstrated the feasibility and acceptability of 1 potential tool for the toolkit prototype. The first author also conducted semistructured virtual interviews with 21 family caregivers and 2 focus groups with 7 PLWD to explore their experiences during the COVID-19 pandemic [29]. Findings showed a substantial need for in-home care strategies to manage stress among PLWD and care partners, specifically strategies not reliant on in-person training or interaction with people outside the home. Cumulatively, these studies provide a preliminary understanding of the in-home care stress management needs of PLWD and their care partners, as well as the potential of 1 stress management tool for PLWD; however, the knowledge gained is not sufficient to fully understand the stress experiences of dementia caring dyads, or the potential of a more comprehensive dyadic stress management toolkit. In this way, these studies provide a foundation for the proposed study.

Methods

Study Design

This study consists of 2 phases. The first phase will address the *discover*, *define*, and *design* stages of HCD using qualitative, semistructured focus groups with dementia caring dyads to develop a stress management toolkit prototype (aim 1). The second phase will address the *validation* step of HCD by user testing the prototype, and exploring the feasibility of collecting stress-related outcomes (aims 2 and 3). The trial is registered in ClinicalTrials.gov (NCT05465551).

Phase 1: Discover, Define, and Design (Aim 1)

Overview

Phase 1 will use qualitative focus groups with dementia caring dyads to *discover* and *define* the experiences, perceptions, and preferences of PLWD and their care partners regarding stress and stress management. Their preferences and recommendations regarding key components and format of the stress management toolkit will be explored to *design* the prototype.

Phase 1 Participants and Recruitment

PLWD and their primary, informal care partners will be recruited together as participant dyads [30]. Inclusion criteria for participants with dementia are as follows: (1) age 60 years and over with a diagnosis of dementia of any type; (2) able to express self verbally; and (3) English speaking. We will purposively sample PLWD who experience some degree of stress, operationalized as demonstrating at least two symptoms listed on the Neuropsychiatric Inventory within the most recent 4 weeks as reported by the PLWD or their care partner [31-34]. Exclusion criteria for participants with dementia are as follows: (1) has a hearing or visual impairment that limits their ability to participate in the screening process or to participate in a focus group. Inclusion criteria for care partner participants are as follows: (1) age 21 years and older; (2) identify as a primary care partner of someone with dementia; and (3) English speaking [32,35]. Exclusion criteria for care partner participants are as follows: (1) has a hearing or visual impairment that limits their ability to participate in the screening process or to participate in a focus group. Dyadic eligibility criteria include the following: (1) both the PLWD and care partner reside in the same household or personal residence in the community; (2) dyad has lived together for at least one month; and (3) dyad has telephone or internet access. Dyads will be excluded if they reside in assisted living or other long-term care settings.

The projected sample size for this phase is 12-16 dyads based on similar prior studies, but up to 25 dyads will be enrolled if necessary to reach data saturation [35,36]. Dyads will be recruited through several regional and national dementia and caregiver community support organizations that provide a range of services, resources, and referrals to PLWD and their caregivers. Recruitment organizations provide support through in-person, as well as virtual educational offerings, advocacy events, and social engagement activities. Recruitment flyers and study information will be distributed through in-person and virtual events. The research team will attend in-person and virtual offerings to provide more detailed information regarding the study. Interested individuals will be able to contact the research team directly to learn more about the study and to determine eligibility. Designated staff members at recruitment organizations will also collect names/contact information for individuals that express interest and agree to be contacted directly. An eligibility determination form with the criteria outlined above will be completed by a research team member (MH) for all interested individuals that are contacted regarding study participation.

Phase 1 Consenting Procedures

Eligible participants will provide consent verbally to participate in phase 1 of this study. To complete the consent, participants will review a study information form with a research team member. The study information will be sent by email, by postal mail, or reviewed verbally with potential participants depending on their preference. After reviewing the information sheet, participants will then be asked verbally if they wish to participate in the study. Both members of the dyad must provide verbal consent. The researcher obtaining consent will use an inclusionary, person-centered approach throughout the discussion by incorporating several strategies to enhance the PLWD's ability to remain engaged and empowered throughout the consent discussion [37,38]. This will include strategies such as assessing for verbal and nonverbal cues indicative of the person's interest and degree of engagement in the conversation, by offering multiple opportunities for the PLWD to ask questions, by using language that is understandable to the PLWD, by frequently restating the key features of the study in different ways, by asking the PLWD to restate the key features throughout the discussion, by offering information in multiple ways (ie, written, verbal, visual examples), by offering breaks in the discussion, by offering to schedule a follow-up call to complete the discussion at another time.

Phase 1 Focus Group Guide and Data Collection

Four focus groups (n=3-4 dyads/group) will be held virtually over Zoom (Zoom Video Communications, Qumu Corporation) or in-person, dependent on safety and participants' preference. Focus groups were selected as they allow for collaborative idea generation to evolve more quickly through group discussion, which is an essential component of the *design* step of HCD [27,39]; however, individual or dyadic interviews will be used if scheduling focus groups with dyads becomes a challenge or if needed to optimize engagement for PLWD. A trained research team member (MH) will facilitate the focus groups using a semistructured focus group guide, which will concentrate on dyads' experiences and perceptions regarding stress, stress management, and the toolkit prototype. Participants will be asked to discuss their experiences with stress at home and how they manage stress currently. The focus group facilitator will then present a visual demonstration of what a tangible stress management toolkit could entail; for example, tools such as dementia-friendly music devices, social robot pets and dolls, acupressure and massage tools, weighted blankets and garments,

prompted journals, aromatherapy, and bright light therapy devices. The group will be asked if these tools seem relevant or potentially useful to them and if the tool seems like it could fit into their daily lives at home. They will be asked to describe other tools that could be a good fit for the toolkit. The group will then be asked how they would like a stress management toolkit to look, how they would like it to be delivered to them, and what additional information they would like to have included with the toolkit. The focus group guide will include questions directed at PLWD and care partners. The topics discussed may be modified based on findings that emerge throughout the study.

Focus groups are anticipated to last about 90 minutes and will be audio recorded and transcribed using Zoom's virtual conferencing platform. A trained research team member will take detailed notes using a semistructured note-taking guide. Immediately after each focus group session, the notetaker and the group facilitator will develop postgroup summaries and debrief notes that highlight key points from the group [40,41]. If necessary, additional focus groups or individual interviews will be held if it seems that the perspectives of PLWD or care partners or both are not fully reflected in the dyadic focus groups, or if data saturation is not reached to fully inform the development of the toolkit prototype.

Information pertaining to the sociodemographic and diagnosis characteristics (such as age, race and ethnicity, gender, education, marital status, dementia type, duration of diagnosis, relationship between dyad composition, duration of having lived together, residence geographical location [urban, suburban, or rural]) of the dyad will be collected prior to scheduled focus groups. To further describe the degree of stress of the sample, information will also be collected pertaining to concepts such as the perceived stress of participants with dementia and care partners, and dyadic strain (as perceived by PLWD and care partners). Psychometrically sound measurement tools will be used to obtain this information (Table 2), which will be collected using questionnaires completed by phone, hardcopy, or electronically depending on participant preference. A care partner–specific questionnaire as well as a PLWD-specific version questionnaire will be completed by each dyad. Each questionnaire is anticipated to take approximately 10-15 minutes to complete. Participants will complete questionnaires before their scheduled focus group electronically, by hardcopy, or by phone depending on their preference.

Table 2. Measures to be collected to describe degree of stress of participants.

Operationalized measure	Measurement instrument (number of items)	Psychometric properties	Source of completion
Perceived stress of PLWD[a]	Perceived Stress Scale: reported by PLWD (10)	• Cronbach α=.74 • Convergent validity established with the Geriatric Depression Scale [42-44]	PLWD
Perceived stress of care partner	Perceived Stress Scale: reported by care partner (10)	• Cronbach α=.80-.84 • Convergent validity established with the Geriatric Depression Scale [42-44]	Care partner
Dyadic strain	Dyadic Relationship Scale: reported by PLWD (10)	• Cronbach α=.84-.86 • Construct validity established through confirmatory factory analysis [45]	PLWD
	Dyadic Relationship Scale: reported by care partner (11)	• Cronbach α=.84-.89 • Construct validity established through confirmatory factory analysis [45]	Care partner

[a]PLWD: people living with dementia.

Phase 1 Data Analysis

Stress-specific measures to describe the sample will be scored for each participant using measurement scoring guidelines [42,43,45]. Descriptive statistics (means, SDs, medians, frequencies, percentages) will be calculated to describe the sociodemographic, diagnosis, and stress-specific characteristics of the sample.

This study will use a rapid qualitative analysis approach with purposeful data reduction activities to facilitate ongoing and iterative data analysis [40,41]. All groups will be recorded and transcribed using Zoom's transcription function. Immediately after each group, the first author will code notes and summaries by identifying patterns, diverging points, critical quotations, and key points. Prior research on intervention development and HCD pertaining to discovering and defining the problem (ie, stress, stress management) and designing the prototype (eg, characteristics, components, delivery) will be used to generate initial categories for the analysis and will provide a scaffold to build off for the coding process [19,20,27,46]. A list of initial codes, definitions, and exemplar quotations will be kept in a codebook. At least one other analyst will listen to the audio recording or refer to transcripts, review notes, and summaries, and then add to and modify the codebook developed by the first author. Differences in coding will be indicated using highlighting and comments to be discussed among analysts during weekly meetings to reach consensus regarding codes and code groups (or themes) [41]. Data will be compared within and across focus groups iteratively throughout the study. Initial codes and themes will be presented to at least two participant dyads. They will provide feedback and participate in discussions with the research team to finalize the findings, which will inform development (eg, specific tools, components, features, user guides, delivery techniques) of the prototype. Multiple phases of feedback may be needed prior to finalizing the prototype [19,27,47].

Phase 2: Validate (Aims 2 and 3)

Phase 2 will address the *validate* step of the HCD process (Table 1). A total of 10 dyads (who were not involved in phase 1) will use the prototype toolkit for 2 weeks and measures of usability, feasibility, acceptability, and stress-related outcomes will be collected (Figure 1).

Figure 1. Study overview. PI: principal investigator.
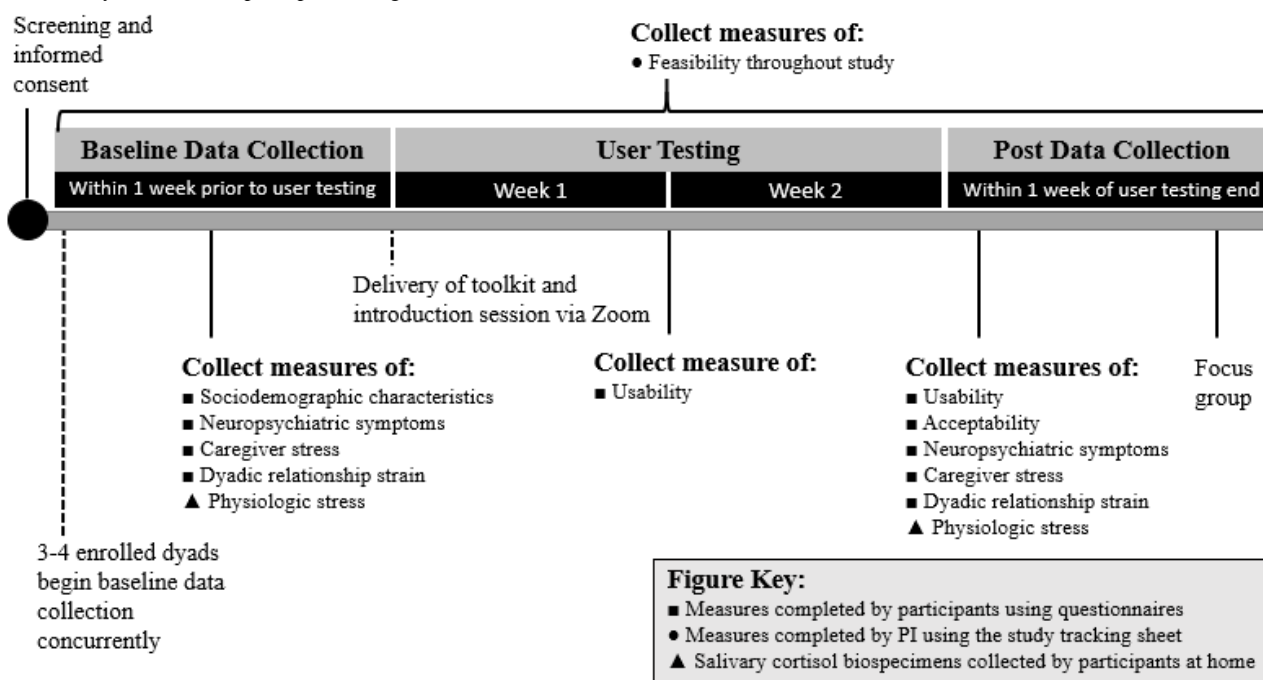
Phase 2 Participants and Recruitment

Similar eligibility criteria will be used in phase 2 as were used in phase 1 with few additional criteria to address contraindications to the collection of salivary cortisol biospecimens. In addition to the phase 1 criteria, participants will be excluded if they (1) currently receive cytokine-based therapy; (2) currently receive radiation therapy to the salivary glands or thyroid; (3) are diagnosed with Cushing or Addison disease. Dyads will also be excluded in phase 2 if they participated in phase 1. The same recruitment strategy used in phase 1 will be used in phase 2 as well. Ten dyads was selected as the projected sample based on prior studies that have used HCD with this population [26,27], but up to 20 may be enrolled if data saturation is not reached.

Phase 2 Consenting Procedures

All participants will provide signed consent to participate in this phase of the study. Eligible dyads will be sent an informed consent form electronically or as a hardcopy depending on their preference. Electronic forms will be distributed by email via an electronic-consenting platform and hardcopies will be sent by U.S. Mail. Similar steps used in phase 1 will be followed in phase 2 to obtain consent with the exception that both members of the dyad will provide signed consent, as opposed to verbal consent.

Phase 2 User Testing Procedures

Dyads will receive a toolkit and toolkit user guide by mail after collection of baseline data. Dyads will participate in an introduction session with a trained research team member via Zoom or phone to review how to use the toolkit. Dyads will use the toolkit in the home for 2 weeks. A 2-week duration was selected based on prior home-based studies with this population that have used HCD [48,49]. Dyads will be encouraged to use at least one tool from the toolkit at least once a day to manage

day-to-day stress and to mitigate the risk of negative outcomes related to excess stress.

Phase 2 Measures

Aim 2

Usability will be measured by examining the frequency of use of the toolkit by participants. At the end of weeks 1 and 2 of user testing, dyads will complete a brief questionnaire to indicate tools that were used and by whom (ie, PLWD or care partner), number of days the toolkit was used over the past week, and each participant's general response to the toolkit. The toolkit will be considered to have a high degree of usability if participants use it on average 9 or more days/14-day intervention period [28,50]. *Feasibility* will be measured throughout the study by examining several measures such as study enrollment and withdrawal rates, and adverse effects and injuries [51]. The prototype will be considered feasible if enrollment rate is 50% or more, withdrawal rate is 25% or less, and no adverse events or injuries were reported [52-54]. *Acceptability* will be measured at the end of week 2 of user testing. Dyads will complete item scales pertaining to what they found most beneficial and satisfying regarding the toolkit, and challenges experienced when using the toolkit. An acceptability survey will be developed for this study that will be modified from prior tools used to measure acceptability of nonpharmacologic dyadic-focused interventions for patients with chronic conditions and their care partners [55,56].

Usability, *feasibility*, and *acceptability* will be further explored through qualitative focus groups (3 groups in total; n=3-4 dyads/group) convened after participants have completed posttest questionnaires. Similar procedures used for focus groups in phase 1 will be used in phase 2 to explore the usability, feasibility, acceptability of the toolkit, and participants' recommendations regarding modifications and refinements needed to improve the toolkit. Throughout the study, we will

also keep a tracking sheet of the specific tools and cost of each toolkit delivered to participants in phase 2. We will ask questions pertaining to cost during the focus groups to begin to explore participants' perceptions of cost and willingness to pay for such a toolkit out-of-pocket as a component of acceptability [57].

Aim 3

Stress-related participant-reported outcomes (eg, neuropsychiatric symptoms of dementia, caregiver stress, dyadic

relationship strain) measured using psychometrically sound measurement tools [32,42,45] and *salivary cortisol biospecimens* of participants with dementia and care partners [58] will be collected at baseline and after user testing (Figure 1 and Tables 3 and 4). Outcome measure collection will be feasible if the measure can be collected in 80% or more of participants at baseline and after data collection timepoints.

Table 3. Phase 2 outcome measures for aim 2.

Outcome	Measure	Measurement	Data collection tool
Usability	• Frequency of toolkit use	• How many days in the past week was the toolkit used by the participant with dementia/care partner? (range 0-7 days)	• Questionnaire
Feasibility	• Enrollment rate	• Percentage of participants enrolled	• Study tracking sheet
	• Withdrawal rate	• Percentage of participants that withdraw	
	• Adverse events/injuries	• Number of adverse events and injuries	
Acceptability	• Satisfaction	• Toolkit satisfaction scale (1=not satisfied at all to 5=very satisfied)	• Questionnaire
	• Perceived benefit	• Toolkit benefit scale (1=not at all beneficial to 5=very beneficial)	

Table 4. Phase 2 outcome measures for aim 3.

Outcome	Measurement	Psychometric properties	Data collection tool
Neuropsychiatric symptoms of dementia	• Neuropsychiatric Inventory-Questionnaire [34]	• Cronbach α (range)=.71-.88 • Percentage agreement between raters: 93.6%-100% • Test-retest reliability range (r)=0.79-0.86 [34,59,60]	• Questionnaire
Caregiver stress	• Perceived Stress Scale [43]	• Cronbach α (range)=.75-.82 • External validity established through CFA[a] [42,44]	• Questionnaire
Dyadic relationship strain	• Dyadic Relationship Scale [45]	• Cronbach α (range)=.84-.89 • External validity established through CFA [45]	• Questionnaire
Physiologic stress	• Salivary cortisol biospecimens	• N/A[b]	• Oral swab

[a]CFA: confirmatory factor analysis.

[b]N/A: not applicable.

Phase 2 Data Collection

Aim 2

Feasibility data will be collected by the research team throughout the study using a tracking sheet stored on a secure institutional server. Usability and acceptability data will be collected using questionnaires completed electronically, by hardcopy, or verbally by phone in accordance with participant preference. Similar data collection procedures described in phase 1 will be used to collect questionnaire data in phase 2. Sociodemographic and diagnosis characteristics of the dyad will also be collected using a questionnaire. Similar qualitative data collection

procedures used in phase 1 will be used to collect focus group data in phase 2.

Aim 3

Stress-related participant-reported outcome measures will be collected using questionnaires completed electronically, by hardcopy, or verbally by phone, depending on participant preference. *Salivary cortisol biospecimens* will be collected by participants using oral swab kits. Participants with dementia and care partners will each provide 10 samples in total. Five samples (per participant) will be collected over the course of 1 day at baseline and the remaining 5 will be collected over the course of 1 day after data collection. Participant dyads will

receive sample kits by postal mail at least one week prior to the 2 data collection timepoints (baseline and after). Each dyad will participate in a telephone or Zoom session with a research team member to review how to collect saliva samples prior to the scheduled data collection timepoint. During this session, participants will be asked to not complete the sample collection if any of the following are present on the day of data collection: (1) a fever >101°F, (2) upper respiratory infection with nasal drainage, and (3) inflammation of the throat. As appropriate, an alternative day will be identified if any of these symptoms are present, or the data collection will be canceled and documented as incomplete in the study database.

A research team member will be available by phone or Zoom for participants to ask questions and receive support during the collection of salivary samples. Participants will also be able to access video instructions provided by Salimetrics [61]. Detailed methods for saliva collection and handling can be found online [62]. In brief, each Salimetrics kit contains 1 oral swab, 1 swab storage tube, and sample collection instructions. Participants peel back the protective package around the swab and place it under their tongue for 2 minutes after which it is placed into the prelabeled storage tube. The swab-containing storage tube is then placed in the refrigerator. On each measurement day (baseline and after) each participant will provide a saliva swab at waking, 30 minutes after waking, 60 minutes after waking, 1 hour before or after dinner, and 1 hour before bedtime for a total of 5 swabs per time point, per participant [63]. Care partners may assist the PLWD in collecting their samples. The swabs will be shipped to the corresponding institution's biomarker laboratory using a prepaid package with a small ice pack, which will be picked up by FedEx personnel for delivery. Samples will be immediately frozen and stored at the biomarker laboratory at –20°C until assayed by a Salimetrics-certified laboratory. Collection and storage methods follow the assay manufacturer (Salimetrics) recommendations and have been validated [64].

Phase 2 Data Analysis

Aim 2

Descriptive statistics (means, SDs, frequencies, percentages) will be calculated for measures of usability, feasibility, and acceptability. Similar rapid qualitative analysis methods that were used in phase 1 will be used to analyze phase 2 focus group data.

Aim 3

Percentage of participants with data collected will be calculated for each outcome measure at each data collection timepoint. To further describe the study sample, the Neuropsychiatric Inventory, Perceived Stress Scale, and Dyadic Relationship Scale measures will be scored for each participant according to measurement scoring guidelines at each timepoint and group means (SDs) will be calculated. We will not assay the salivary cortisol specimens in this study, but will do so as a secondary analysis in a future study.

Ethics Approval

This study was approved by the Duke Health System Institutional Review Board (HUM00186832).

Results

This study received IRB approval in August 2022 and is anticipated to be completed by July 2024. Expected outcomes of phase 1 are a working prototype of a dyadic stress management toolkit for PLWD and their care partners. Phase 2 will yield preliminary data to support the feasibility and acceptability of the toolkit, as well as data to inform the design (eg, measurement selection, recruitment, data collection methods) of a future study to examine efficacy. The goal is that by using an HCD approach that incorporates stakeholder engagement at the onset of development, this intervention will be more applicable and acceptable to families living with dementia. Exploring feasibility and acceptability in the early stages of intervention development will help determine whether costlier efficacy testing is warranted [65]. Data generated from this study will act as a stepping stone in the development of a stress management intervention for dementia caring dyads that has an increased likelihood of being implemented and sustained in the future.

Discussion

Expected Findings

The need for home-based stress management interventions for PLWD and their care partners was amplified by the COVID-19 pandemic [29,66]. Tangible stress management tools exist that are passive in nature (eg, low user burden, minimal training required) and safe for use by older adults, but there remains a paucity in research focused on the use of such tools by PLWD and their care partners. Furthermore, no prior studies have focused on combining multiple tangible tools to promote stress management among community-dwelling dementia caring dyads. Findings will expand state of the science by developing and user testing a tangible stress management toolkit for dementia caring dyads using an HCD approach. Qualitative findings pertaining to usability, feasibility, and acceptability will elucidate areas to refine the toolkit. In addition, insights relating to participants' attitudes toward the cost of toolkits will provide preliminary information pertaining to the scalability of this intervention. Examining the feasibility of collecting several stress-related outcome measures will also inform measurement selection in a future efficacy study. This study will yield a working prototype of the stress management toolkit, as well as preliminary data to support the feasibility and acceptability of the intervention.

This study incorporates several innovative components including the use of HCD. HCD involves identifying problems, co-designing solutions with key stakeholders, and user testing solutions with end users early in the intervention development process. HCD is a promising approach to identifying solutions for families living with dementia as many nonpharmacologic interventions have demonstrated limitations in broader implementation and sustainability in this population. A second innovation is the inclusion of salivary cortisol samples as a biologic measure of stress. Few nonpharmacologic intervention studies have examined intervention effects from a physiologic stress-response perspective. This study will help determine

whether salivary cortisol is a feasible outcome to include in a future study to determine efficacy of the toolkit intervention, as well as other intervention studies focused on community-dwelling dementia caring dyads. Strengths of this study are the use of predefined measures of usability, feasibility, and acceptability; a national recruitment strategy; multiple stakeholder engagement strategies; and remote and in-home data collection methods. Offering multiple ways to engage in this study provides a more equitable approach by circumventing barriers to support service access and research participation (eg, rurality, transportation, limited internet access).

Potential limitations of this study include issues relating to recruitment and measurement. Stress and stress management experiences and preferences are dependent on individual customs, cultures, and historical and social contexts. Thus, the specific components of the toolkit will depend greatly on the individual experiences of participants in phase 1. Although we will use a national recruitment strategy with the intent of recruiting a diverse sample in terms of sociodemographic, disease, and caregiving characteristics (eg, race/ethnicity, rurality, dementia type, relationship between dyad), it is likely that the prototype will be more relevant to some dyads compared with others. Throughout the design process we plan to incorporate multiple opportunities to personalize the toolkit based on individual and dyadic preferences to enhance generalizability and applicability. In terms of measurement limitations, many of the proposed measures in phase 2 are based on self or proxy report, which carries an innate potential for biased responses. This is particularly significant for measures of usability and acceptability of the toolkit as prior studies demonstrate discrepancies in perceived versus actual use of self-care interventions, and an increased risk of providing socially acceptable responses on satisfaction surveys [67,68]. To address this concern, we will include verbiage in questionnaire directions and verbally encourage participants to provide honest responses to these measures. We will reassure participants that they will not be judged or treated differently based on the responses they provide. The small sample for this study is congruent with feasibility study design guidelines; however, findings will be limited in terms of generalizability and future testing will be needed to determine efficacy. These limitations notwithstanding, this study is well positioned to provide the necessary data to inform the design of a successful pilot efficacy trial in the future.

Future Directions

If findings demonstrate feasibility and acceptability of the toolkit, a critical next step will be determining efficacy of the toolkit intervention for improving stress-related outcomes through a larger randomized controlled trial [69]. Future research may also explore the cost-benefit of the toolkit, as well as optimal "dose" or amount of toolkit use needed to yield clinically significant effects. It will also be important to examine how contents and delivery of the toolkit may be tailored for dyads based on their individual and cultural preferences. Findings from this feasibility study will provide necessary data to inform measurement selection, data collection methods, and recruitment capacity for future studies.

Conclusions

PLWD and their care partners are in desperate need of home-based strategies to reduce stress and promote well-being. This study uses an HCD approach to develop and user test a tangible stress management toolkit *with* and *for* dementia caring dyads. This study will be the first to combine several stress management tools into a comprehensive toolkit designed for use by PLWD and their care partners. Using an HCD that involves stakeholder engagement at the onset of development will increase the applicability of the intervention to the target population. By examining feasibility and acceptability early in the development process, this study will act as a foundation for future testing.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the preparation of this study protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Summary of peer review from the Research Education Core of the Duke/University of North Carolina Alzheimer's Disease Research Center (ADRC).
[PDF File (Adobe PDF File), 374 KB - resprot_v11i12e43098_app1.pdf]

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Abbreviations

HCD: human-centered design
PLWD: people living with dementia

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Load-Induced Glenohumeral Translation After Rotator Cuff Tears: Protocol for an In Vivo Study

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Abstract

Background: Rotator cuff tears are a common shoulder injury, but they sometimes remain undiagnosed, as symptoms can be limited. Altered shoulder biomechanics can lead to secondary damage and degeneration. In biomechanical analyses, the shoulder (ie, the glenohumeral joint) is normally idealized as a ball-and-socket joint, even though a translation is often observed clinically. To date, no conclusive changes in glenohumeral translation have been reported in patients with rotator cuff tears, and it is unknown how an additional handheld weight that is comparable to those used during daily activities will affect glenohumeral translations in patients with rotator cuff tears.

Objective: This study aims to assess the load-induced glenohumeral translation (liTr) in patients with rotator cuff tears and its association with the load-induced changes in muscle activation (liMA).

Methods: Patients and asymptomatic controls will be recruited. Participants will fill out health questionnaires and perform 30° arm abduction and adduction trials, during which they will hold different handheld weights of a maximum of 4 kg while motion capture and electromyographic data are collected. In addition, fluoroscopic images of the shoulders will be taken for the same movements. Isometric shoulder muscle strength for abduction and rotation will be assessed with a dynamometer. Finally, shoulder magnetic resonance images will be acquired to assess muscle status and injury presence. The dose-response relationship between additional weight, liTr, and liMA will be evaluated.

Results: Recruitment and data collection began in May 2021, and they will last until the recruitment target is achieved. Data collection is expected to be completed by the end of 2022. As of November 2022, data processing and analysis are in progress, and the first results are expected to be submitted for publication in 2023.

Conclusions: This study will aid our understanding of biological variations in liTr, the influence of disease pathology on liTr, the potential compensation of rotator cuff tears by muscle activation and size, and the association between liTr and patient outcomes. The outcomes will be relevant for diagnosis, treatment, and rehabilitation planning in patients with rotator cuff tears.

Trial Registration: ClinicalTrials.gov NCT04819724; https://clinicaltrials.gov/ct2/show/NCT04819724

International Registered Report Identifier (IRRID): DERR1-10.2196/43769

Introduction

The shoulder (ie, glenohumeral joint) is a unique joint primarily stabilized by the rotator cuff muscles [1]. These muscles facilitate shoulder motion and center the glenohumeral joint [2]. This type of stabilization facilitates a large range of motion [2], which is a prerequisite for many daily, occupational, and recreational activities. An injury to the rotator cuff can therefore lead to an unstable joint and affect joint functionality, negatively affecting patients' activities and quality of life. Furthermore, altered shoulder biomechanics can lead to secondary damage and degeneration, such as tendinopathy or osteoarthritis [3]. The motion of a healthy shoulder mainly comprises rotation and very small to no translation due to stabilization through muscle forces. Glenohumeral stability is affected by the muscle cross-sectional area; the level of muscle activation; and the shoulder anatomy, including the critical shoulder angle and glenoid inclination [4-6].

Degenerative partial and complete ruptures of the rotator cuff are common injuries with a steady increase in prevalence with aging [7]. Yamamoto et al [8] reported a total prevalence of rotator cuff tears of 20.7%, with the 0% prevalence in the age group of 20 to 29 years increasing to 50% in those aged 80 to 89 years. The clinical manifestation of degenerative rotator cuff tears varies largely among patients; some have no complaints, and the diagnosis is an incidental finding, while others have severe pain and a limited range of motion that is marginally restored with conservative treatment [9]. In patients with end-stage degenerative rotator cuff lesions, especially with tears of the supraspinatus muscle, this deficit manifests radiologically as a narrowing of the subacromial space [10], presumably caused by the muscular force of the deltoid muscle pulling the humeral head superiorly toward the acromion.

The general population study of Yamamoto et al [8] revealed that 36% of patients with current symptoms had rotator cuff tears, while 17% of asymptomatic participants were also diagnosed with rotator cuff tears. However, to date, possible reasons for this symptomatic discrepancy are poorly understood. Differences in symptomatic and functional limitations may be related to glenohumeral instability in patients with rotator cuff tears. A dysfunctional rotator cuff potentially leads to insufficient joint centering, and tears of the supraspinatus tendon may cause a superior glenohumeral translation. A greater superior translation may affect the pressure around the glenoid cavity and the labrum, possibly leading to pain and impingement and thereby limiting shoulder mobility.

Common kinematic models assume that the glenohumeral joint is a ball-and-socket joint [11], without any consideration of the common clinically observed translation. No conclusive changes in shoulder translation have yet been reported in patients with rotator cuff tears [12-15]. Moreover, it is still unknown how additional handheld weight (comparable to that experienced in situations during daily, occupational, or recreational activities) affects glenohumeral translation in patients with rotator cuff

tears. Intact shoulder muscles' compensation mechanisms for the lacking muscle force of injured muscles are also largely unknown. Such mechanisms may lead to overloading of the uninjured muscles, which can eventually lead to degenerative changes secondary to the original injury.

The current state of research in the field and in our research shows that our proposed framework, applied in a previous pilot study [16] for assessing load-induced glenohumeral translation (liTr), is feasible. Our preliminary clinical analyses have shown that many people aged 45 years and up have degenerative tendon changes despite an absence of symptoms. Clinical observations and results reported in the literature raise the following questions: (1) Is the load-induced increase in deltoid muscle activity with increasing additional load in patients with symptomatic rotator cuff tear greater than that in asymptomatic or healthy joints? (2) Does liTr in the injured joint increase with increasing additional load? (3) Is liTr greater in patients with rotator cuff tears than in age-matched asymptomatic controls and young healthy controls? (4) Is liTr associated with load-induced changes in muscle activation (liMA)? (5) Is there a correlation between the patient's functional scores and liTr? (6) Is liTr related to muscle morphology, tear size and type, and shoulder anatomy? (7) Are measurements of liTr using motion analysis and single-plane fluoroscopy comparable?

Evidently, there are a variety of factors to consider, including anatomical, morphological, functional, and injury-related factors. Answering these questions will provide information to help clarify the biomechanical limitations of an injured rotator cuff and their impact on treatment, therapy, and daily life. Hence, this study aims to assess the dose-response relationship between liTr and liMA in patients with rotator cuff tears and in age-matched asymptomatic and young healthy participants.

Methods

Objectives and Hypotheses

This study will test the overall hypothesis that rotator cuff tears affect glenohumeral translation and that this functional instability depends on the additional load applied, anatomical and morphological variations, and the type and severity of the injury. We propose that greater liMA of the deltoid muscle is associated with greater liTr and that liTr is altered by rotator cuff injury and may be related to patients' functional scores, muscle cross-sectional area, tear size and type, critical shoulder angle, and glenoid inclination. We also propose that this person-specific relationship is associated with corresponding load-dependent changes in shoulder muscle activity.

Our primary objective is to investigate the dose-response relationship between liMA and liTr in patients with rotator cuff tears and asymptomatic control participants.

Hypothesis 1 is as follows: liMA is positively associated with liTr. Because the shoulder is primarily stabilized by rotator cuff muscles, we expect that the presence of a muscle tear will require additional activity of the remaining intact muscles to

stabilize the shoulder. Hence, the dose-response relationship between additional load and relative change in muscle activity with rotator cuff tears will be stronger than in uninjured shoulders.

The secondary objectives are to investigate the in vivo dose-response relationship between additional weight and glenohumeral translation, to understand the biological variation in liTr, the influence of disease pathology on the liTr, the potential compensation by muscle activation and size, and the influence of liTr on patient outcomes. The secondary hypotheses are listed as follows:

- Hypothesis 2.1: liTr is greater in shoulders with rotator cuff tears than in healthy shoulders.
- Hypothesis 2.2: An increase in liTr is part of natural aging, and its variation is related to sex and shoulder anatomy assessed by the critical shoulder angle and the glenoid inclination.
- Hypothesis 2.3: liTr increases with injury severity and depends on injury type.
- Hypothesis 2.4: liMA and side-to-side differences in muscle size (ie, muscle cross-sectional area) increase with the presence of injury and injury severity.
- Hypothesis 2.5: There is a biological variation in liMA and in the compensation effect by muscle activation and muscle size (ie, muscle cross-sectional area).

- Hypothesis 2.6: Large values of liTr are associated with poor functional scores.

In this study, the correlation between liMA and liTr and their relation to patients' functional scores, muscle activation and size, tear size and type, and shoulder anatomy (critical shoulder angle and glenoid inclination) will be analyzed.

Study Design and Participants

This study entails cross-sectional, experimental multimodal (clinical, biomechanical, radiological) data collection with multiple conditions and a control group. A total of 25 patients aged 45 to 85 years with unilateral symptomatic rotator cuff tears will be recruited from our clinic. Orthopedic surgeons will inform patients who fulfill the inclusion criteria about the study, and eligible candidates will be contacted. Additionally, 25 asymptomatic controls will be recruited to achieve the same age and sex distribution as in the patient group. Moreover, because of the clinically observed high prevalence of rotator cuff tears in persons without symptoms, we will also recruit 25 sex-matched young asymptomatic controls aged between 20 and 30 years to allow for elucidating the effect of the natural aging process. Detailed inclusion and exclusion criteria for the cohorts are shown in Textbox 1.

Textbox 1. Inclusion and exclusion criteria for this study.

Inclusion criteria

Patients:

- Aged 45 to 85 years (n=25)

- Diagnosed unilateral rotator cuff tear: partial or complete supraspinatus muscle tear, with or without injury to other rotator cuff muscles

- Prior operative treatment of the ipsilateral shoulder or elbow

- Clinical history or symptoms of the contralateral glenohumeral joint

- Range of motion <30° in abduction and flexion

Control participants:

- Two age groups: 20 to 30 years (n=25) and 45 to 85 years (n=25)

- No previous known elbow and shoulder injury or symptoms

- Clinical history of the glenohumeral joint

- Prior conservative or operative treatment of the shoulder or elbow

- Range of motion <90° in abduction and flexion

Exclusion criteria

- Inability to provide informed consent

- BMI>35 kg/m^2

- Neuromuscular disorders affecting upper limb movement

- Additional pathologies influencing the mobility of shoulder joints

- Contraindications for magnetic resonance imaging (eg, neurostimulator and claustrophobia)

- Prior neuromuscular impairment (eg, stroke)

- Diagnosed with active rheumatic disorder

- Other major medical problems

- Pregnancy

- Currently enrolled in another experimental (interventional) protocol

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Experimental Protocol

Each participant will undergo a recruitment and information process before coming to the University Hospital Basel for all planned data collection. Before the assessment, written informed consent will be obtained. Participants will then complete health questionnaires to receive functional scores of the shoulders. Next, fluoroscopic images of a loaded and unloaded 30° shoulder abduction test will be captured, and a 3D motion analysis of the same abduction tests will be performed. Isometric shoulder strength for abduction and internal/external rotation will be assessed with a dynamometer. Finally, magnetic resonance imaging (MRI) images of both shoulders will be taken (Table 1). The estimated total time for each participant is approximately 4 hours. The SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) checklist, compiled with recommended items to be addressed in a clinical protocol, is provided in Multimedia Appendix 1.

Table 1. Schedule of enrollment and assessments.

| | Study period | |
	Enrollment	Allocation
Time point	Precall	0
Enrollment		
Eligibility screen	✓	
Informed consent		✓
Allocation	✓	
Study groups		
Patients		✓
Control participants (45-85 years)		✓
Control participants (20-30 years)		✓
Assessments		
Functional scores		✓
3D motion analysis		✓
Fluoroscopy		✓
Dynamometer		✓
MRI[a]		✓

[a]MRI: magnetic resonance imaging.

Functional Scores

Functional scores revealing the patient's pain, arm range of motion, and ability to perform daily living activities will be assessed using a shortened version of the Disabilities of Arm, Shoulder, and Hand (DASH) questionnaire (QuickDASH) [17] and additional questionnaires, including the Constant Score [18], American Shoulder and Elbow Surgeons Shoulder Score [19], Subjective Shoulder Value [20], and numerical pain rating scale scores. Additionally, participants will complete the EQ-5D-5L [21] questionnaire to assess their general health status.

Abduction Test

Participants will be asked to perform a loading/unloading shoulder abduction test until 30°. This test involves abducting the arms to 30° in the scapular plane and then adducting the arms back to the initial (reference) position. All arm movements are performed bilaterally in an upright seated position, with shoulders in the neutral position (hanging arm with thumb toward the front). To control the maximal amplitude of arm abduction, a string is attached to the lower arm and adjusted to the desired maximum position by using a goniometer. Before data collection, participants will be asked to perform exercise movements in the scapular plane. To ensure a comparable speed of movement, verbal commands will be given to the participants.

Single-Plane Fluoroscopy

Single-plane fluoroscopic images (Multitom Rax, Siemens Healthineers) will be captured for the following three conditions: without additional weight and in randomized order with 2-kg and 4-kg handheld weights. The rest time between each condition will be at least 30 seconds. Images will be acquired first for the right shoulder independent of the symptomatic side. After a rest period of at least 1 minute, the same tests will be repeated in the same order to obtain images of the left shoulder. The alignment of the scapular plane will be checked by fluoroscopy. Images will be captured with a pulse rate of 10 Hz to minimize radiation exposure. Image dimensions will be calibrated with a reference ball (Ø=25 mm) placed in the field of view.

Motion Capture Data

Motion data of this 30° abduction test will be captured with and without additional handheld weights of 1, 2, 3, and 4 kg. The order of the loading conditions will be randomized to minimize fatigue. The task will be interrupted if the participant's pain exceeds 7 out of 10. Participants will perform 3 trials of each arm movement while kinematic data are collected using a 10-camera Vicon system (Vicon) at a frame rate of 240 Hz. To assess 3D joint angles, retroreflective markers (Figure 1) will be placed on the upper extremity according to the International Society of Biomechanics guidelines [22].

Figure 1. Placement of markers and sensors: (A) anterior and (B) posterior view.
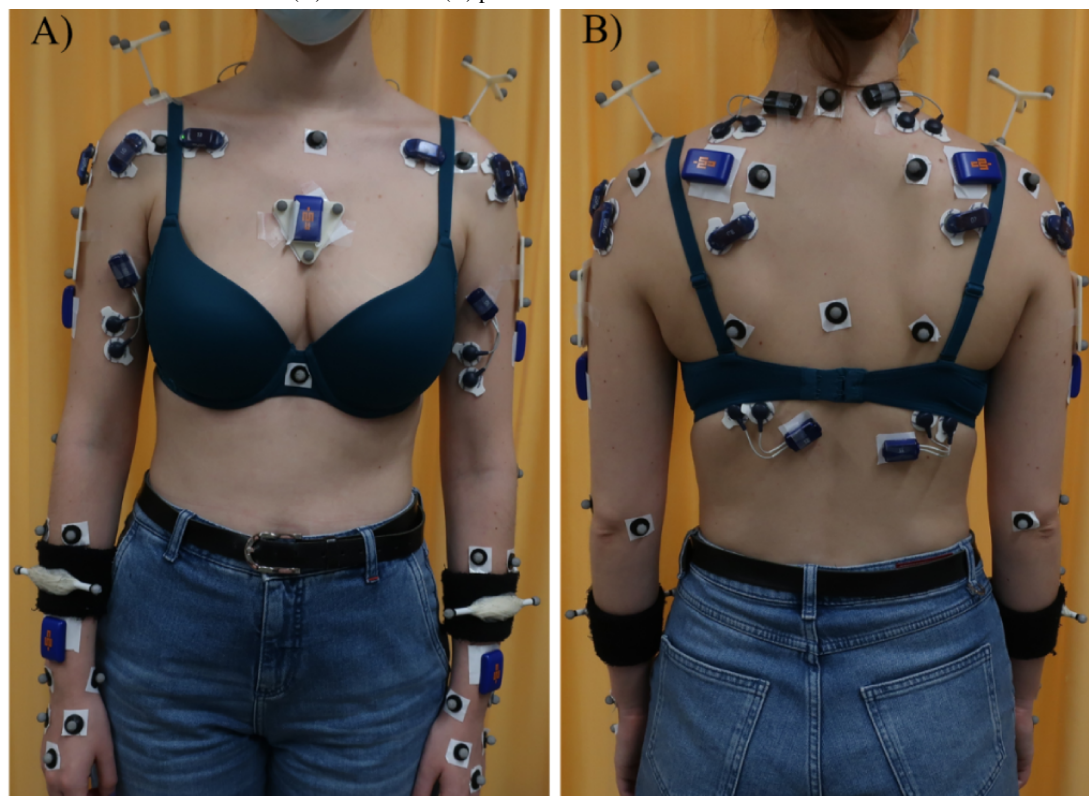
Electromyographic Data

Electromyographic data of the infraspinatus, biceps brachii, anterior, middle, and posterior parts of the deltoid, clavicular part of the pectoralis major, latissimus dorsi, and upper trapezius muscles will be recorded during all arm movements. Surface electrodes (Myon AG) will be placed over the corresponding muscles following the guidelines of the SENIAM (Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscles) project [23] and Criswell [24] (Figure 1). Electromyographic signals will be normalized using the maximal voluntary isometric contraction recorded during the following standard tests (captured during a 5-second trial): empty can, internal rotation 90°, flexion 125°, palm press, and extension [25,26]. Since these tests do not specifically account for the biceps brachii, an additional trial will be captured during maximal contraction against resistance with the elbow flexed at 90°. In the case that a participant cannot reach 90°/125° in flexion or 90° in abduction, these tests will be adapted to the participant's capabilities by reducing the test angles.

Inertial Sensors

Inertial sensor data will also be collected during the loaded and unloaded abduction tests. Additionally, participants will be asked to perform full arm abduction, flexion, and internal and external rotations movements (without additional handheld weight). Inertial sensors (Vicon Blue Trident) will be placed on the participants' thorax, scapulae, humeri, and forearms [27] (Figure 1). Accelerations and angular velocity will be captured for the various movements.

Isometric Shoulder Strength

Shoulder strength will be tested under isometric conditions using a dynamometer (Biodex System 4 Pro, Biodex Medical Systems). Isometric shoulder strength will be assessed for abduction at 10° and 30° in the scapular plane. The participant will be in a seated position with the arm extended in neutral rotation. The protocols comprise 3 repetitions of 5 seconds of pushing and 5 seconds of resting for both abduction angles. Isometric shoulder strength will also be measured for internal and external rotation at neutral rotation in 15° abduction (scapular plane). Participants will be seated with a 90° flexed elbow [28]. The protocol comprises 3 repetitions of 5 seconds of external rotation and 5 seconds of internal rotation with a 5-second rest in between. Both shoulders will be tested in a randomized order. The maximum value of 3 trials will be calculated and recorded as the participant's maximum isometric strength for each movement.

MRI Visualization

MRI will be performed using a 3T scanner (Prisma, Siemens Healthineers) with dedicated shoulder and body array coils. No contrast agent will be administered to the participants. Both shoulders will be scanned. The MRI protocol consists of an axial proton density turbo spin echo (TSE) sequence with fat saturation, a sagittal T1-weighted TSE sequence, a sagittal and a coronal T2-weighted BLADE sequence, and a coronal T1-weighted volumetric interpolated breath-hold examination Dixon sequence (Table 2).

Table 2. Characteristics of the MRI[a] sequences.

MRI sequence	Repetition time/echo time (ms)	Slice thickness (mm)	Field of view (mm)	Matrix
PD[b] TSE[c] FS[d] axial	4500/34	2	140	320×320
T1 TSE sagittal	762/11	3	159	384×384
T2 BLADE sagittal	4210/72	3.6	160	320×320
T2 BLADE coronal	3400/75	3.6	150	320×320
T1 VIBE[e] Dixon coronal	4.04/1.23 (TE[f]1) and 2.46 (TE2)	1.3	238×332	184×256

[a]MRI: magnetic resonance imaging.

[b]PD: proton density.

[c]TSE: turbo spin echo.

[d]FS: fat saturation.

[e]VIBE: volumetric interpolated breath-hold examination.

[f]TE: echo time.

Outcome Parameters

The primary and secondary end points are summarized in Textbox 2.

Textbox 2. End points of the experimental protocol.

Primary

- Load-induced glenohumeral translation (liTr) from fluoroscopy
- Load-induced muscle activation of the deltoid muscle

Secondary

- liTr from motion capture
- Anatomical parameters
- Injury type
- Functional scores

Other

- Age, body height, body mass, and sex of the participant
- Isometric shoulder muscle strength
- Muscle cross-sectional area and fatty infiltration
- Conservative treatment and duration of physiotherapy

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liTr Measure

Fluoroscopy-based and motion capture–based liTr will be measured (Figure 2).

On the fluoroscopic images, the glenohumeral joint center, humeral shaft, most lateral point of the acromion, and inferior and superior glenoid edges will be registered. The glenohumeral joint center will be determined as the geometric center of a circle comprising the articulating surface of the humeral head [29-32]. Hence, glenohumeral translation during arm abduction and adduction will be measured as the inferior-superior component of a glenoid coordinate system [33] (Figure 2A). The arm abduction angle will be measured as the angle between a line passing through the glenohumeral joint center, the humerus shaft midpoint, and the vertical line.

Glenohumeral translation will also be assessed using instrumented motion analysis. The calibrated scapular and humeral landmarks will be used along with equations outlined by the International Shoulder Group [34] and the functional joint center method to determine the instant glenohumeral joint center within the humerus reference system. The vertical distance from the glenohumeral joint center to the acromion marker will be calculated for a neutral trial and with the arm in 30° shoulder abduction for each loading condition. Motion capture–based liTr will be calculated for each participant as the differences in the distance between the glenohumeral joint center and the acromion under different loading conditions (Figure 2B).

Figure 2. Load-induced glenohumeral translation (liTr). (A) Fluoroscopy-based and (B) motion capture–based measurements. GH: glenohumeral joint center.
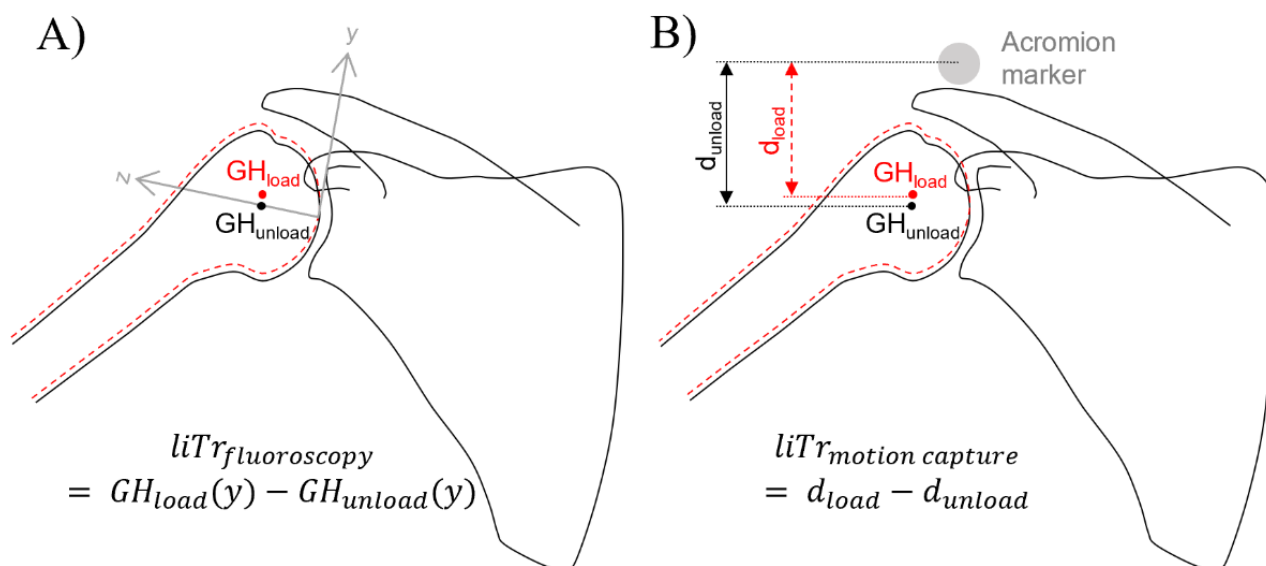
liMA Measure

First, an independent component analysis–based filtering will be applied to the electromyographic data to remove electrocardiogram contamination [35]. Then, additional noise artifacts will be removed by a modified bandpass filter of 10 Hz to 450 Hz [36]. For each muscle, liMA will be computed for each loading condition of the abduction test as the root mean square of the electromyographic signal during the loaded arm positions relative to the root mean square of the electromyographic signal during the unloaded arm position [37]. Electromyographic data will be normalized to the maximal voluntary isometric contractions for visual presentation of the electromyographic trajectories.

Critical Shoulder Angle

Participants' critical shoulder angle will be measured on an anterior-posterior double-obliquity fluoroscopy image of the shoulder. This is defined as the angle subtended by a line parallel to the glenoid and a line through the inferior-lateral edge of the glenoid and the inferior-lateral edge of the acromion [5]. The critical shoulder angle has been shown to be reproducible and significantly greater in patients with rotator cuff tears than in the general population [5]. High angles (>35°) have been associated with rotator cuff tears and greater joint instability [38]. Although it can be assumed that there are no side-to-side differences in the critical shoulder angle [39], it will be measured for both shoulders of all the participants (left and right).

Glenoid Inclination

The glenohumeral joint is also affected by the orientation of the glenoid; thus, the glenoid inclination can aid our understanding of various shoulder conditions. Indeed, an abnormal glenoid inclination might be associated with rotator cuff tears and superior glenohumeral translation [40]. For each participant, the glenoid inclination will be measured on the initial fluoroscopy image as the angle between a line from the upper

to the lower glenoid rim (glenoid plane) and a second line set on the floor of the supraspinous fossa [6,40].

Greater Tuberosity Angle

The greater tuberosity angle will be measured on the initial fluoroscopy image as the angle between a line parallel to the humerus diaphysis through the glenohumeral joint center and a line from the upper border of the humeral head to the most superolateral edge of the greater tuberosity [41]. A greater tuberosity angle over 70° has been observed to predict rotator cuff tears [41].

Subacromial Space

The subacromial space will be measured on the initial fluoroscopic image as the shortest acromiohumeral distance [42,43]. An acromiohumeral distance between 7 mm and 14 mm is usually considered normal, but below 7 mm, has been associated with rotator cuff tears [43]. A narrow subacromial space might compress the supraspinatus tendon, causing pain [44,45].

Muscle Cross-sectional Area

Measurements of the muscle cross-sectional area will be performed on the MRI images using dedicated software (Sectra PACS, Sectra Medical Systems). The cross-sectional area of all rotator cuff muscles will be measured at 2 different positions on parasagittal reformatted images [4]. The cross-sectional area of the deltoid will also be measured on the axial plane at the middle of the glenoid [4].

Tear Size, Type, and Location

Information about tear size, type, and location will be retrieved from MRI images and previous shoulder reports or previous radiological shoulder images of the patients, if available. Tear size will be classified into (1) partial or (2) complete supraspinatus tendon tear. Tear type will be classified into supraspinatus tendon tear without injury to other rotator cuff tendons (type A) and with injury to other rotator cuff tendons muscles (type B). Both will be used as indicators for injury

severity. Additionally, the value of a combined classification will be investigated. Tear location will be defined as the distance from the anterior margin of the tear at the footprint to the intra-articular portion of the bicep. This will allow us to assess whether most anterior fibers of the supraspinatus tendon are intact [46,47]. Tear location will also be analyzed in comparison to shoulder strength and muscle activity. Partial and full-thickness ruptures will be classified according to the classifications of Ellmann [48] and Patte [49], respectively, allowing us to evaluate how advanced the rotator cuff tear is.

Statistics and Determination of Sample Size

All study-related data will be entered into and stored using a web-based Research Electronic Data Capture (REDCap; Vanderbilt University) system [50,51]. All statistical analyses will be performed in R statistical software [52]. Overall, 25 patients with 1 symptomatic shoulder with a rotator cuff tear, 25 age- and sex-matched asymptomatic control participants, and 25 sex-matched young control participants will participate in this study. This means that a total of 150 shoulders will enter the analysis. Comparisons between the fluoroscopy-based liTr and motion capture–based liTr will be made. Reproducibility and agreement will be assessed by the mean and standard deviation of differences and Bland-Altman plots. Precision in estimating the liTr will be assessed by average relative standard errors and R^2 values from a global model. Potential deviations from a linear relationship will be assessed by random effects models for a quadratic term. The influence of covariates on the liTr and the biological variation of liTr will be assessed by mixed models applied to the original glenohumeral translation measurements with the liTr as a random effect. Dependence between the shoulders will be considered by bivariate random effects.

Participant Characteristics

Descriptive statistics will be used to describe the characteristics of the participants in each group. Mean and standard deviation of age, sex, body height, body mass, BMI, conservative treatment (if applicable), time since injury, and duration of physiotherapy will be calculated to describe the participants.

Sample Size Calculation

From a pilot study data consisting of 18 participants (8 patients and 10 asymptomatic controls), we found a correlation of 0.37 between the liTr and liMa for the treatment group and an overall correlation of 0.63 for all individuals included in the study [16]. Using these findings, we considered different correlation scenarios between liTr and liMa for a different power of analysis (Figure 3). For a 5% significance level, 90% power, and a correlation of 0.37, we need 76 shoulders. Considering a possible dropout rate of 5%, we need 80 shoulders for the first hypothesis in this study. We also powered the analysis for the secondary hypotheses and used the repeatability investigation, which suggested a measurement error with a standard deviation of 0.16 mm for the sphere method when assessing the liTr by comparing a load of 3 kg with no load. Moreover, the pilot study revealed a population standard deviation of 1.09 mm for the liTr, suggesting a substantial biological variation in the liTr. Thus, it should be possible to estimate this variation and assess the effect of covariates. Based on our clinical findings, we expect to observe incidental findings of rotator cuff tears in two-thirds of asymptomatic shoulders in participants aged 45 years or older. Therefore, we expect to have 75 shoulders with rotator cuff tears. Within the 75 shoulders with rotator cuff tears, it will be possible to detect a difference of 0.8 mm in liTr with a power of 90%.

Figure 3. Sample size estimation for different scenarios for power and correlation.
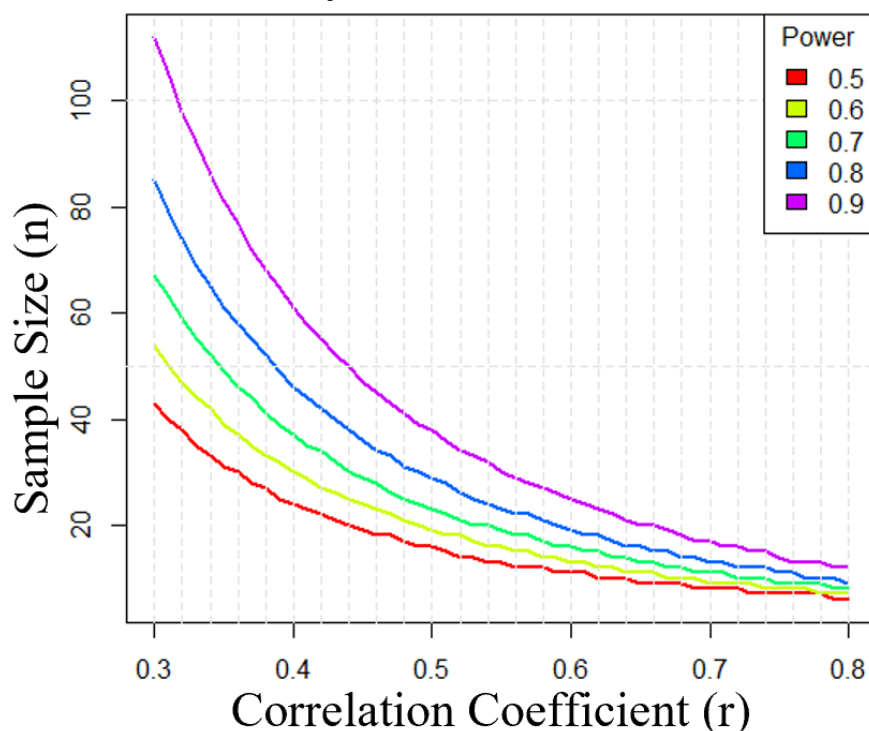
We adopted this sample size calculation post hoc after the aforementioned clinically relevant finding. We kept the recruitment of 75 participants but adapted the study post hoc to 3 groups with 25 participants in each. For any significant findings, this post hoc adaptation will be further investigated in the analysis stage by power calculation to assess potential limitations for the main analysis and reporting of results to avoid relying on findings by chance.

Ethics Approval

This study protocol was approved by the Ethics Committee Northwest Switzerland (2021-00182; Multimedia Appendix 2) and registered on ClinicalTrials.gov (NCT04819724). Prior to participation, written informed consent will be obtained from all participants. Participants can withdraw from the study at any time. This study is conducted in accordance with the Declaration of Helsinki, the principles of Good Clinical Practice, the Human Research Act, and the Human Research Ordinance, along with other locally relevant regulations.

Safety Considerations

Fluoroscopy data will be used in this study to measure the glenohumeral translation. Fluoroscopy is a low-dose x-ray application routinely used in clinical practice. The estimated effective dose will be maximally 0.01 mSv. A standard x-ray of the chest, which is considered to have minimal radiation exposure, has an effective dose of 0.1 mSv and is comparable to exposure to 10 days of natural background x-ray volume [53]. To limit radiation exposure, fluoroscopy images will only be taken for 0-, 2-, and 4-kg handheld weights during the 30° abduction test in the scapular plane. Therefore, 1- and 3-kg handheld weights will not be included in the fluoroscopy-based liTr measurements.

Results

Recruitment and data collection began in May 2021, and they will last until the recruitment target is achieved. Data collection is expected to be completed by the end of 2022. As of November 2022, data processing and analysis are in progress, and the first results are expected to be submitted for publication in 2023.

Discussion

This experimental protocol will allow for a comprehensive analysis of clinical, functional, and biomechanical data. Furthermore, using MRI, asymptomatic rotator cuff tears will be revealed, aiding our understanding of the effect of rotator cuff tears on glenohumeral motion, especially in asymptomatic shoulders. We expect that rotator cuff tears will have a greater glenohumeral translation and that this will depend on the additional load applied and the anatomical parameters. In addition, a greater liMA of the deltoid muscle is expected with greater liTr. These outcomes might also be associated with muscle cross-sectional area, tear size, and type.

With our infrastructure, electromyographic/motion capture data and fluoroscopy images cannot be acquired simultaneously. Hence, we cannot completely rule out differences in the execution of the abduction tests. However, prior to data collection, exercises will be practiced, and verbal commands will be given to ensure comparable movements.

Glenohumeral translation is an important surrogate for shoulder instability that represents not only functional limitations but also a risk factor for the development of joint degeneration, including osteoarthritis. The results of this study will provide the first evidence of a dose-response relationship between additional weight and glenohumeral translation in patients with rotator cuff tears. Confirming this dose-response relationship and its impact on functional scores and modulating effects by tear type and size, muscle cross-sectional area, critical shoulder angle, and glenoid inclination will elucidate the importance of limiting additional weight during daily activity in this population. Revealing the effects of additional load on muscle activity of the intact rotator cuff tendon in the injured joint will provide evidence of potential overload in these muscles that may lead to secondary damage in other tissues in the injured joint. This study can be considered a proof of concept of a potential diagnostic test (loading shoulder abduction test) for glenohumeral translation. The recommendation based on our results will directly impact activity limitations in patients with rotator cuff tears and influence treatment choice and rehabilitation regimens. The results of this study will be presented at national and international conferences and published in peer-reviewed open-access journals.

Authors' Contributions

EC, AM, CN, JG, and DB contributed to the study design. EC was responsible for ethical approval and wrote the manuscript. AM was a major contributor to writing the manuscript. EC, FE, and AMM are involved in participant enrollment. FE and AMM provided support for clinical aspects. AM, AMM, and DB conceived the study and acquired funding. BKK contributed to the radiological analysis. SA assisted with the statistical analysis. All authors read and approved the final manuscript.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) checklist.
[PDF File (Adobe PDF File), 120 KB - resprot_v11i12e43769_app1.pdf]

Multimedia Appendix 2
Ethics approval.
[PDF File (Adobe PDF File), 72 KB - resprot_v11i12e43769_app2.pdf]

Multimedia Appendix 3
External funder confirmation.
[PDF File (Adobe PDF File), 104 KB - resprot_v11i12e43769_app3.pdf]

Multimedia Appendix 4
External peer-review report by the Swiss National Science Foundation.
[PDF File (Adobe PDF File), 126 KB - resprot_v11i12e43769_app4.pdf]

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Abbreviations

DASH: Disabilities of Arm, Shoulder, and Hand
liMA: load-induced changes in muscle activation
liTr: load-induced glenohumeral translation
MRI: magnetic resonance imaging
REDCap: Research Electronic Data Capture
SENIAM: Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscles
SPIRIT: Standard Protocol Items: Recommendations for Intervention Trials
TSE: turbo spin echo

Assessing the Quality of the World Health Organization's Skin NTDs App as a Training Tool in Ghana and Kenya: Protocol for a Cross-sectional Study

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Abstract

Background: Neglected tropical diseases (NTDs) affect over 1.5 billion people worldwide, the majority of them belonging to impoverished populations in low- and middle-income countries (LMICs). Skin NTDs are a subgroup of NTDs that manifest primarily as skin lesions. The diagnosis and treatment of skin NTDs entail considerable resources, including trained personnel and financial backing. Many interventions are being launched and evaluated, particularly mobile health (mHealth) interventions, such as Skin NTDs App, a training and decision support tool offered by the World Health Organization (WHO) for frontline health workers (FHWs). As most digital health guidelines prioritize the thorough evaluation of mHealth interventions, it is essential to conduct a rigorous and validated assessment of Skin NTDs App.

Objective: We aim to assess the quality of version 3 of Skin NTDs App, developed for the WHO by Universal Doctor and Netherlands Leprosy Relief as a training and decision support tool for FHWs.

Methods: A cross-sectional study will be conducted in 2 LMICs: Ghana and Kenya. We will use snowball sampling recruitment to select 48 participants from the target population of all FHWs dealing with skin NTDs. The sample group of FHWs will be asked to download and use Skin NTDs App for at least 5 days before answering a web-based survey containing demographic variables and the user Mobile App Rating Scale (uMARS) questionnaire. A semistructured interview will then be conducted. Quantitative and qualitative data will be analyzed using SPSS (version 25; SPSS Inc), with statistical significance for all tests set at a 95% CI and $P \leq .05$ considered significant. Data derived from the semistructured interviews will be clustered in themes and coded to enable analysis of various dimensions using ATLAS.ti.

Results: The estimated completion date of the study is in the third quarter of 2022. The results are expected to show that Skin NTDs App version 3 has a good reported user experience, as assessed using the uMARS scale. No differences are expected to be found, except for those related to experience in dermatology and the use of mobile technology that could influence the final score. Semistructured interviews are expected to complete the results obtained on the uMARS scale. Moreover, they will be the previous step before assessing other aspects of the app, such as its efficiency and how it should be disseminated or implemented.

Conclusions: This study is the first step in a qualitative and quantitative assessment of Skin NTDs App as a training and support tool for FHWs diagnosing and managing skin NTDs. Our results will serve to improve future versions of the App.

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Introduction

Neglected tropical diseases (NTDs) are a group of 20 diseases and conditions identified by the World Health Organization (WHO), which affect over 1.5 billion people. Most of afflicted individuals are women and children living in impoverished populations in tropical and subtropical regions [1]. If not detected or treated, some of these diseases are fatal or can become chronic and irreversible, not only causing lifelong disabilities but also stigma and social exclusion, thereby perpetuating a cycle of poverty with a direct impact on development and economic productivity in low- and middle-income countries (LMICs) [2]. The combination of these factors renders the control of NTDs both necessary and complex.

NTDs had not received global prioritization until 2005, when the WHO established a new strategy to target the group as a whole [1]. Now, NTDs are classified in 2 groups: those that are potentially preventable through large-scale chemotherapy interventions and those that can only be addressed through individual case management [3].

Skin NTDs are a subgroup of NTDs that manifest primarily as lesions on the skin and can be detected through visual screening [4,5]. This group consists of Buruli ulcer, cutaneous leishmaniasis, deep fungal infections, post-kala-azar dermal leishmaniasis, leprosy, lymphatic filariasis, mycetoma, onchocerciasis, scabies and other ectoparasites, and yaws. As most of these conditions do not benefit from large-scale preventive drug administration, they rely on early diagnosis and treatment, which, in turn, relies on considerable resources, including trained personnel and financial backing [4].

Frontline health workers (FHWs) have been identified as vital to the impact of any campaign intended to tackle NTDs [6]. The term FHWs refers to any health worker who directly provides service to a community. As they often have insufficient specialized medical knowledge, data collection procedures, and contact with peers, FHWs need to be equipped with knowledge and tools that will facilitate their role in diagnosing, treating, and referring patients to another level of the health system.

New methods to improve the clinical management and epidemiological surveillance of many diseases, including infectious and skin diseases, have recently been developed [7]. The WHO has recognized that mobile health (mHealth) can be a significant component in delivering global health care and can provide considerable support for FHWs [8]. However, the most recent systematic review of mHealth strategies for dealing with skin NTDs concluded that work is needed to homogenize interventions and thereby reduce methodological limitations [9].

To support FHWs with new technologies, the WHO's Department of Control of NTDs has developed Skin NTDs App [10], a mobile version of the training guide they published in 2018 [11]. This App helps FHWs diagnose and manage skin NTDs by using an algorithm based on identifying signs and symptoms and provides extra information about these diseases. The recently released version 3, a combination of WHO's Skin NTDs and SkinApp, developed by the nongovernmental organization (NGO) Netherlands Leprosy Relief, has several new features. As yet, the new app is not publicly available, and no evaluations have been conducted. Moreover, studies have shown that relying on the system of "star"-rating iOS and Android devices is insufficient within the exponentially expanding market of medical apps [12].

Most digital health technology frameworks include evaluation of mHealth interventions as a crucial step in ensuring quality and enabling end users to not rely solely on popularity [13-15]. At this point, it is important to emphasize that quality refers to not only clinical effectiveness but also other important domains such as, among others, usability, interoperability, technical security, and data protection [13]. The user version of the Mobile App Rating Scale (uMARS) [12] has been found to be a simple and reliable tool for classifying and rating mobile health apps based on objective and subjective quality domains [14,15].

As the developers of Skin NTDs App have ambitious plans and expectations, it is essential to conduct a rigorous and validated assessment of this app. This paper describes the protocol for a cross-sectional study aimed to assess the engagement, functionality, aesthetics, and quality information for the real end user in their actual context of version 3 of Skin NTDs App in accordance with a validated tool. In addition, a secondary goal of this study will be to determine whether any of the demographic information collected has an impact on the final uMARS score, since the developers of Skin NTDs App do not intend to customize the app when implementing it in any setting.

Methods

Study Design

Between April 2022 and May 2022, we will conduct a cross-sectional study among 98 FHWs based in 2 LMICs: Ghana and Kenya.

Ethics Approval

This study will be conducted in accordance with the ethical principles established by the World Medical Association in the *Declaration of Helsinki–Ethical Principles for Medical Research Involving Human Subjects* [16]. This protocol has been approved by the ethics committee of Universitat Oberta de Catalunya.

Additionally, to ensure that the protocol also meets the ethical requirements in the countries where the study will be conducted, it has been already submitted in Ghana to the Ethical Committee of Kwame Nkrumah University of Science and Technology, Kumasi. The authors have also initiated the process to submit the protocol in Kenya to the Ethical Committee of Coast General Teaching and Referral Hospital, Mombasa.

Participants and Eligibility

All FHWs who deal with skin NTDs in both selected countries on a daily basis, are responsible for the diagnosis and management of skin NTDs, who own a smartphone device (Apple or Android), and have downloaded Skin NTDs App and used it on at least 5 different days for at least 10 minutes each day are considered eligible. Moreover, participants will need to have access to email or WhatsApp to provide informed consent.

Exclusion criteria are a low comprehension of the English language and refusal to sign the informed consent form.

The target population is the same for both parts of the study. Participants will be asked to read the information sheet (for more detail, see Multimedia Appendix 1) before signing the informed consent form.

Sample Recruitment

The difficulty of having direct contact with FHWs in these 2 countries necessitates nonprobabilistic snowball sampling, a recruitment technique in which selected participants are asked to identify and contact other potential subjects among their acquaintances to participate in the study. Despite the fact that this method is nonrandomized, it seems to be the most effective way to identify a difficult-to-reach audience, when participants are contacted digitally, and researchers are located in another continent.

The chain of contacts will originate from a medical officer in WHO's Department of Control of NTDs, who will contact colleagues who work on skin NTDs in the WHO regional and country offices and international NGOs by mail. The country offices will be asked to invite FHWs to participate in the study through Ministries of Health or national NGOs. All FHWs who meet the inclusion criteria and sign the informed consent form will be sent the survey and, if applicable, scheduled for interview (Figure 1).

Figure 1. Diagrammatic representation of snowball sampling recruitment. uMARS: user Mobile Application Rating Scale; WHO: World Health Organization.
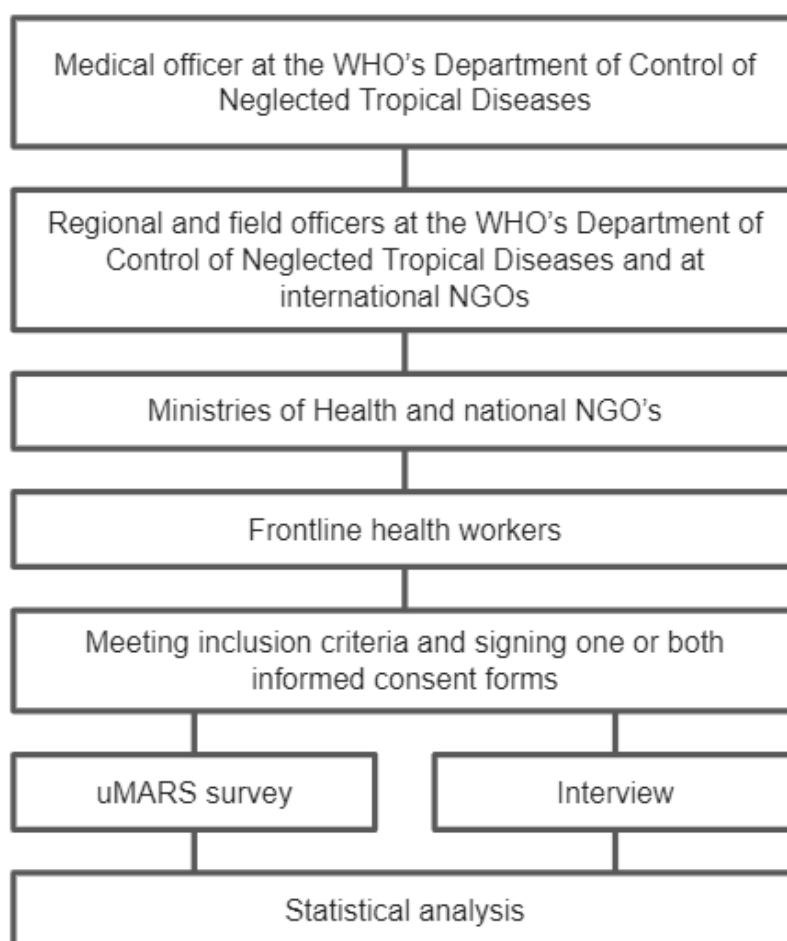
Sample Size Calculation

Sample size was calculated on the basis of the 6 stages of the intervention maturity life cycle described by the WHO in *Monitoring and Evaluating Digital Health Interventions* [17], a schematic and practical guide to know which have to be the

goals in each stage, how many participants are required, and which are the measurement targets.

Skin NTDs App is currently in the prototype phase, which corresponds to stages 1 and 2 of the 6 stages of the intervention maturity life cycle, according to WHO guidelines. As a result, the WHO advises testing it with a sample size of between 10 and 100 users.

Taking into account that 100 is the maximum recommended number of participants and the web-based modality of this study, we assume a dropout rate of 50%. These calculations leave a final sample size of 50 participants.

Outcomes

Demographic Variables

Participants will be asked to complete an anonymous survey of various demographic data, which will include the following: age, gender ("Male," "Female," "nonbinary," and "transgender"), country of residence ("Ghana" and "Kenya"), type of FHWs (3 specified categories will be provided as these are most common: "Medical Doctor," "Nurse," "Community Health Worker," and "Other" under which participants will be asked to add their own category), frequency of dealing with skin NTDs ["Rarely (<1 case/month)," "Occasionally (1-3 cases/month)," "Frequently (4-6 cases/month)," and "Usually (>6 cases/month)"], experience and training in dermatology ("Trained and experienced," "Not trained but with experience with dermatology patients," and "Neither trained nor experienced"), work environment ("rural" and "urban"), working institution ("Public healthcare setting," "Private healthcare setting," and "NGO"), knowledge of mobile technology ("High—I'm able to use mobile technologies without having many issues," "Medium—I'm able to use mobile technologies but sometimes I need some help," and "Low—I'm not able to use mobile technologies without supervision and help"), and languages (open answer for participants to enter the languages they can speak).

uMARS Questionnaire

The uMARS is a simple, objective, and reliable tool developed for users by Stoyanov et al [12] to classify and assess the quality of health-related mobile apps. The tool assesses 20 items clustered into 4 objective subscales (engagement, functionality, aesthetics, and information quality) and 1 subjective subscale. Participants rate each item using a Likert scale from 1 to 5 (1="Inadequate," 2="Poor," 3="Acceptable," 4="Good," and 5="Excellent"). There is also the option "not applicable" if an item cannot be assessed. There is an extra category entitled *App-Specific* with descriptive purposes only that contains 5 more items and can be adjusted and adapted by researchers. This category evaluates the perceived impact of the app on users' knowledge, attitudes, intentions to change, and the likelihood of actual change. We will add 9 questions to complete this domain, relating to app discovery, time using the app, frequency of use, notification updates, usefulness, translation features, patient record features, and desktop version.

The uMARS score is calculated separately based on the original recommendation from the authors of this scale. Hence, 2 scores

will be obtained: app quality mean score and app subjective quality score. This division is made to strengthen the objectivity of the uMARS as a measure of app quality. All those questions rated as "not applicable" will be excluded from the mean scores.

Semistructured Interviews

Semistructured interviews are a validated qualitative method for exploring the perspectives, perceptions, and opinions of participants. Semistructured interviews combine prepared questions with others that arise during the interview [18].

In this study, interviewers will ask 8 questions in the same order and using the same words to each participant—a standardization that will facilitate comparability [19]. Questions will be open-ended, neutral, clear, and in familiar language. The structure of the interviews will be as follows: a brief presentation of the interviewer and the study, a general question related to the overall use of Skin NTDs App, 8 core questions directly relating to information needed for app assessment, and unplanned questions that arise during the interview based on the participants' answers.

It is estimated that semistructured interviews will be conducted in a minimum of the 10% of the final sample size or until information saturation is reached.

Data Collection and Study Procedure

Once a participant has signed the initial consent form, an email will be sent with the first part of the survey and details of the study procedure. This information will include the following: links to download the app, a recommended time of app usage before answering the survey, and information about the interviews.

Participants will receive an email over the following days with a Google Forms link through which they can enter their demographic data and answers to the uMARS questionnaire. In the last section of the survey, participants will need to indicate whether they would like to participate in the next phase of the study—the semistructured interviews.

A separate email or WhatsApp message will be sent to those who wish to participate in the interviews. Participants will receive an information sheet and a second consent form, which must be signed and returned before the participant can be interviewed.

Once informed consent has been obtained, participants and researchers will schedule a semistructured interview at a mutually convenient time. Interviews will be carried out via video calls using Google Meets; therefore, participants will receive an email or WhatsApp message with a link specifying a date and time.

Once the interviewer has reminded the interviewee why audio recording is necessary, audio recording will start and continue throughout the interview. The questions will be asked as previously described (for more detail, see Multimedia Appendix 2). Interviews will last between 25 and 40 minutes, during which time the interviewer will take notes and repeat questions or words as required to fully understand the interviewee's meaning.

Researchers will use Otter.ai software to transcribe all interviews for analysis. During the data collection phase of the study, researchers will send as many reminders to participants as they deem necessary.

Statistical Analysis

Quantitative data will be collected in Excel (Microsoft Inc) to be analyzed using SPSS for Windows (version 25; SPSS Inc). Statistical significance for all tests will be set at a P value of ≤.05. To describe the quantitative information received from the uMARS scores, a descriptive analysis will be carried out. Measures of frequency, central tendency, and dispersion will be used to describe this data, which will be shown in tables. Depending on sample size, a Shapiro-Wilk or Kolmogorov-Smirnov test will be used to assess the normality of data (P≤.05). In the bivariate analysis, a chi-square test will be used to compare categorical variables. Depending on whether the distribution is normal, quantitative data will be compared using a Student t or Mann-Whitney U test. A multivariate analysis will be performed using a logistic regression analysis to add the covariates that could skew the main association under analysis. Finally, a cluster analysis will be performed to identify similar groups based on the observed values of several variables. A 95% CI will be assumed and P≤.05 will be considered to indicate a significant difference.

Selected quotes will be returned to participants for approval. Qualitative data derived from the semistructured interviews will be analyzed using ATLAS.ti (Scientific Software Development GmbH). We will identify attributes, cluster them into different themes, and then code these themes to analyze the various dimensions explored during the interviews.

Results

The results of this work are expected during the third quarter of 2022. First, Skin NTDs App version 3 is expected to obtain a result of >3 out of 5 points on the uMARS. In addition, it is expected that the results will not show any difference by sex, type of work environment or working institution, or country. However, it is suspected that those variables related to experience in dermatology or the use of mobile technology may be determining factors when evaluating the user experience with the App. On the other hand, the perceptions collected from the semistructured interviews are expected to be the element to understand the reason for the results obtained on the uMARS.

Moreover, they will be the previous step before assessing other aspects of the App, such as the efficiency, how it should be disseminated or implemented, etc.

Discussion

Principal Findings

Skin NTDs comprise a subgroup of 13 NTDs that present primarily as lesions on the skin and can be detected through visual screening. They rely on early diagnosis and treatment, which implies that the resources consumed are significant. However, if not detected or treated, they can potentially turn chronic and irreversible, thus favoring a cycle of deteriorating health and socioeconomic status, which does nothing to help the overall development of LMICs.

Any solution that helps improve their current management should be considered and studied in detail. Among them, the WHO has identified the use of mHealth as a critical component in tackling the complexities underlying skin NTDs.

In this line of work, Skin NTDs App is an initiative by the WHO's Department of Control of Neglected Tropical Diseases as a training and decision support tool to assist FHWs who diagnose and manage skin NTDs in their daily practice. Through the uMARS questionnaire and semistructured interviews, this novel cross-sectional study will investigate how FHWs quantitatively and qualitatively rate the quality of Skin NTDs App version 3.

Considering that the app is still under development and has not yet been implemented in countries where skin NTDs are prevalent, this study represents a chance to include the feedback of the real end users in upcoming versions. Moreover, this action is likely to influence the subsequent impact of any implementation campaigns that may be undertaken.

Limitations

There are various limitations associated with this study.

The first limitation that arises and may seem relevant is the decision behind choosing Ghana and Kenya to perform this study. This was based on 3 factors: (1) Skin NTDs App can only be downloaded in English; hence, the choices are limited to countries where English is an official language; (2) these 2 countries have a long history of web-based disease tracking and are endemic for at least 8 skin NTDs each; and (3) to ensure an adequate sampling, countries were chosen on the basis of the accessibility to key officials and program managers and their chances to further contact enough respondents.

Regarding the methodology used, snowball sampling is a nonprobabilistic and nonrandomized method; hence, the sample may not be representative of the general population. However, because the study will be conducted entirely on the internet and the participants and authors are in different places, this is the only way we can connect with FHWs—a highly specialized group that can be challenging to reach in LMICs if contacted remotely.

On the other hand, it is also important to point out some limitations of the uMARS. First, this tool has only been validated among young people using 2 specific apps related to other health areas. However, its high reliability and the inclusion of both objective and subjective domains make it the only questionnaire available that is validated and simple for users to assess health apps.

Another requirement is that FHWs will have to use the app for at least 5 days as opposed to the 10 minutes originally required by the original uMARS publication. Since there will not be any direct control over that, this statement cannot be guaranteed. To determine whether they have fulfilled it or not, a question has been added to the survey.

Finally, it is important to highlight that this study does not claim to assess the clinical effectiveness of Skin NTDs App. This would require a randomized clinical trial and exceed the scope of this study. Although this is version 3, there are still issues to address, including whether information in the app is updated in response to the most recent research.

Conclusions

In conclusion, the findings of this study will be used to enhance upcoming releases of Skin NTDs App by examining FHWs' perspectives. In the future, this tool might be made available to LMICs in an effort to improve the management of skin NTDs. Thus, to develop an app that has a larger chance of being used widely around the world, it is crucial to evaluate the true impact of Skin NTDs App on the real end users—that is, FHWs—and include their thoughts in this initial phase.

Data Availability

All data sets generated during the study will be deposited in available repositories or added to the main manuscript when published. Data derived from the uMARS survey will be published in a data sheet file. On the other hand, data from the semistructured interviews will be shared in a document format only with the most relevant sentences or answers from participants. All data considered confidential will not be shared.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Information sheet.
[DOCX File , 9 KB - resprot_v11i12e39393_app1.docx]

Multimedia Appendix 2
Semi-structured interview.
[DOCX File , 14 KB - resprot_v11i12e39393_app2.docx]

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Abbreviations

FHW: frontline health worker
LMIC: low- and middle-income country
mHealth: mobile health
NGO: nongovernmental organization
NTD: neglected tropical disease
uMARS: user Mobile Application Rating Scale
WHO: World Health Organization

Protocol

Using Intervention Mapping to Develop an mHealth Intervention to Support Men Who Have Sex With Men Engaging in Chemsex (Budd): Development and Usability Study

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Abstract

Background: Chemsex refers to the intentional use of drugs before or during sex among men who have sex with men (MSM). Engaging in chemsex has been linked to significant negative impacts on physical, psychological, and social well-being. However, no evidence-based support tools have addressed either these harms or the care needs of MSM who engage in chemsex.

Objective: The purpose of this paper was to describe the development of a mobile health intervention (named *Budd*) using the intervention mapping protocol (IMP). Budd aims to support and inform MSM who participate in chemsex, reduce the negative impacts associated with chemsex, and encourage more reasoned participation.

Methods: The IMP consists of 6 steps to develop, implement, and evaluate evidence-based health interventions. A needs assessment was carried out between September 2, 2019, and March 31, 2020, by conducting a literature study and in-depth interviews. Change objectives were selected based on these findings, after which theory-based intervention methods were selected. The first version of the intervention was developed in December 2020 and pilot-tested between February 1, 2021, and April 30, 2021. Adjustments were made based on the findings from this study. A separate article will be dedicated to the effectiveness study, conducted between October 15, 2021, and February 24, 2022, and implementation of the intervention. The Budd app went live in April 2022.

Results: Budd aims to address individual factors and support chemsex participants in applying harm reduction measures when taking drugs (drug information, drug combination tool, and notebook), preparing for participation in a chemsex session (articles on chemsex, preparation tool, and event-specific checklist), planning sufficient time after a chemsex session to recover (planning tool), seeking support for their chemsex participation (overview of existing local health care and peer support services, reflection, personal statistics, and user testimonials), taking HIV medication or pre-exposure prophylaxis in a timely manner during a chemsex session (preparation tool), and contacting emergency services in case of an emergency and giving first aid to others (emergency information and personal buddy).

Conclusions: The IMP proved to be a valuable tool in the planning and development of the Budd app. This study provides researchers and practitioners with valuable information that may help them to set up their own health interventions.

International Registered Report Identifier (IRRID): RR1-10.2196/39678

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Introduction

Background

Chemsex is defined as the intentional use of drugs before or during sex among men who have sex with men (MSM) to extend and intensify sexual sessions [1]. Chemsex could include a variety of drugs [1-3]. The use of ecstasy, cocaine, crystal methamphetamine, new psychoactive substances, γ-hydroxybutyrate or γ-butyrolactone, speed, and ketamine is mainly described in a chemsex context in Belgium and the Netherlands [4-6]. Chemsex sessions can last several days, usually involve multiple sexual partners, and are primarily organized at people's (private) homes [2]. A systematic review reports that the prevalence of chemsex varies from 3% to 29%, depending on the definition and setting [7]. Throughout this paper, in an effort to improve readability, we will use the term *chemsex participants* to refer to MSM who engage in chemsex.

Over the past decade, this combination of sexual behavior and the use of illicit drugs has been the subject of increasing research [8,9]. Although chemsex is associated with a range of sexually and psychologically beneficial outcomes such as increased sexual confidence, a greater desire for sex, increased sexual pleasure, and stronger feelings of intimacy and closeness [10,11], there is also extensive research that links chemsex with a wide range of high-risk behaviors and consequent physical, psychological, and social health harms [12,13]. These harms, which are comprehensively described further in this paper, include increased risk of HIV and sexually transmitted infection (STI) transmission [14,15]; anxiety and depression [16,17]; poor performance at work [2,18]; drug dependence; and drug overdose [19,20], with reports of unconsciousness and death [21,22].

These negative impacts pose a public health challenge for health professionals [9,23]. It is important to understand how interventions can be used effectively to reduce the potential impact of high-risk behavior in this key population. Of note, intervention programs that deal specifically with chemsex are scarce [21,24]. MSM who engage in chemsex and who look for care and support often do not access the specialized help they need [6,25]. Traditional drug counseling services usually have insufficient knowledge of sexual health problems, whereas sexual health clinics often lack expertise on substance use [26]. In addition, chemsex participants seem to seek knowledge about harm reduction practices mainly on the web or within the community as opposed to consulting health care providers [27]. Easily accessible evidence-based interventions should therefore be set up alongside traditional counseling services to promote harm reduction.

Goal of the Project

On the basis of these findings, we launched the *Chemified project* in September 2019. This project was initiated to address the lack of evidence-based support tools and the current information and care needs of chemsex participants [6]. The ultimate goal of the project was to develop a mobile health (mHealth) intervention (named *Budd*) to support and inform chemsex participants, reduce the negative impacts associated with chemsex, and encourage more reasoned participation. The rationale for choosing an mHealth intervention is described in more detail in a dedicated article [28]. In short, on the one hand, mobile apps are considered to be facilitators of chemsex, thereby contributing to the health problem [28]; for example, geospatial dating apps are used to search for sexual partners, keep each other informed about chemsex sessions, discuss drug- and sex-related preferences, and exchange information regarding the availability or possibility of purchasing drugs [2,29-31]. On the other hand, mobile apps can be part of the solution. People who participate in chemsex already make frequent use of web-based resources; therefore, they are already familiar with how they work [32]. In addition, for many people, a smartphone is a communication tool that is permanently switched on, which makes it possible to provide support and care when and where they are needed, including during chemsex sessions.

Methods

Overview

This paper describes the development of the Budd app using the intervention mapping protocol (IMP) [33]. The IMP is a systematic approach that aims to support the development of theory- and evidence-based health promotion interventions [33]. The method increases both effectiveness and efficiency through an iterative process of evidence review, application of theory-based strategies, and consultation with stakeholders [33].

The IMP has already been successfully applied to develop a range of eHealth programs for several health behaviors such as a healthy diet [34,35], physical activity [36], alcohol consumption [37], sexual health [38,39], mental health promotion [40,41], and cyberbullying [42].

The IMP consists of 6 steps to be taken to develop, implement, and evaluate health promotion interventions [33,43]. In each step, the program designer applies findings from evidence, theory, and their own research. When the tasks in 1 of the 6 steps are completed, it serves as a starting point for the next step [33]. This paper focuses on the first 4 steps of the IMP. A separate article will be dedicated to the effectiveness study and implementation of the intervention. The application of each of the first 4 steps (Figure 1) is outlined and described in the following sections.

Figure 1. Intervention mapping steps applied to the Chemified project.
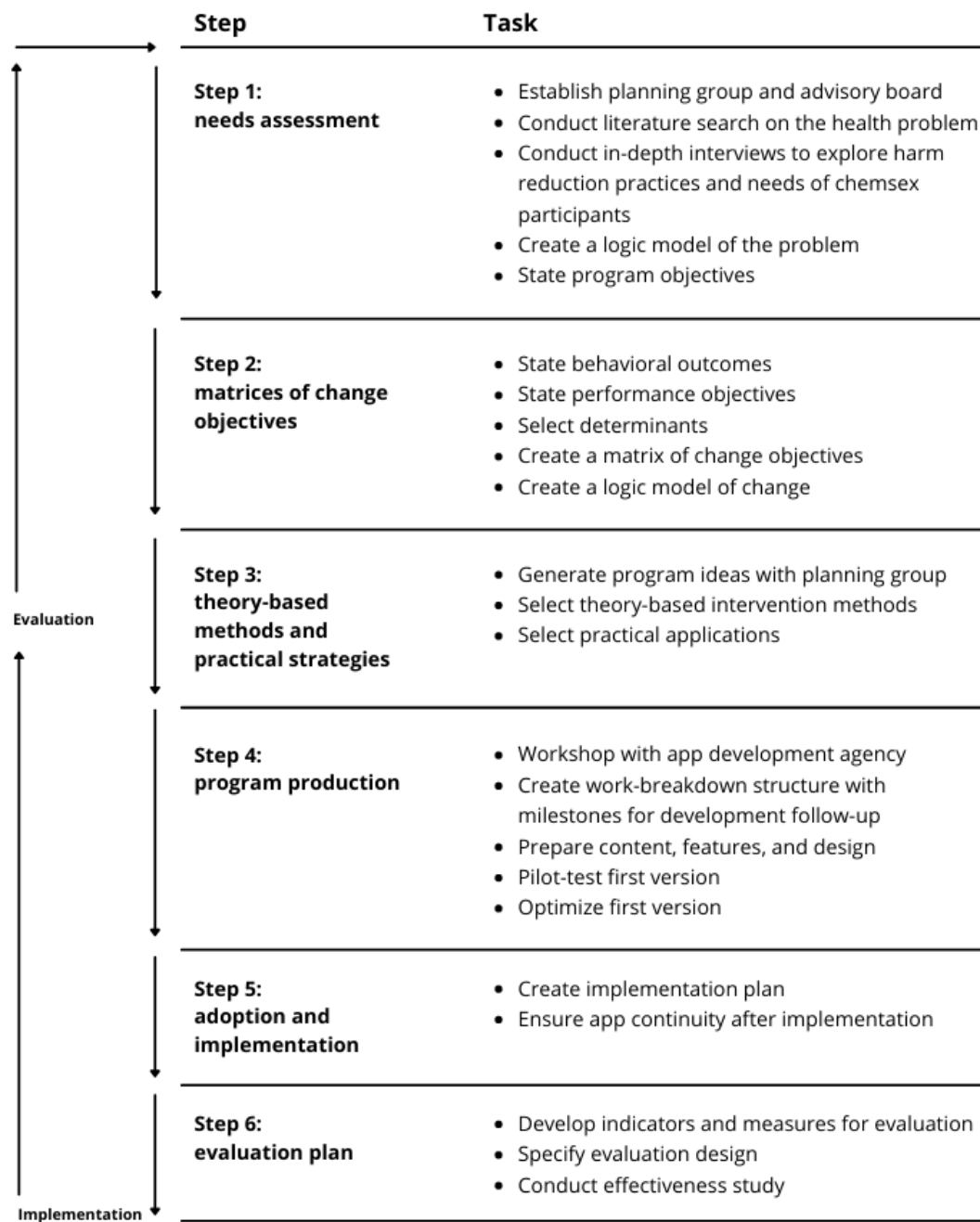
Step 1: Needs Assessment—Logic Model of the Problem

Task 1: Establish Planning Group and Advisory Board

A planning group and an external advisory board were established at the start of the project in September 2019. The planning group was a collaboration between the Institute of Tropical Medicine (ITM) and the University of Antwerp and consisted of 5 people: a mental health scientist and sexologist with expertise in supporting chemsex participants (ITM), head of the HIV and STI outpatient department of ITM, a professor of *Health Communication* and *Media Uses & Effects* (University of Antwerp), a professor of *Strategic Communication and Persuasive Technology* (University of Antwerp), and a junior researcher with a background in sociology and experience in the development of mHealth apps (ITM).

The project benefited from the different partners' combined expertise in health communication and technologies, persuasive communication, and technologies with regard to chemsex participants. The first author (CH) scheduled individual or planning group meetings with group members on a weekly basis to discuss the progress of the project and obtain advice. These meetings took place regularly to ensure continual evaluation and timely adjustment.

A group of key stakeholders served as an external advisory board. This group consisted of professionals from the Flemish center of expertise on alcohol, illegal drugs, and psychoactive medication and the Flemish expertise center for sexual health (Sensoa).

Potential app users were engaged in all phases of intervention planning. The reason for involving them at each decision point was to increase the probability of designing an intervention that is more likely to be effective and accepted because their involvement ensures that the intervention best meets the needs of the target group and the context in which it will be used [43].

Task 2: Conduct a Needs Assessment to Create a Logic Model of the Problem

Overview

A needs assessment was performed between September 2, 2019, and March 31, 2020. First, existing literature was consulted to analyze the health problem of *participating in chemsex* to get a clear picture of the associated health risks and risk behaviors. Second, the possible determinants of each of the risk behaviors were identified through in-depth interviews and behavior change theories (BCTs). Our intervention did not aim to include determinants on the environmental level (eg, health care providers and peers), which is why only determinants on the individual level were identified.

Literature Search on the Health Problem and Risk Behavior

The literature search involved articles retrievable via the PubMed, ScienceDirect, and Google Scholar databases. The following search terms were used: "chemsex," "drugs," "risks," "health," "behaviour," "motivation," "MSM," "sexualized drug use," and "men who have sex with men," as well as combinations of these terms. Relevant papers were selected and reviewed. In addition, the reference lists of the selected articles were reviewed manually to identify other relevant articles.

Analysis of Behavioral Determinants: Personal Factors

Intervention mapping uses a multitheory approach because different theories may focus on specific aspects of behavior or behavior change [43,44]. The BCTs we selected to guide the selection of determinants for our intervention were the social cognitive theory (SCT) [45,46], the theory of planned behavior (TPB) [47,48], and the precaution adoption process model [49]. The rationale for choosing these BCTs is based on existing literature and described in the *Results* section.

After analysis of the problem, data were collected through 20 semistructured in-depth interviews with Flemish chemsex participants [6]. The aim of these interviews was to gain more insight into the specific Flemish chemsex context and also complement the results of the analysis of the problem by exploring the determinants of chemsex behavior and the needs of the key population. The interview guide explored current risk reduction practices (before, during, and after a chemsex session) and the needs of chemsex participants. Specific methods, participant characteristics, and detailed results have been published in a dedicated article [6]. The results of the interviews enabled us to assign relevance to the health risks of MSM engaging in chemsex and the underlying determinants. The results also helped us to formulate achievable performance objectives (step 2 of the IMP) based on the preventive measures MSM take when participating in chemsex.

Task 3: State Program Objectives

The information gathered from this first step results in a logic model of the problem [33]. On the basis of this model, the planning group selected the program objectives.

Step 2: Matrices of Change Objectives—Logic Model of Change

The tasks in step 2 (Figure 1) were completed through consulting existing literature, expert opinion of the planning group, results of the in-depth interviews, and BCTs. First, behavioral outcomes were described. These were derived from the logic model of the problem to achieve the program objectives identified in the previous step. Second, these behavioral goals were further operationalized into performance objectives, which are specific goals that define who and what will change as a result of the intervention [33]. Third, factors that influence behavior, referred to as determinants in intervention mapping terminology, were identified for each performance objective [33]. Finally, the behavioral objectives, associated performance objectives, and determinants were formulated and presented in a matrix. A logic model of change was created to summarize these outcomes.

Step 3: Theory-Based Methods and Practical Strategies

In step 3, theoretical methods were selected that have an impact on each behavioral determinant [33]. These behavior change methods (BCMs) are conceptualized as a process of change derived from theory [43]. Next, the BCMs were turned into practical applications (PAs). An application is the specific strategy in which the methodology is expressed in the intervention [50].

To successfully carry out this step, a list was created of all BCMs that were predicted to achieve the change objectives. We used BCTs and results from empirical research to establish this list. After a detailed discussion with the planning group, we reduced the long list of potential BCMs into a short list, and these BCMs formed the building blocks of the first version of the Budd app.

At this stage of the IMP, one often goes back and forth between steps 3 and 4 [33]; for example, we adjusted the choice of certain BCMs and PAs after carrying out a pilot study of the first version of the Budd app (carried out in step 4; refer to the *Task 2: Carry Out Pilot Study* section).

Step 4: Program Production

In step 4, the selected PAs were organized and built into a coherent intervention [43].

Task 1: Define and Develop Structure, Components, and Content

A workshop with the planning group and the app development agency marked the start of the actual development process. Three goals guided this workshop: introduce the app developers to the project and the potential app users, set priorities, and draw up an app development plan. The entire development process was divided into 5 milestones (Multimedia Appendix 1). Each milestone was assigned a time frame that had to be approved by the planning group and adjusted by the app development

agency as necessary. The first version of the Budd app was developed in December 2020.

Task 2: Carry Out Pilot Study

Study Design and Respondent Recruitment

To evaluate the first version of the Budd app, we performed a mixed methods usability evaluation. Think-aloud testing was followed by administering a usability questionnaire and completed by conducting semistructured interviews after an app testing period of 2 weeks. Our objectives were to (1) identify design, usability, and functionality issues; (2) assess acceptability; and (3) assess satisfaction with the intervention components.

We collected feedback from 8 chemsex participants, of whom 4 (50%) were recruited from the respondents who participated in the in-depth interviews (step 1) and ticked the box on the informed consent form indicating that, at a later stage, they would like to provide feedback on the developed intervention. The remaining (4/8, 50%) respondents were recruited through pre-exposure prophylaxis (PrEP) or HIV and STI consultation at ITM.

The eligibility criteria included being aged at least 18 years; self-identifying as a male member of the lesbian, gay, bisexual, transgender, queer, and similar minority community; being able to understand, and express oneself in, Dutch or English; having intentionally used drugs to have sex within the past 12 months; and owning a smartphone.

Procedures

The study was conducted at ITM by CH between February 1, 2021, and April 30, 2021. At the start of the study, the procedure was explained, and the participants signed the informed consent form. The researcher helped each participant install the app on their smartphone. First, participants completed a preset list of different tasks of varying levels of complexity that cover the full range of functionalities of the app (Multimedia Appendix 2). The researcher was not allowed to help participants complete the tasks. To evaluate usability, the think-aloud method was applied to understand respondents' thoughts as they occurred and attempted to cope with the issues they encountered [51]. After performing all of the tasks, the study participants filled out the 10-item system usability scale (SUS) questionnaire [52]. The SUS is a widely used validated method for assessing the usability of a system [53]. Next, the study participants tested the Budd app in their own environment for 2 weeks. After this test period, a follow-up interview took place at ITM to assess the (1) design, (2) usability, (3) satisfaction with the included intervention components, and (4) acceptability. The interview guide can be found in Multimedia Appendix 3.

Data Analysis

A pragmatic analysis approach was used to analyze the usability testing and follow-up interviews [54]. In both exercises, the researcher took extensive notes [55,56]. This method was chosen to save time and resources in data processing and subsequent analysis [56]. During the usability test, the researcher collected data by observing the study participants carrying out the tasks while also writing down the thought processes and feedback

they shared. During the usability test as well as the in-depth interview 2 weeks later, notes were categorized in a template with subject headings created beforehand [57]. For the usability test, the notes were structured into the categories *usability issues* and *ideas for improvement*. The usability issues were further specified for each intervention component. For the follow-up interview, the researcher registered the main outcomes for each of the 4 topics by writing a summary for each topic discussed. Notes from both studies were analyzed by conducting a deductive thematic analysis [58].

After completing the tasks, all participants completed the SUS questionnaire. The scale consists of 10 questions measured using a 5-point Likert scale (ranging from strongly disagree to strongly agree) and is based on 3 usability criteria: effectiveness, efficiency, and user satisfaction [59]. The final score from the SUS can range from 0 to 100 points. A score of >68 points is above average and indicates adequate usability. In this study, the individual SUS scores of the participants were summed and then divided by the number of participants to obtain a mean usability SUS score.

Task 3: Optimizing the Intervention

The pilot study allowed for the collection of valuable feedback, and these results were then translated into concise modifications and additions to the first version. The second version of the Budd app was finalized in November 2021.

Ethics Approval

Appropriate ethics approval was granted by the ITM institutional review board on December 6, 2019, for the in-depth interviews (1344/19) and on December 15, 2020, for the pilot study (1442/20). Informed consent was obtained from all participants.

Results

Step 1: Needs Assessment—Logic Model of the Problem

Task 1: Establish Planning Group and Advisory Board

A planning group with research partners, an advisory board with stakeholders, and a group of potential users have been involved and consulted from the start of the project.

Task 2: Conduct a Needs Assessment to Create a Logic Model of the Problem

Literature Search on the Health Problem and Risk Behavior

We found that *participating in chemsex* is associated with a wide range of health risks and related risk behaviors. Although the majority of chemsex participants do not identify with problematic use and experience fewer minor consequences [10,11], there is a group of chemsex participants who do experience harms resulting from their participation. The health problems associated with chemsex can largely be divided into 4 categories. Each category is explained in more detail in the following sections.

The first cluster of chemsex health problems cited in the literature involves drug-related physical harms. An acute risk, frequently reported, is drug overdose [8,60]. The degree of

overdose and its effects can range from aggression, heart palpitations, breathing difficulties, panic attacks, delusions, hallucinations, dehydration, overheating, memory loss, and unintentional injury to loss of consciousness and even death [8,60]. Depending on the type of drug, there are also many potential long-term risks, including substance dependency, alterations of cognitive functions, heart disease, psychosis, high blood pressure, movement disorders, and weight loss [2,61].

The risk behaviors contributing to these health problems are a variety of high-risk drug use practices. Polydrug use is the norm for many MSM engaging in chemsex, although percentages vary between 7% and 78.3%, depending on the study locations and definition used (starting from 2 or 3 substances) [2,13,62-64]. Other important risk behaviors include the use of crystal methamphetamine [29,65] and new psychoactive substances [66], injecting drug use during sex (known as "slamming") [18,29,67,68], sharing user equipment (snorting devices and injecting equipment) [18], using high doses [2], extensively redosing [2,69], and going multiple days without sleep [67].

The second cluster of reported chemsex health problems is related to sexual health. Taking drugs before or during sex helps MSM to experience sex without inhibitions [70,71]. This ensures that people are prepared to participate in a wide range of sexual acts, which sometimes go beyond their limits [2]. Chemsex has been associated with high-risk sexual behaviors, including group sex; condomless anal intercourse; fisting; bondage, discipline, sadism, and masochism; having a high number of sexual partners; long sexual sessions that can lead to rectal and penile trauma; and transactional sex [2,7,18,26,63,66,72,73].

MSM who engage in chemsex are more likely to contract HIV, hepatitis C, and other STIs than those who do not engage in chemsex [18,62,74]. Taking drugs can also lead to sleep problems and memory impairment, which, when combined with prolonged sex sessions, can cause people to forget about taking antiretrovirals for HIV management or PrEP [75]. Certain drugs have also been shown to interact with antiretroviral drugs, which is reflected in a negative impact on clinical HIV outcomes [75].

Chemsex participants may also experience difficulty in having sex without drugs because the drugs used hugely increase sexual drive and desire [2]. In this context, being unsatisfied with one's sex life is associated with participating in chemsex [60]. The strong feelings of intimacy and connection experienced during a chemsex session disappear after the drugs wear off, contributing to the level of dependency in which a large proportion of chemsex participants are in search for connection [76]. Some chemsex participants also report being the victim of nonconsensual sex while under the influence of drugs [2,60]. A recent study among MSM in Amsterdam showed that 41.4% of the participants who engage in chemsex reported passing out and not remembering what happened while under the influence of drugs [77].

The third cluster of chemsex health problems being increasingly reported in the literature involves the adverse impact of chemsex on mental health [17,78,79], although research on the topic remains limited. A recent systematic review found a positive association between chemsex and depressive symptoms, anxiety,

and dependence on drugs or other substances [80]. The practice of slamming, especially, is associated with a greater number of mental health symptoms [29,66].

The acute mental health risks of participating in a chemsex party are caused by the substances used. Depending on which drugs are used, risks can include agitation, confusion, feelings of anxiety, aggression, restlessness, and irritability [2]. With crystal methamphetamine specifically, there is a risk of extreme paranoia and panic attacks [29,70]. People often experience poor concentration, difficulty with information processing, and feelings of anxiety and irritation in the days after a chemsex party (*comedown*) [2,6]. These feelings are a result of using stimulant drugs (crystal methamphetamine, ecstasy, and mephedrone) [81]. In the long term, drug use can also lead to anxiety disorders, depression, psychosis, memory problems, and personality changes [2,81].

Anecdotal evidence at our clinic at ITM further indicates an impact on other areas of chemsex participants' lives. Some state that they struggle with relational, financial, and work-related factors as a result of their participation in chemsex. There is limited evidence fully identifying the social impact that chemsex behaviors have on chemsex participants' lives. In a study among chemsex participants in Dublin, 25% of the participants reported that chemsex had a negative impact on their lives [15]. The impact on the work situation seems to be most pronounced during the *comedown* period because people experience difficulties in working efficiently, concentrating, and feeling motivated. As a result, chemsex participants are more likely to perform poorly at work or report sick on the days after a chemsex party [2,18]. Chemsex participants who use methamphetamine report that the use of the drug reduces their ability to fulfill daily tasks [82].

Analysis of Behavioral Determinants: Personal Factors

The determinants of chemsex participation were identified and categorized on the basis of a literature review guided by the selected BCTs and in-depth interviews.

Awareness is defined as the degree of knowledge and understanding of one's own unhealthy behavior [49]. The findings from the interviews indicate that the effects of drugs can greatly reduce the awareness of one's own risk behavior during a chemsex session [6]. Respondents report losing themselves completely in the intense feelings of sexual arousal and disinhibition [6]. Only when a person is also aware that they are engaging in risk behavior (eg, know how much time they leave between 2 dosages and know their own [sexual] boundaries) can they consider changing this behavior. Awareness of one's own risk behavior is seen as an essential first step in the process of behavior change, according to the precaution adoption process model [49]. In an attempt to increase awareness, we included this essential determinant in the development of our intervention.

The transfer of knowledge is often a key element in traditional health education [50]. Information about health behavior and the health risks of certain behaviors is necessary to enable behavior change. The in-depth interviews strongly emphasized this need for reliable information [6]. Particular attention needs

to be paid to information about chemsex drugs, the effect of combined chemsex drugs, how best to act in the event of an emergency, and an overview of existing (drug and sexual) health care services. Respondents indicated that a lack of information often hindered them in adopting risk reduction practices [6]. This need is also reflected in studies conducted in other countries, such as a UK study that showed a need for reliable and nonjudgmental information about safe drug practices [8] and the European Men-Who-Have-Sex-With-Men Internet Survey 2017, which found that respondents scored low on HIV and STI transmission knowledge, postexposure prophylaxis knowledge, PrEP knowledge, HIV test and treatment knowledge, and hepatitis A and B test knowledge [83]. Knowledge is thus a presumably important determinant in practicing safer chemsex.

According to the SCT, human behavior is, to a large extent, determined by the expectations one has of a behavior [46]. One of these expectations is the person's belief about their ability to successfully influence their environment [46]. This concept of *self-efficacy* is a central concept in the SCT, the importance of which is widely recognized. In the context of our intervention, the SCT is cited in several studies as a suitable model for behavior change among individuals who take drugs. Numerous studies have shown that self-efficacy plays an important role in abstinence, substance relapse, and adopting harm reduction measures [84,85]. More specifically, a UK study shows that engaging in chemsex is associated with lower sexual self-efficacy [86]. A study among MSM who had tested positive for HIV and who were using methamphetamine shows that being convinced to be able to say *no* to drugs (*drug assertiveness skills*) was associated with reduced frequency and amount of drug use as well as less sexual sensation seeking and unprotected sex [87]. Higher self-efficacy also has a direct positive effect on HIV treatment adherence [88,89] and PrEP adherence among MSM in the United States [90].

The TPB states that the best way to predict behavior is to ask people whether they intend to exhibit that behavior: the behavioral intention [47,48]. According to Fishbein and Ajzen [47], this behavioral intention is determined by 3 factors: the person's own views (attitude), the views of others (subjective norm), and the estimation of the person's own possibilities of carrying out the behavior (perceived behavioral control, based on the concept of *self-efficacy* mentioned previously).

The TPB is one of the most widely applied behavior change models and has been shown to be effective in explaining and predicting a wide range of health behaviors [91]. Several studies report that the TPB is an appropriate model for explaining, understanding, and predicting a variety of chemsex-related health behaviors, some of which we identified in step 1 of the IMP. These include safer sex behaviors [92], condom use [93,94], therapy adherence [95], intention to enter drug and alcohol treatment [96], and the use of safe injecting procedures [97]. Furthermore, a meta-analysis supported the use of the TPB as a valuable framework for designing interventions to reduce heterosexual risk behavior [98]. Therefore, we considered the TPB suitable to guide us in the development of our intervention.

Task 3: State Program Objectives

We created a logic model of the problem based on the information gathered in this step (Figure 2).

The results of the interviews helped to assign relevance to the health harms and risk behaviors. On the basis of this information, the planning group selected five program objectives: (1) increase safer drug use, (2) improve planning and monitoring of participation in chemsex sessions, (3) facilitate access to health care and support, (4) increase therapy compliance (HIV medication and PrEP), and (5) enhance assistance of other participants during a chemsex session.

Figure 2. Logic model of the problem. PrEP: pre-exposure prophylaxis; STI: sexually transmitted infection.
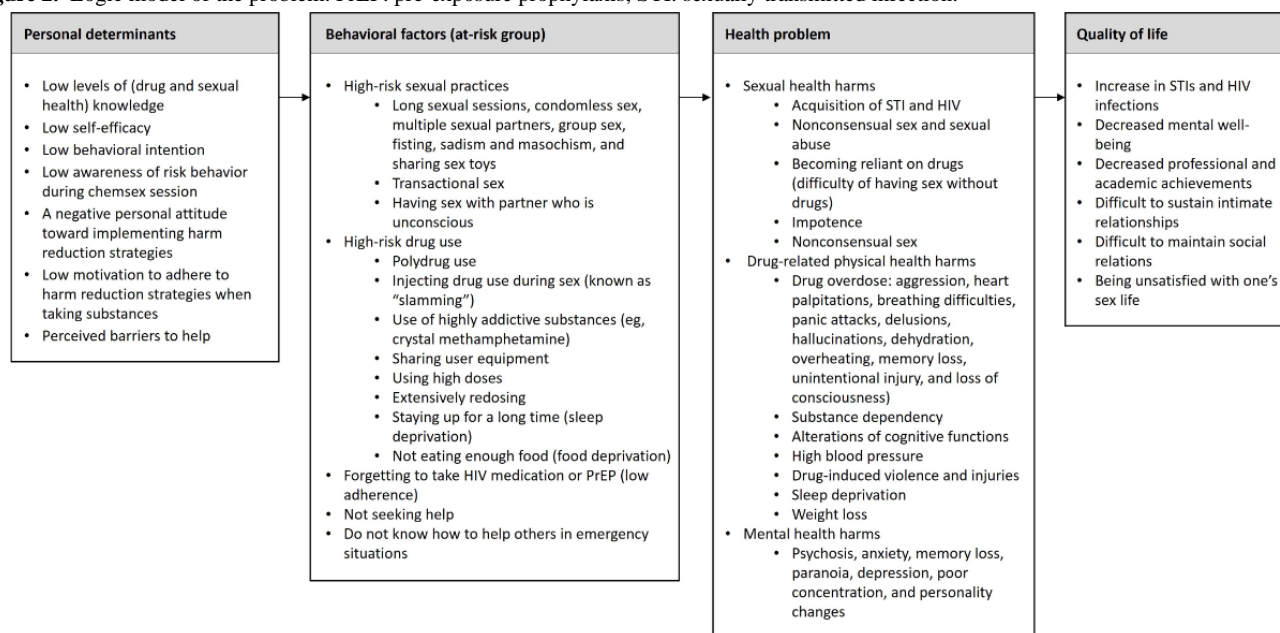
Step 2: Matrices of Change Objectives—Logic Model of Change

On the basis of the program objectives, we formulated 5 behavioral outcomes for the intervention (Figure 3). For all 5 subbehaviors, separate matrices of change were created (Multimedia Appendix 4).

Figure 3. Logic model of change. MSM: men who have sex with men; PrEP: pre-exposure prophylaxis.

Personal determinants

Awareness
Knowledge
Self-efficacy
Behavioral intention
Attitude

Performance objectives

MSM who engage in chemsex…
- Avoid dangerous drug combinations, apply dosing-related harm reduction strategies, hydrate and eat sufficiently during a chemsex session, and bring harm reduction materials to the chemsex session
- Prepare for participation in a chemsex session, and plan sufficient time after a chemsex session to recover mentally and physically
- Seek timely support for their chemsex participation
- Take HIV medication or PrEP in a timely manner during a chemsex session
- Contact emergency services in case of an emergency, and give first aid to others

Behavioral outcomes

MSM who engage in chemsex…
- Apply harm reduction measures when taking drugs
- Deliberately plan participation in chemsex sessions
- Contact support services when needed
- Adhere to HIV medication or PrEP (if applicable)
- Assist others during a chemsex session

Health and quality-of-life improvement

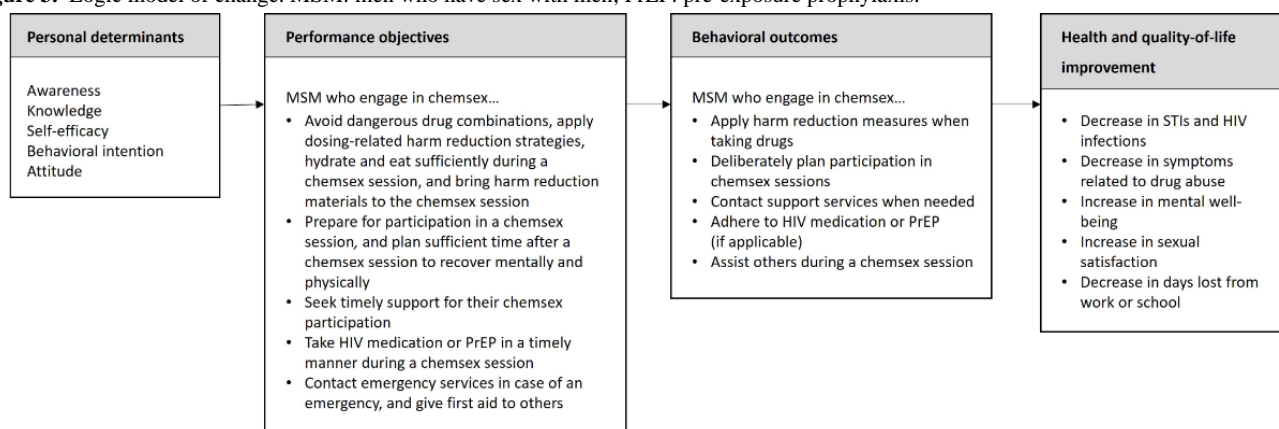- Decrease in STIs and HIV infections
- Decrease in symptoms related to drug abuse
- Increase in mental well-being
- Increase in sexual satisfaction
- Decrease in days lost from work or school

Step 3: Theory-Based Methods and Practical Strategies

Multimedia Appendix 5 lists the BCMs and PAs used in the Budd app; for example, "providing information" is used as the main BCM to increase the user's knowledge, attitudes, and behavioral intentions [33]. A relevant theory for knowledge transfer is the elaboration likelihood model [99]. This theory states that people are more likely to think about a particular information message than others depending on the situation or context. According to this model, changes resulting from central information processing are more stable, more persistent, and more predictive than those resulting from peripheral processing. People often do not process information centrally because they do not have time, they are not motivated, the information is too difficult to understand, and so on. With the Budd app, we try to promote this central processing of information. Established methods to stimulate this are active learning, participation, and personal relevance, often in combination [99]. To ensure the relevance of the included information and to match the users' beliefs as much as possible, we created the initial version of the app based on the results of the interviews and made final adjustments based on the results of the pilot study. The Budd app contains 7 PAs based on the BCM of "providing information." The user receives both general information (eg, PA1: drug information about commonly used chemsex drugs [Figure 4], PA3: articles about chemsex-related topics such as "Safer chem use," "STIs and chemsex," and "Chems and consent" [Figure 5], PA4: an overview of health care and support in Flanders (the Flemish region of Belgium), and PA5: emergency information) and more tailored information (eg, PA2: assessing the interaction of drugs the user takes during a chemsex session using the drug combination tool [Figure 6] and PA6: testimonials from other MSM who participate in chemsex). A knowledge quiz (PA7) with feedback per completed question was also integrated into the app to promote central information processing.

Another example is the BCM "self-monitoring of behavior" to increase impact on the determinant *awareness*. This method is widely used in health interventions and has been found to be effective for a variety of health behaviors [100-102]. Self-monitoring encourages users to record their behaviors and gain insight into their chemsex participation. We have translated this method into the following 6 PAs:

- PA8: a mood survey related to participation in chemsex sessions (at check-in, check-out, and 2 days later)
- PA9: a notebook with time stamps to allow the user to monitor drug intake (especially useful for monitoring gamma-hydroxybutyrate and gamma-butyrolactone intake) during the chemsex session
- PA10: a journal where reported data are centralized (Figure 7) and which can also be used to make daily entries
- PA11: a personal checklist related to each planned chemsex session where the user can list to-do items or materials to bring with them (Figure 8)
- PA12: reflection on answers to the questions from the preparation tool (2 days after the chemsex session)
- PA13: a *personal statistics* page that contains a visual representation of mood, number of chemsex sessions participated in, evolution of chemsex sessions per month, and number of hours spent on average at a chemsex session (Figure 9)

Figure 4. Practical application 1: drug information.
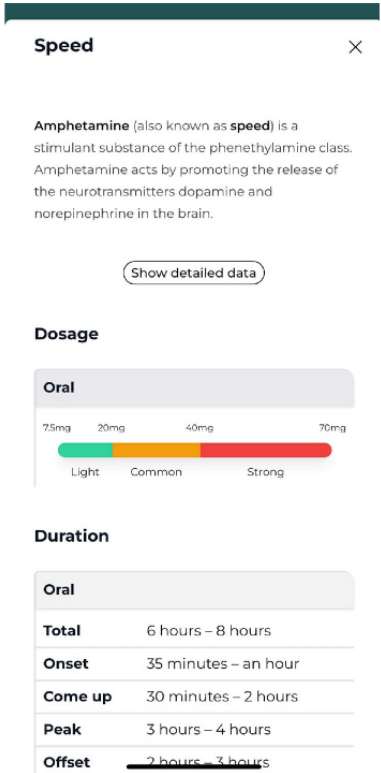
Figure 5. Practical application 3: articles about chemsex-related topics.
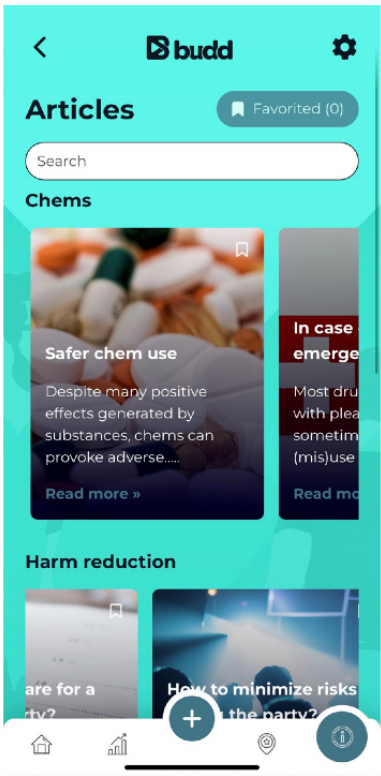
Figure 6. Practical application 2: drug combination tool.
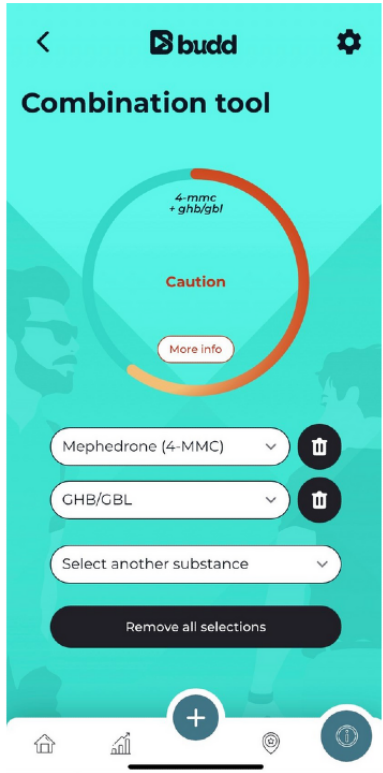
Figure 7. Practical application 10: journal.
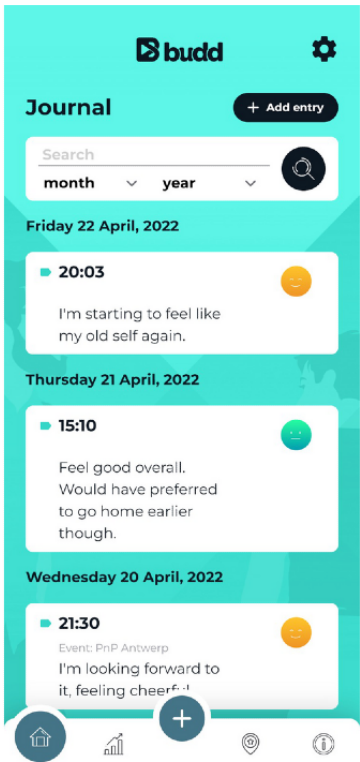
Figure 8. Practical application 11: personal checklist.
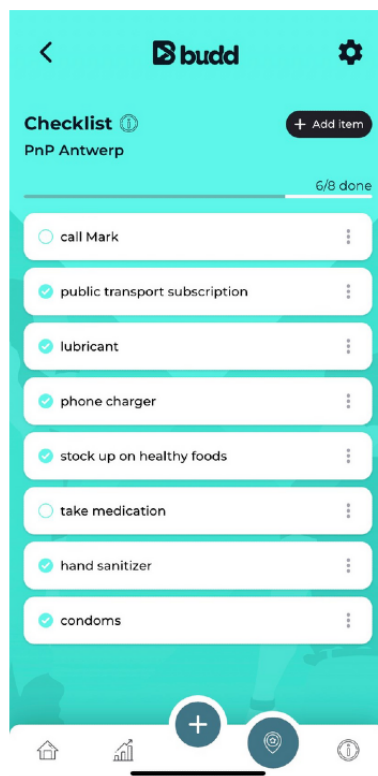
Figure 9. Practical application 13: personal statistics page.
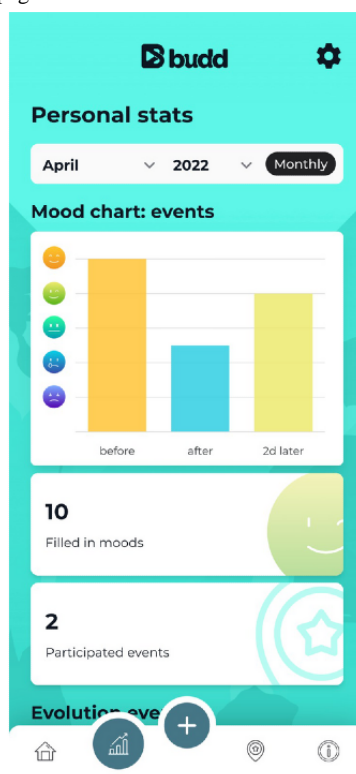
Step 4: Program Production

Task 1: Define and Develop Structure, Components, and Content

During a workshop with the planning group and app developers, we performed the Must Have, Should Have, Could Have, Won't Have This Time exercise [103] to determine app components and set priorities. After the exercise, all possible features were classified into one of the following four categories: (1) must haves (required; otherwise, there is no workable product), (2) should haves (these requirements are very desirable, but without them the product is still usable), (3) could haves (options that will only be included if there is enough time and budget), and

(4) won't haves (will not be discussed in this phase but may be discussed in the future). On the basis of this exercise, the app developers created the first version of the user flow ([Figure 10](#)).

The workshop concluded with a brainstorm session about possible app names and designs.

Figure 10. First user flow.
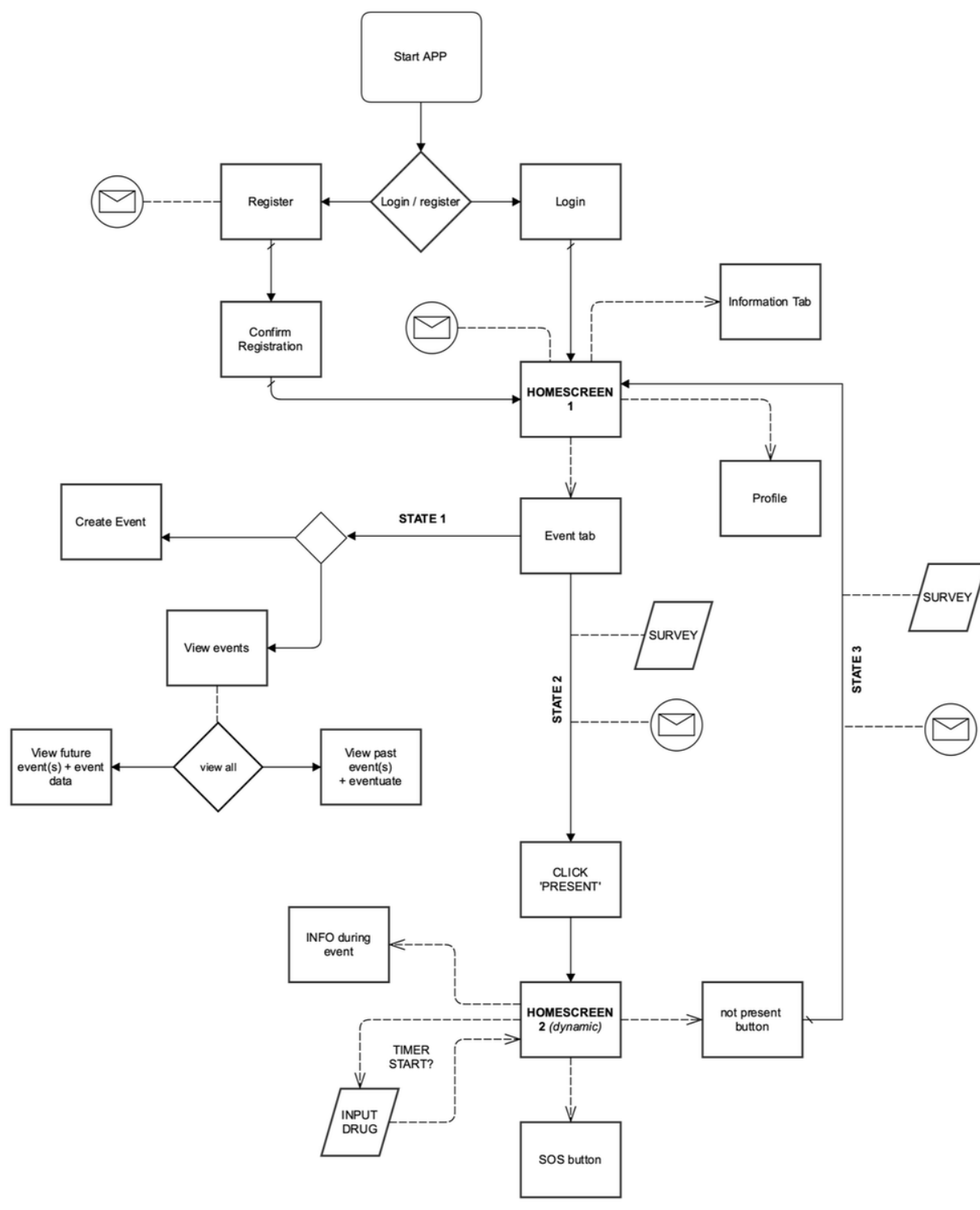
Task 2: Carry Out Pilot Study

This section discusses the results of the pilot study on the first version of the Budd app.

Executing a Set of Tasks

The participants performed various tasks within the Budd app, providing us with a rich data set containing their feedback. The usability issues and ideas for improvement mentioned by the respondents were classified according to their intervention components. All results can be found in Multimedia Appendix 6.

SUS Score

The average usability score was 76.88, which indicated the need to make only minor usability improvements to the first version.

Follow-up Interview

Respondents used the app for different purposes; for example, some (4/8, 50%) of them found the informative articles especially useful because they contained practical, to-the-point, and clearly defined information. Of the 8 respondents, 2 (25%) found the process of planning chemsex sessions helpful because it increased awareness of participation before attending a session, whereas 2 (25%) found this component to be less meaningful because they usually do not know in advance when they will participate in a chemsex session as these sessions happen unexpectedly more often than not or at the last minute.

Respondents also provided feedback on potential improvement of the app components. Some (5/8, 63%) of them mentioned that basic information on different substances was lacking, whereas others (2/8, 25%) stated that information on specific new psychoactive substances and the risks of slamming was missing. Respondents also stated that the section on drug combinations could be worded more in layman's terms. When checked in on the app at a chemsex session, respondents found it inconvenient that they could not easily return to the rest of the app because they had to check out first.

Finally, respondents also shared ideas for adding intervention components. These focused mainly on expanding the substance-related–information section, giving a voice to other chemsex participants, adding ways to keep track of thoughts, and increasing awareness of time during a chemsex session.

The main usability issues had already been addressed in the usability test ("Performing tasks"). The answers to the questions about usability were therefore rather limited. The 2-week test period did lead to some suggestions to improve usability that were not noticed during the first test. These included the following: it is inconvenient that there is no chemsex session overview, public holidays are not visually indicated in the calendar view, have the weeks start on Monday when "adding a new event," and the red bar bearing the legend "Call emergency service" overlaps with text at the bottom of the screen.

Three factors were surveyed to assess acceptability: frequency of use, whether people expect to continue using the app (*intention to use*), and whether they would recommend the app to others. The frequency of use reflects the same finding as the preference for certain intervention components. Some (2/8,

25%) of the respondents only used the app just before and during a chemsex session, whereas 13% (1/8) used it primarily to read all the information, and 38% (3/8) used the app very regularly for the information it provides and to support their participation in chemsex. All respondents stated that they intend to continue to use the app when it is generally available. The reasons for this were varied and included the following: will use it (1) depending on frequency of participation, (2) because it has a scientific basis, (3) to monitor substance use, (4) to monitor participation in chemsex, (5) as a personal safety tool, and (6) for the educational aspect. All respondents were also willing to recommend the app to others but again for different reasons: to (1) prepare people just starting to participate in chemsex, (2) make people more conscious about their participation in chemsex, and (3) inform people about assessing the interaction of drugs using the drug combination tool. Of the 8 participants, 3 (38%) stated that they hoped that it would become a common tool in the community so that the use of the app during parties would become easier.

In general, the respondents were very positive about the design of the app. This may also be partly due to the fact that we had already carried out a small-scale design review with 5 respondents at the start of the development process. The respondents found the layout and structure to be clear. However, the respondents felt that some parts of the interface could be more consistent; for example, the placement of certain buttons and whether pop-ups should be used. The font, according to the respondents, is easy to read. The use of color was also well received, with respondents describing the colors used as neutral, calm, and generating the feeling that "we take care of you."

Task 3: Optimizing the Intervention

Overview

After carrying out the pilot study, the results were discussed with the planning group. We prioritized the refinements and revisions of the app based on the frequency and relevance of respondent feedback and feasibility within the study period. An overview of the second scope with all changes and additions is presented in Multimedia Appendix 7.

The Budd App

In the following sections, we describe in brief the different components developed for the revised intervention, which went live on April 26, 2022. The Budd app consists essentially of 2 modules: an information module and individual support.

The information module is at all times accessible to the app user. This page consists of 6 parts (Figure 11).

Figure 11. Information page.
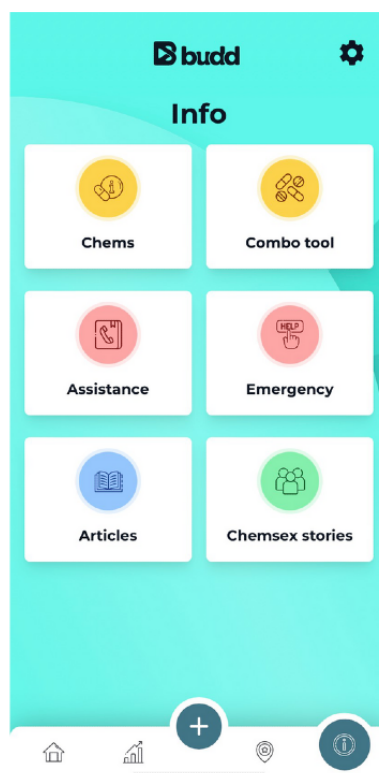
First, the articles cover 3 topics: chemsex drugs, harm reduction, and safer sex. Examples of articles include the following:

- "Safer chem use"
- "How to tackle the comedown"
- "TasP, PEP and PrEP: What does it mean in HIV prevention?"
- "STIs and chemsex"
- "Safe(r) slamming"

Second, the module contains "Chemsex stories," which are testimonials consisting of other chemsex participants' experiences. The topics include "How I handle the comedown," "It's not about crossing boundaries," and "It started to affect everything in my life."

Third, this module also contains specific information on the most commonly used drugs in the context of chemsex. For each substance, the app user will find some product information, dosage (light, medium, or strong), duration of the effects, and description of the effects.

Fourth, by using the "Combination tool," app users can easily check the interaction among different drugs (Figure 6). The tool allows users to *combine* up to 4 different substances because we are aware that chemsex participants usually take >2 drugs during a chemsex session. At the top of this screen a circle appears whose boundary ring can fill up according to the risk and can be colored purple (low risk), light orange (caution), dark orange (unsafe), or red (dangerous). In this way, the risk can be assessed at a single glance. More detailed information on interactions among the selected substances can be found by clicking the "More info" button.

Fifth, this module contains an overview of designated local health care professionals and peer support services such as drug counseling services, sexologists, psychologists, HIV and AIDS reference centers, peer support groups, and locations where drugs can be tested to check whether they are "safe."

Sixth and last, the information page contains an "Emergency info" button. When app users click on this button, they will find an overview of a number of emergency situations that can occur during a chemsex session and a step-by-step plan of how best to act in such situations, including overdose, heatstroke, and unconsciousness. In addition, there is a step-by-step plan, an instruction video, and an illustration of how someone can be placed in the recovery position. This page also contains a list of symptoms that indicate when a person should dial 112 (emergency services). This "Emergency info" page also contains a red button, clicking on which opens 2 buttons in the app: a (smaller) red button and a (smaller) blue one. Clicking on this smaller red button would connect the app user to 112, whereas clicking on the blue one would connect the user to his personal safety buddy. This *buddy* is someone the app user trusts and whose contact details can be added to the Budd app so that they can be easily contacted during a chemsex session.

In addition to using the Budd app to access general chemsex information, it can be used to gain a better understanding of one's own chemsex participation and to participate in a more conscious way. To enable this, we included app components that can be of assistance to users before, during, and after participating in a chemsex session.

Via the "Events" page, app users can plan chemsex sessions in the app. The app user needs to fill in a few details such as event name, start date, end date (optional), location (optional), and notes (optional).

When a session is planned, there are 2 ways to prepare.

The preparation tool can be used to set intentions and consider certain harm reduction strategies. The tool includes an 8-item questionnaire, with questions such as "When do I intend to go home?" "How will I get home safely after the event?" "Which chems do I certainly want to avoid taking during this event?" "Have I set an alarm for my medication intake?"

Alternatively, an individualized and event-specific checklist can be completed. This checklist is a to-do list for the corresponding event. App users can add items here that they do not want to forget or certain things that they still need to organize. It is also possible to let the app suggest items such as mobile phone charger, lubricant, medication, and hand sanitizer.

When the app user has planned a chemsex session, he can check-in by moving a slider. The app now knows that the person is attending a chemsex session. If the app user unexpectedly ends up at a chemsex session, he can also click "Already at event" on the "Events" page; automatically, an event will be created. When checking in, Budd will ask the user to fill in a mood survey. This can be filled in quickly and easily by moving a bar from left to right and choosing an appropriate emoji.

Once the user has checked in at the session, the app changes to a dark mode. A stopwatch (measuring time in minutes) starts running in the menu bar to clarify that the app user is currently at a session. In this view, the checklist and the notebook can be used. The notebook sets a time stamp for each note. This allows the user to track the progress of the chemsex session and possibly monitor the time elapsed between each drug dose. The most relevant harm reduction components are shown centrally on the screen: the drug combination tool and emergency information. The other buttons of the app are still accessible in this view, but these pages are now also displayed with a dark background.

When the app user returns home, he needs to check out of the event. Budd will again ask him to fill in the mood survey. Two days after checking out (during the *comedown* period), Budd will ask this for the last time. In addition, at this time, 2 reflection questions are asked related to the preparation tool questionnaire filled in by the user before the chemsex session. By comparing the answers provided before and after the chemsex session, the app user can examine the extent to which his set intentions were achieved. App users may review this information as well as their answers on the mood survey via the "Personal stats" page and "Journal" on the home screen.

Finally, the "Personal stats" page displays a variety of data collected by the Budd app; for instance, app users can check out their average mood before, after, and 2 days after a chemsex session on monthly and yearly bases. App users can also see how many sessions they have participated in throughout the months (and in total) and for how many hours they were present at a chemsex session on average.

Discussion

This paper describes the systematic developmental process and ensuing content of an mHealth intervention to support and provide practical tools to chemsex participants to reduce the negative impacts associated with their engagement in chemsex and encourage more reasoned participation.

Principal Findings

Although using the IMP to develop an intervention involves a time-consuming and complicated process, it proved to be a valuable tool in the planning and development of the Budd app. By conducting the needs assessment, we obtained a comprehensive picture of the health issues. Regularly consulting the external advisory board, performing a literature study, and conducting in-depth interviews made it possible for us to gain insight into, and assign relevance to, the health risks, risk behaviors, and associated behavioral determinants. As a result of the needs assessment and the identification of determinants, the intervention focuses on offering reliable information to users and enables them to self-monitor their behavior, formulate personal intentions, review any discrepancies between these intentions and current behavior, and plan and manage their time. The app components and content were grounded in theory (BCTs) and extensively tested during a pilot study. This resulted in a user-friendly intervention with components that are endorsed by the end users. Steps 5 and 6 of the IMP will be elaborated on in a dedicated article.

Our study has a number of strengths. To our knowledge, this chemsex intervention is the first to use a combination of theoretical grounding and empirical evidence. Second, this process uses a bottom-up approach at all stages by giving potential end users (chemsex participants) and stakeholders an opportunity to co-design the intervention. We involved them throughout all phases of the development process, which allowed the user perspective to play a significant role and increases the likelihood of long-term sustainability of the intervention [33]. Moreover, we have tried to integrate all of the preferences of the potential users as they emerged from the pilot study. Although the intervention was developed in a local context, the lessons learned from using the IMP are generalizable to other settings and contexts, making the lessons relevant to researchers and practitioners internationally, especially given the paucity of evidence-based interventions. This study will provide them with practical and accessible tools and materials that can assist them in setting up health interventions. This knowledge can help other professionals to reduce the amount of time they need to develop their own interventions.

Limitations

There are some limitations worth noting. Applying all 6 steps of the IMP is a particularly time-consuming task, as has also been mentioned by other studies [104,105]. With complex behaviors such as chemsex participation, identifying the full health problem is a long process. The iterative nature of the IMP has the pitfall of keeping the planning group stuck in the process of exploratory research, pretesting, fine-tuning, and intervention development. It is possible to conduct continual research into determinants for which performance goals are then formulated with accompanying BCTs and PAs. Usually, one does not have the time and resources necessary to carry out the IMP meticulously according to the instructions. In addition, this can become an issue because mHealth interventions evolve rapidly, and creating as well as maintaining an mHealth

intervention and ensuring that it stays relevant is critical. We included persons with sufficient experience and expertise on the IMP in the planning group to avoid these issues. In addition, we focused on the personal determinants of unhealthy behavior because the design of the Budd app focuses on the individual user. However, we recognize that social and physical environmental conditions also have a strong impact on behavior [43]. We acknowledge that environmental factors are important in the context of chemsex, such as peer pressure and normalization of drug use (by peers and sexual partners) [11,106,107], a lack of knowledge and expertise among traditional addiction services about chemsex [6,9,26], and experience of shame or stigma regarding sexualized drug use among health care professionals [4,6,8,106,108]. Now that the app is available to the end users, we want to broaden our scope to these possible environmental determinants. As of September 2022, we are working on a follow-up study where we want to look at the health problem from an ecological perspective, as has also been described in the IMP [43]. We aim to explore the interpersonal, organizational, community, and societal factors that influence the behavior of MSM engaging in chemsex. In this way, we can also target the ecological environment of MSM participating in chemsex to attain sustainable behavior change.

Conclusions

This paper demonstrates how the IMP can be used to design and develop a rigorous theory- and evidence-based intervention to support and inform chemsex participants in reducing the negative impacts associated with chemsex and encourage more reasoned participation. This intervention is unique because no evidence-based mHealth interventions exist yet to support chemsex participants. Notwithstanding the aforementioned limitations, we conclude that our study contributes to the evidence base of chemsex mHealth interventions. The results can be used as input for other mHealth interventions aimed at supporting chemsex participants. The results of the effectiveness study may also contribute to the knowledge about how to support chemsex participants in participating more safely in chemsex sessions.

Data Availability

The data sets analyzed in this study are available from the corresponding author on reasonable request.

Authors' Contributions

CH, KP, HV, TP, and EF were responsible for the conceptualization of the study. CH, KP, HV, TP, and EF were responsible for the methodology. CH conducted the literature study, in-depth interviews, and pilot studies. TP and EF were responsible for resources. CH was responsible for data curation. CH prepared the original draft of the manuscript. CH, KP, HV, TP, and EF reviewed and edited the manuscript. CH was responsible for project administration. CH, TP, and EF were responsible for funding acquisition.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Milestones of the development process.
[DOCX File , 140 KB - resprot_v11i12e39678_app1.docx]

Multimedia Appendix 2
Executing tasks in the Budd app.
[DOCX File , 15 KB - resprot_v11i12e39678_app2.docx]

Multimedia Appendix 3
Post–pilot study interview guide.
[DOCX File , 15 KB - resprot_v11i12e39678_app3.docx]

Multimedia Appendix 4
Matrices with change objectives.
[PDF File (Adobe PDF File), 198 KB - resprot_v11i12e39678_app4.pdf]

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Multimedia Appendix 5
Theoretical methods and practical applications used in the Budd intervention.
[PDF File (Adobe PDF File), 182 KB - resprot_v11i12e39678_app5.pdf]

Multimedia Appendix 6
Results of the Budd pilot study.
[PDF File (Adobe PDF File), 2071 KB - resprot_v11i12e39678_app6.pdf]

Multimedia Appendix 7
Overview of the second scope of the Budd app.
[PDF File (Adobe PDF File), 233 KB - resprot_v11i12e39678_app7.pdf]

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Abbreviations

BCM: behavior change method
BCT: behavior change theory
IMP: intervention mapping protocol
ITM: Institute of Tropical Medicine
mHealth: mobile health
MSM: men who have sex with men
PA: practical application
PrEP: pre-exposure prophylaxis
SCT: social cognitive theory
STI: sexually transmitted infection
SUS: system usability scale
TPB: theory of planned behavior

Protocol

Perceived Workload Using Separate (Filtering Facepiece Respirator and Face Shield) and Powered Air-Purifying Respirator and Integrated Lightweight Protective Air-Purifying Respirator: Protocol for an International Multisite Human Factors Randomized Crossover Feasibility Study

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Abstract

Background: The design of personal protective equipment (PPE) may affect well-being and clinical work. PPE as an integrated item may improve usability and increase adherence by healthcare professionals. Human factors design and safety may reduce occupational-acquired diseases. As an integrated PPE, a lightweight protective air-purifying respirator (L-PAPR) could be used during health procedures where healthcare professionals are exposed to airborne pathogens. The human factors affecting the implementation of alternative PPE such as L-PAPR have not been thoroughly studied. The population of interest is health care professionals, the intervention is the performance by PPE during tasks across the three PPE types 1.) N95 respirators and face shields, 2.)traditional powered air-purifying respirator(PAPR), and 3.) L-PAPR. The outcomes are user error, communications, safety, and end-user preferences.

Objective: This study will assess whether the L-PAPR improves health care professionals' comfort in terms of perceived workload and physical and psychological burden during direct patient care when compared with the traditional PAPR or N95

and face shield. This study also aims to evaluate human factors during the comparison of the use of L-PAPR with a combination of N95 respirators plus face shields or the traditional PAPRs.

Methods: This is an interventional randomized crossover quality improvement feasibility study consisting of a 3-site simulation phase with 10 participants per site and subsequent field testing in 2 sites with 30 participants at each site. The 3 types of respiratory PPE will be compared across medical tasks and while donning and doffing. We will evaluate the user's perceived workload, usability, usage errors, and heart rate. We will conduct semistructured interviews to identify barriers and enablers to implementation across each PPE type over a single continuous wear episode and observe interpersonal communications across conditions and PPE types.

Results: We expect the research may highlight communication challenges and differences in usability and convenience across PPE types along with error frequency during PPE use across PPE types, tasks, and time.

Conclusions: The design of PPE may affect overall well-being and hinder or facilitate clinical work. Combining 2 pieces of PPE into a single integrated item may improve usability and reduce occupational-acquired diseases. The human factors affecting the implementation of an alternative PPE such as L-PAPR or PAPR have not been thoroughly studied.

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Introduction

Background

This study aims to evaluate human factors during the comparison of the use of lightweight protective air-purifying respirator (L-PAPR) with a combination of N95 respirators plus face shields or the traditional powered air-purifying respirators (PAPRs). Health care professionals include medical doctors, nurses, respiratory therapists, physical therapists, and occupational therapists. The rationale for this research is to evaluate human factor–friendly options for hospitals facing a shortage of disposable N95 respirators or other respirators approved by the National Institute for Occupational Safety and Health (NIOSH). We evaluate the use of PAPRs to protect health care professionals against exposure to aerosols containing the coronavirus SARS-CoV-2 during direct patient care. In these situations, the design of personal protective equipment (PPE) may impact overall well-being and the PAPR design may hinder or facilitate clinical work [1]. The use of PAPRs is an alternative to conventional PPE and is currently used for the care of patients with Ebola and SARS-CoV-2 [2,3]. During the tragic 2014-2016 Ebola outbreak in West Africa, in which many health care workers died, health care professionals commonly used 10 or more distinct and disparate pieces of PPE to protect themselves. Simple protocols to correctly and comfortably don or apply PPE (donning) and remove or doff PPE (doffing) can save lives by reducing infection [2,3]. In Ebola, fear led to donning and doffing protocols that were cognitively burdensome and presented a safety risk [4]. The need to integrate PPE is a necessary design challenge to render it simple, safe, and user-friendly [5]. The use of a face shield in PPE combined with respirators can limit the visualization of facial expressions as they are obscured by the respirator [6]. In these situations, the PPE design can impact professional morale and present an obstacle to clinical care. During the COVID-19 pandemic, health professionals reported discomfort after wearing N95 respirators and eye protection (goggles or face shields) for extended shifts

[7]. In addition, N95 respirators were in short supply worldwide during the pandemic, which required taking unusual decontamination measures so that they could be reused; however, decontamination does not clean PPE and led to concerns of wearing stained and unclean PPE [7]. The use of reusable PAPRs may offer improved usability, patient interaction leading to more humane clinical care, and reusability and sustainability, limited only by the maximum number of disinfection cycles before filters degrade.

The L-PAPR is an integrated PPE that may confer safety and comfort advantages to workers, which a clinician can don and doff without an assistant, unlike the traditional PAPR where assistance is needed to don and doff safely. The L-PAPR may reduce the respirator supply challenges as it is designed for multiple years of use rather than a single use only and this may in turn reduce solid waste production. Combining 2 pieces of PPE into a single integrated item may improve usability and comfort, increasing the adherence to an adequate use of PPE, and thus minimizing the risk of occupational-acquired diseases. Studying the human factors that can affect the use and implementation of alternative PPE could support the decision-making process when defining PPE usability for health care settings during the COVID-19 pandemic and in ongoing or future infectious disease outbreaks worldwide.

The PAPR is an air-purifying respirator that uses a blower to force air through the filter cartridges into the user's breathing zone (Figure 1B). The process creates a flow of air within the faceplate and hood or helmet, providing a higher assigned protection factor than the reusable elastomeric air-purifying faceplate (half mask) or N95 respirators [8]. A PAPR could be used during health procedures in which the health care professional is exposed to aerosol pathogens to reduce acute respiratory infections [8]. PAPRs can reduce the user-inhaled aerosol concentration to at least one-quarter of that in air, compared with a one-tenth reduction for N95 respirators. This is largely due to its perfect fit to the user' face, which reduces

the inhalation of unfiltered ambient air. Traditional PAPRs have ventilation systems attached and connected to a filtered air supply mechanism. L-PAPRs are battery-operated ventilation systems that allow independent ventilation and air filtration without the encumbrance of the hose. The models we will use for this study are the Versaflo (PAPR A; 3M) [9] and the TIKI Medical Respirator (L-PAPR B; Figure 1A,B) [10].

Figure 1. (A) Traditional powered air-purifying respirator (PAPR) and (B) lightweight protective air-purifying respirator (L-PAPR).

A previous study demonstrated that PAPRs mitigate the hemodynamic brain effects induced by the prolonged use of N95 respirators during 12- and 24-hour shifts [7]. In another study, health care professionals indicated a preference for PAPRs over N95 respirators in high-risk settings compared with "usual circumstances," citing comfort, ease of communication, and an enhanced sense of personal safety [3]. A systematic review identified no difference in the contamination of health care professionals by comparing a PAPR with other respiratory protection equipment; additionally, the PAPR was identified as providing greater heat tolerance despite decreased mobility and auditory function [8].

This study aims to evaluate human factors during the comparison of the use of a lightweight PAPR with a combination of N95 respirators plus face shield or traditional PAPR to provide data on usability, design, and implementation for future work. We propose to measure the perceived workload during clinical tasks while using 3 combinations of PPE, first in a simulation project with 3 sites (Stanford, CA, USA; Bologna, Italy; and São Paulo, Brazil), followed by on-site implementation in places of care—COVID-19 wards and the intensive care unit (ICU) at 3 clinical sites (1 in Bologna and 2 in São Paulo, where health care for severe COVID-19 is provided).

Objectives

The specific objectives of this study are follows:

1. To measure the perceived workload of 3 PPE combinations and to evaluate and compare across objectives 2-4.
2. To measure human errors, equipment failure, and human factors across each of the 3 PPE conditions over a single continuous wear episode.
3. To observe the effects of PPE on interpersonal communications.
4. To evaluate parameters related to stress across PPE conditions and tasks to evaluate the usability perception of health care professionals about the 3 PPE conditions.

Methods

Study Design

This is an interventional crossover human factors feasibility study combining a simulation study (phase 1) performed in 3 sites (Stanford, Bologna, and São Paulo). Field testing (phase 2) will be performed in 2 sites (Bologna and São Paulo) across 3 ICUs. The results from phase 1 will be integrated with a collaborative study conducted at Stanford (CA, USA). The study design and phases of the research are summarized in Figure 2.

Figure 2. Phases of the study design and sites where the protocol will be put into action. L-PAPR: lightweight protective air-purifying respirator; PAPR: powered air-purifying respirator.
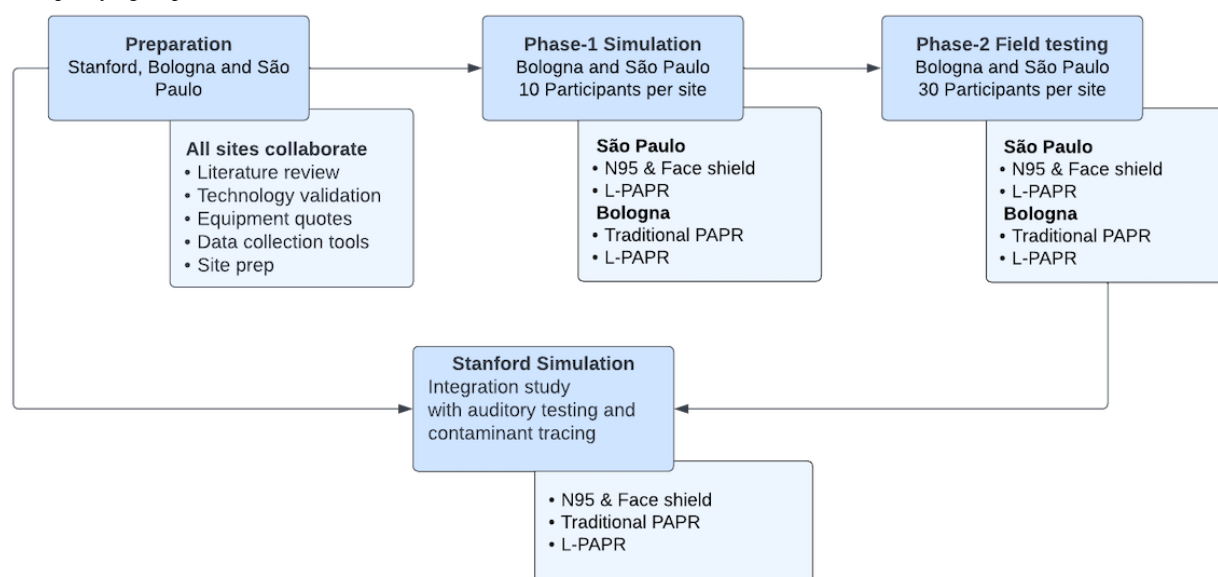
Inclusion and Exclusion Criteria

See Textbox 1 for details.

A limited number of participants who join the simulation in phase 1 may also volunteer to participate in the field observation phase of the study to provide observations for error similarity between field and simulation sites. Participants who withdraw from the study for any reason after initial consent will be excluded from the analysis.

This research is a 2-phase project consisting of a simulation phase and a field test phase. The results from the simulation phase will be augmented with a parallel study performed at Stanford, where visual and auditory testing will be provided. Stanford will also use part-task trainers as well as high-fidelity

complex simulations. During the simulation phase, the Stanford site will test multiple intubation methods. Training with complex and part-task trainer simulations allows testing of the fidelity of part-task trainers. Their lower cost may make them a more viable option in lower-resource settings [11].

This assessment of PPE evaluates human factors in the relationship between PPE (technology) and the clinician (end user). It is hoped that insights from this research might be used to tailor the design of PPE technology for mucosal protection in situations such as admissions, emergency department and ICU care, and in triage centers, where first responders deliver the patient for emergency medical services. According to the Clinical Human Factors Group, "Human factors are organizational, individual, environmental, and job characteristics that influence behavior in ways that can impact safety" [12].

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

1. Physicians, residents, nurses, and other health care staff who work the majority of a full-time equivalent in the intensive care unit, the emergency department, or the operating room.

2. Adult health care professional working at the site hospitals who are knowledgeable to complete the simulation exercises.

3. Competent to give informed consent.

Exclusion criteria

1. Minors, health care professionals under 18 years of age.

2. Nonhospital site employees.

3. Clinicians without experience of caring for patients with COVID-19.

4. COVID-19 exposure.

5. Positive prestudy screening for COVID-19, including respiratory symptoms or fever.

6. Participants who fail the NIOSH fit test for the L-PAPR.

7. Any individual for whom simulation is contraindicated.

Sample Size Justification

This is an early feasibility study across 3 continents and multiple languages using a mixed methods approach. In this study, descriptive statistics and mixed methods will be used to ascertain the findings. Recommendations vary from 10-12 per group to 60-75 per group for feasibility size; however, this depends on the study objectives [13]. In this feasibility study, it is not expected that statistical significance will inform study results as it is not powered to report this with accuracy. Formative usability testing and interviews will be carried out with 5-7 individuals as is the standard for this form of research [14]. We selected our usability testing and interview duration to allow for the observation of PAPR use and to observe how well it is suited to COVID-19 intensive care clinical tasks. Saturation of data is our aim, but we chose the number of participants based on studies with similar sample sizes and these studies used interviews lasting 15-20 minutes to reach saturation [14-16]. It was necessary for us to comply with the pandemic research and health policy restrictions put in place by our institutions across 3 continents as the research will be conducted even under pandemic surge conditions. Phase 2 will again use mixed methods; in the quantitative phase 2, field observations will be performed with 30 individuals at each site. In simulation and field testing we aimed for usability numbers and not for statistical significance. A sample size of 30 participants for the quantitative field testing phase was determined using a usability calculation for the conditions across 2 user groups (nurses and physicians) and not for statistical power as it would be premature to conduct a full study before feasibility is established and in addition, the sites were funded and equipped adequately for feasibility alone. Later, using the findings from this pilot feasibility work we will be positioned to apply for full study funding.

Randomization

Participants will be recruited among health care professionals employed in field settings. Participants will be computer randomized and assigned to 1 of 3 PPE conditions on the day of the study and randomization will occur before study and between conditions. The Stanford simulation site will compare the 3 PPE types, namely, A (L-PAPR), B (respirator and face shield), and C (traditional PAPR). São Paulo and Bologna sites will have 1 intervention arm, A (L-PAPR), and 1 comparator arm, B (respirator and face shield, São Paulo) or C (traditional PAPR, Bologna). The randomizing sequence for each site will be AB or BA (São Paulo) and AC or CA (Bologna). A minimum of 10 participants will be recruited in each simulation site. As this is a crossover design, participants will be assigned to the intervention and comparator arms, and they will be randomized to the use of equipment to reduce order effects, a well-documented phenomenon that suggests different orders or times in which the interventions are presented can influence outcomes.

Recruitment

The investigators will follow recruiting procedures established by their institutional review boards (IRBs). They will work with hospital staff to explain the study to the potential participants for usability testing, interviews, and field observations. The

participant may refuse involvement, in which case another potential participant may be approached. Participants will be recruited using posters visible in common clinical areas, via an email to appropriate departments, and by word of mouth from clinical and research staff in São Paulo, Bologna, and Stanford. Interested volunteers can contact the sites for information by email, phone, or in person. During recruitment, participants will be informed that activities in the simulation phase will occur outside of their routine work shift, to avoid disruption of inpatient care. Participants will be informed about the times and dates of the simulation in advance. Participants will be compensated according to the policies approved for this study by the hospital and university IRBs and their time will be protected to enable them to complete these tasks.

Consent

Participants will sign an informed consent form in their native language. The risk to participants is less than what they encounter in a clinical workday. Before signing, the participants who gave consent will receive detailed information on the types of PPE and monitoring devices to be used, including photographs, infographics, and instructional videos to facilitate their understanding of the methods to be employed. The participants will be informed that they can withdraw at any time of the study. Each participant will be provided with a unique code to protect their anonymity. The investigators will ensure participants understand the implications of their involvement (risk and benefits), their right to withdraw, that their participation is voluntary, and how information collected during the study will be used and reported. Participants' comprehension of the materials will be tested using teach-back methods and a questionnaire. The informed consent script "Verbal Consent Script to Inform Participants in a Research Study: Field Observations" will be used to guide this discussion and versions for each country can be accessed from Multimedia Appendix 1.

Phase 0: Preparation

In this preparatory phase, we will plan a consultation with the WHO for an internal equipment review, and we will test the chosen technology on-site, define data collection, prepare our cross-country site communication network, translate forms to be usable in all site languages, and prepare materials for institutional and WHO IRB approvals (Multimedia Appendix 2).

Phase 1: Simulation Phase

The simulation will be performed in the institution's simulation laboratories according to different tasks. The methods for tasks will be as uniform as possible and the fine-tuning of these methods will be augmented during weekly communications with study investigators and research personnel across sites. Participants will use instructional videos and a quick guide, translated into local languages to avoid the effect of excess errors or discomfort that could be attributed to a learning curve that may not occur when participants are familiar with the equipment.

All participants will wear smartwatches while performing the tasks to capture consistent heart rate (HR) and movement

(number of steps). Participants will use the smartwatches during a 24-hour period before or after the simulation study to establish baseline physiological parameters. Following the simulation shift, researchers will administer the National Aeronautics and Space Administration Task Load Index score (NASA-TLX) questionnaire [17] and the System Usability Scale (SUS) questionnaire [18]. The SUS measure is validated for perceived usability of the equipment, while the NASA-TLX is used to measure the cognitive load or thinking effort that the equipment requires while using it. These measures combined can offer us a rough estimate of how useful the equipment is from a human factors perspective. Following this, the researchers will conduct a 15-20-minute semistructured interview to elicit human factors related to the success and failure of PPE implementation. Further details about conducting all steps, including adapted questions and time recording per task, are presented in Multimedia Appendix 1.

The Stanford Simulation Lab located within The Stanford Anesthesia Informatics and Media Lab will accommodate additional tasks. The Stanford Lab is self-contained with computer equipment for testing participants and video equipment for recording the research tasks to review observer accuracy. In this setting, objective confirmation of hearing and visual deficits can be computer tested. Visual acuity will be tested with Snellen charts [19] for distance vision and the Jaeger chart [20] will be used to test reading clarity. The Snellen chart is used in schools' optical stores and many workplaces as a fast validated measure of how far people can see accurately. The Jaeger test asks participants to read different sizes of print to test for reading acuity. Auditory acuity will be tested with the American National Standards Institute–certified Modified Rhyme Test (MRT) [21] word list containing 300 words [22]. From this list, randomized sets of 75 words are generated and participants will be tested in the control condition of no PPE and in each of the 3 conditions they are randomized to. Each set contains 6 monosyllabic words with the same initial consonant. This testing can reveal where language communication has deficits [21]. We will report if auditory deficits increase during the use of any of the 3 PPE conditions. The results will be compared with qualitative feedback and the recording of communication errors during donning, doffing, and medical tasks while performing simulations and in the field.

Phase 2: Field Testing

Steps Overview

Phase 2 field testing will follow simulation testing so that early observations can be applied, and conditions adapted to improve field testing. Over a single shift of direct patient care, the following tasks will be performed, and they will be timed per task and participant. Our hope is that timing the tasks will contribute to assessing how errors occur; for example, we will report whether errors are task related, whether tasks with longer run times produce increased errors, or if errors occur early in the process and become less likely as health care professionals become accustomed to using PPE or performing specific tasks.

Step 1

Participants will be supplied with smartwatches, which will allow their movement (eg, number of steps) and HR to be recorded and automatically uploaded to the smartphone software before being recorded on the smartwatch company servers.

Step 2

Health care professionals will don the PPE to which they are randomized. Researchers will observe the health care professionals using each PPE combination and will record the instances of PPE readjustments (eg, repositioning of the mask) and user or equipment errors. If the health care professional removes the PPE combination for reasons unrelated to the clinical task, this event and the time of occurrence will be recorded.

Step 3

Following the simulation shift, researchers will administer the NASA-TLX questionnaire [17] and the SUS questionnaire [18]. Following this, the researchers will conduct a 15-20-minute semistructured interview to elicit human factors related to the success and failure of PPE implementation. For those seeking more details for conducting all steps including time recording per task, see Multimedia Appendix 1. Table 1 is an approximation of time for tasks, and this was piloted across the sites.

Table 1. Tasks time; comparator and intervention simulation will be randomized.

Start	Stop	Time	Description
		0:15	• Sign consent forms and study check-ins
		0:05	• Donning • Change into PPE[a] and smartwatch function check
		0:15	• Acclimation period • Take baseline vitals
		0:20	• Stanford only, visual and auditory testing
		0:35	• Medical Task Series
		0:05	• Doffing
		0:20	• Take vitals • Survey (NASA-TLX[b] and SUS[c])
		0:20	• Qualitative interview
		0:05	• Debriefing and checkout
		1:40	• Time per PPE session

[a]PPE: personal protective equipment.

[b]NASA-TLX: National Aeronautics and Space Administration Task Load Index score.

[c]SUS: System Usability Scale.

Outcome Measures

We will measure the following outcomes, from both phases 1 and 2 (Figure 3):

- The NASA-TLX score [17], on a scale of 0-100, with higher scores indicating higher perceived workload.
- Health workers' PPE adjustments and the number of errors over a single continuous wear episode (phase 1) or shift (phase 2).
- Errors to observe will include interpersonal communication hindrances during the activities and equipment flaws or breakdowns (phase 1 or 2)

- HR differences as a proxy for stress and the number of steps as a proxy for physical demand. HR and steps will be compared with participant-reported stress outcomes, errors, and time duration of tasks.
- NASA-TLX [17] and SUS [18] questionnaires will be administered and these use a scale of 0-100, with higher scores indicating the best overall usability of the system under study.
- Human factors potentially affecting the implementation of L-PAPR as PPE for health care will be gathered using a semistructured qualitative interview analyzed and coded in the native language and then in English across sites.

Figure 3. Schema of data collection methods and respective outcomes measures. NASA-TLX: National Aeronautics and Space Administration Task Load Index score; SUS: System Usability Scale.
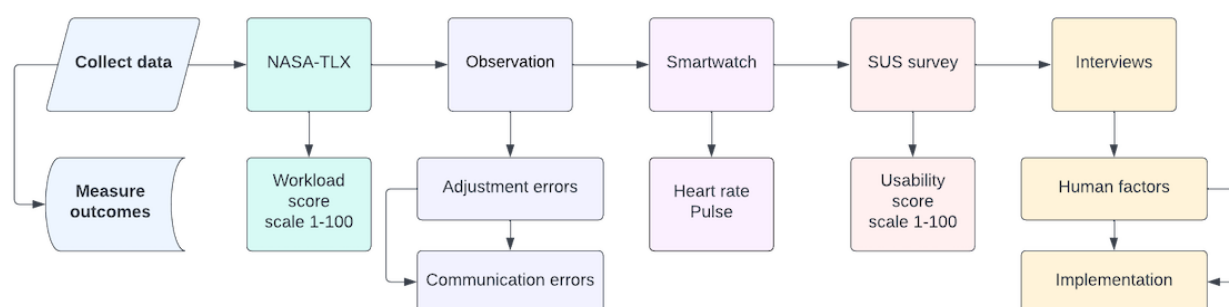
Data Collection

Prior to simulation and field testing, we will provide a video-assisted training procedure with teach-back feedback to

check participant comprehension. The functional simulation sequence can be found in Multimedia Appendix 1. For field testing, participants will be observed during 1 work shift.

During simulation and field testing, each participant will be observed by at least two researchers. Researchers will record adjustments, user errors, and communication problems manually or using an electronic tablet. Data collection tools for expected use errors will reserve free-form note taking for observed unexpected use errors. In addition, simulations will be video recorded to allow for verification of the initial data collection.

Smartwatch Data

HR can serve as a marker for stress and this research will ask participants to wear the smartwatch for 24 hours while not working so that it can serve as a baseline HR without shiftwork wearing PPE. The baseline HR will be collected and compared with HR during the simulation session and the same procedure will take place during field testing and will occur over a single field shift. We will explain as a limitation of our study that it was not possible to control for all environmental effects. Quantitative data for physiological monitoring will be gathered through smartwatches. All sensors are noninvasive: photoplethysmography to monitor HR using infrared light, displacement using the MEMS 3-axis accelerometer, and travel history using connected GPS if attached to a GPS-enabled cell phone. These data are processed to give extra/derivative information: walking and running steps, distance, and calories burnt; HR (beats per minute); connected GPS (distance, pace, and elevation); and sleep (deep and light sleep phases and sleep interruptions) [23].

The reliability of the smartwatches was tested against the validated Hexoskin [24] wearable vests for HR and movement and pulse oximeters for HR. The Hexoskin [24] collects continuously a 1-lead electrocardiogram (256 Hz) and is equipped with 2 respiratory inductive plethysmography sensors technology (128 Hz each) and a 3-axis accelerometer (64 Hz), generating a high-resolution data set (over 42,000 data points per minute). The Hexoskin vests were consistent and superior to the smartwatches for measuring HR variability and activity; however, the condition of extended wear and the need to officially validate decontamination for pandemic conditions meant that we could not use the Hexoskin vests for pandemic research in the ICU.

All data recorded within the smartwatch are sent to a smartphone and then uploaded to smartphone GDPR (General Data Protection Regulation)- and HIPPA (Health Insurance Portability and Accountability Act)-compliant company servers with secure transmission across countries. The sites have IRB-compliant data agreements in place to protect participant privacy for data collection and storage. The smartwatch accelerometer records step frequency and speed. The processes are compliant with Regulation (EU) 2016/679 General Data Protection Regulation compliance [25] and Brazilian Law of Data Protection number 13.703, 2018 [26].

Interviews and Questionnaire

Standard validated questionnaires (NASA-TLX [17] and SUS [18]) are administered following the end of the shift or simulation (Multimedia Appendix 1). The questionnaires and interview questions will be piloted to estimate interview duration so that we can best adapt the questions according to end user feedback. Interviews will be conducted by the researchers following the completion of the shift or simulation set and will contain 12 questions. The interview, containing 12 questions, will be conducted in person or by videoconferencing and will be digitally recorded and transcribed verbatim in each native language and then analyzed by native speakers. Researchers from each language will agree on the representative accuracy of the coded materials translated into English and when there is not a match this will be reported, and the differences explained. In this way, the research can account for cultural and language variances. The interview questionnaire was developed based on the Consolidated Framework for Implementation Research [27] proposed by Damschroder et al [28]. All data will be centralized to a secure REDCap (Research Electronic Data Capture) [29] database with site-specific access and data collection forms. The data flowchart shown in Figure 3 will be used for simulation and field testing.

Project Management

All project members meet remotely every week to work through advances and challenges together and to provide methodological support to remain aligned with the protocol. The principal investigators (PIs) will hire and train researchers, regulate safety conditions, and oversee the data collection and analysis. The coinvestigators will support site preparation for phase 1 and the development of phase 2. The researchers will prepare data collection tools and perform data collection and ensure the materials required are adequate and in good working condition for use in the simulation and in the field. Regular meetings between sites, PIs, and researchers will occur to ensure homogeneous data collection procedures and timely follow-up.

Safety Considerations

All PPEs will be certified according to international standards (the EN 12942 [30] or EN 149 standard [31] for respiratory protective devices). Power-assisted filtering devices incorporate full face masks, half masks, or quarter masks for P5 filters [8]. Additional testing with spectacle usage for the L-PAPR was carried out by BSI UK Labs to assure safety and usability for our participants. The light PAPRs, or PAPRs without a hose, were tested for fit (inward leakage) with participants who wore eyeglasses, under laboratory-controlled conditions and using the test method of the EN 12941 standard. This type of PAPR typically conforms to a maximum allowable total inward leakage rate of 0.05% when on, with positive pressure, compared with a nonpowered, negative pressure filtering facepiece respirator rated at the European Filtering Face Protector (FFP2) standard of less than 11% leakage. BSI UK Labs carried out leakage testing on 10 human participants. No participant experienced a fit [8] with leakage of more than 0.3518%. This leakage is minimal and well below that of an FFP2 filtering facepiece respirator at 8% or 5% N95, assuming completely leakproof or perfect fit [9,10].

During the simulation phase, the number of participants and research assistants in the simulation laboratory will be limited to allow for physical distancing. Research personnel and participants will be prescreened by COVID-19 antigen testing with brands approved by each hospital setting, country and university policy, symptom checking, and vaccination status.

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All involved personnel will be provided with N95 respirators and alcohol hand sanitizer. In the field testing, all measures to avoid potential infection risk will be taken, according to the local infection prevention and control recommendations for the activities in the hospital setting. Researchers will wear N95 respirators and ICU attire and use alcohol hand sanitizer. All devices and surfaces used among participants during the simulation and in the field will be cleaned and disinfected with adequate sanitizers, before, between, and following uses as appropriate.

Quality Assurance

Researchers are trained to ensure consistency in methods, ethics, and data management. Participants will be trained on the use of PPE equipment they will use in the study. We will hold weekly video meetings between the 3 sites with researchers, PIs, and invited experts, to problem-solve and consolidate data collection to ensure standardization. Additional support will be provided as additional needs arise and need to be addressed. Investigators will also communicate by email, phone, and in person when feasible.

Data Management and Governance

Questionnaires are hosted in the REDCap software [29]. We will compare NASA-TLX scores [17] and physiological parameters between the intervention and comparator arms. We will collect HR and the number of steps as an indirect indicator for physical activity and stress over time. Qualitative data will be transcribed verbatim and analyzed as per their content according to Krippendorf [32], identifying themes and categories that emerged from the participants' answers. Quantitative data will analyze differences in the NASA-TLX scores between the intervention and comparator arms. There is a multisite data management and security plan in place agreed upon by the WHO and individual institutional IRBs. Identifiable data will be replaced with numeric coded identifiers. The codes used for participants in phase 1 and phase 2 will aid anonymity. Only research staff, PI, and co-PIs will know who has declined or withdrawn from the study. The identity of participants or those who decline or withdraw will not be shared outside of the local research group. Data will be stored and kept secure in accordance with IRB agreements and country legislation.

Public and Patient Involvement

Public and patient involvement is carrying out research with the public rather than on them. Coproduction in research is the action of patients or members of the public becoming partners with the research team and as partners they will cocreate, co-design, and coproduce element of the research with the research team. There is evidence that public and patient involvement along with research coproduction can improve study quality, increase human factors accuracy, and promote health literacy [33,34]. The study was initiated because of the interest and urgency of clinicians, patients, and members of the public concerning human factors and PPE. Their feedback was formative for developing our research questions and methods. University undergraduates, summer interns, parents, and members of the public were invited to comment and coproduce all aspects of the study. They also assisted with survey design,

testing, and qualitative analysis. Two first-year undergraduate university students are coauthors (WC and SS).

Ethics and Institutional Review Board Approvals

The study was submitted and approved by ethical research committees in all 3 sites (Stanford, São Paulo, and Bologna) and by the World Health Organization (WHO) Ethics Review Committee for COVID-19 (Approval #0100). Details are in Multimedia Appendix 1. See also [17,18,27,35-41].

Results

Our systematic review [42] was completed and informed our protocol. The findings were that PPE implementation involves multilevel transdisciplinary complexity and relies on the development of context-driven implementation strategies. Context-driven strategies can inform and harmonize infection prevention control policy in collaboration with local and international health bodies. The study protocol was presented internally by video and slideshow in fall 2021 to the WHO, Infection and Prevention Control. Stanford is in the preparation and recruiting phase. Bologna and São Paulo have recruited a total of 80 participants. Preliminary results of simulation and the field study from the São Paulo ICU site were presented at ECCMID in April 2022 [43]. The preliminary data show that well-being and comfort are increased with the use of PAPRs by decreasing respiratory effort and eliminating heat accumulation. Participants reported communication difficulties, the noise generated by positive airflow, and facial discomfort with the use of the light PAPRs. The expected publication date for the full multisite study results is December 2022 or the first quarter of 2023.

Discussion

Expected Findings

Prior findings highlight the need for human factors research on PPE. Health care professionals on extended shifts report skin breakdowns, headaches, discomfort, and temporary vascular changes while wearing the N95 respirator [42-46]. We found that manufacturers were open to our suggestions for product improvement based on what we learned while getting the protocol ready and that they are assessing how to improve PPE human factors, safety, and functional use. We will supply them with concrete data following full data collection and provide them with ongoing feedback.

In another example, one of the PAPR designs required a customized 3D-printed add-on for those with spectacles which added to the cost of the device. Approximately 70% of the US working population needs corrective vision according to the Vision Council 2021 first quadrant report [47]. The research team developed an idea that provided a simple and cost-free solution that the manufacturer tested at an NIOSH-approved lab. The solution was viable and demonstrates the cost-saving benefits of including all stakeholders and being transparent with them from the inception of a study.

The expected outcomes of this research are a human factors analysis across conditions and sites. The investigators uncovered

this need through the DeMaND study, which included 52 investigators [46]. We will explore the design improvement of PPE for facial protection, through outcomes such as improvement in perceived workload (mental demand, physical demand, temporal demand, performance, effort, and frustration), experienced stress via HR variability proxy, and a decrease in the need to readjust PPE indicating better ergonomic compatibility. We will report how the qualitative survey aligns with the quantitative measures. This provides details on where manufacturers can use this research to redesign and adapt their products for better usability. The use of human factors, where design is adapted for human preferences, is preferable to expectations that humans will adapt to existing technology [48]. To assess human factors, this study will use quantitative, self-reported metrics related to workload and usability scores. Participants will be engaged across multiple tasks using 3 forms of PPE so they can compare the equipment for breathing, comfort, and ease of use.

Limitations

As stated in the "Methods" section, we note the limitations regarding using the smartwatch as a reliable indicator for HR variability that can be correlated with stress. The internal mechanisms of the smartwatch were not evolved to capture this with reliability, so as an alternative we collected steps and HR with a 24-hour baseline for comparison. Our team has persevered through personal loss, pandemic restrictions, reduced access to laboratory facilities, administrative funding delays, and supply chain shortages. This is especially challenging since this research will be conducted across 3 continents.

Data Transparency

Deidentified aggregated data will be made available to the public with a DOI at the time of results publication.

Dissemination Strategy

We will share study results with participants and staff in the health care settings where they were recruited. Our dissemination strategies include making posters available with summary results for clinic notice boards, and the creation of an easy-to-read summary report through the communication channels of the WHO and the participating institutions. Relevant information for immediate improvements related to the use and adherence to PPE will be discussed with equipment manufacturers and ICU unit managers. The study results will be presented to the WHO Emergencies Program Experts and Advisor Panel for Infection Prevention and Control Preparedness, Readiness, and Response to COVID-19. Results will be shared by the institutions, in scientific meetings, and through social media. The findings will be published in relevant peer-review journals. Dissemination of the results will be discussed in future meetings of the WHO COVID-19 Infection Prevention and Control Research Working Group WHO R&D infection prevention and control pillar. Feedback on the results of the study will be gathered from participants and distributed to key stakeholders.

Conclusion

We are committed to achieving safe pandemic research throughout the pandemic and we will report the limitations we face as a guide to researchers who will face future pandemic conditions. We are awed by the kindness, gentle humor, and resilience of our team. They make research worth the investment and help us to continue, knowing that the total COVID-19–related deaths as of May 2022 was 6.3 million people. Let us make PPE better by improving human factors. Potential future research consists of a larger, well-powered multinational study. We have applied for additional funding to build a multi-PPE use functional template. Members of our team will rewrite PPE technical manuals for clarity, and we are working on an international PPE plan for implementation considering all stakeholders.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary Annex to the Study Protocol.
[PDF File (Adobe PDF File), 2817 KB - resprot_v11i12e36549_app1.pdf]

Multimedia Appendix 2

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Simulation Methods for Human Factors: Assessment of PPE use by Medical Personnel for COVID-19 Patient Care.
[PPTX File , 6011 KB - resprot_v11i12e36549_app2.pptx]

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Abbreviations

GDPR: General Data Protection Regulation
HR: heart rate
ICU: intensive care unit
L-PAPR: lightweight protective air-purifying respirator
MRT: Modified Rhyme Test
N95: National Institute for Occupational Safety & Health (NIOSH)-approved 95% filtration single-use respirator
NASA-TLX: National Aeronautics and Space Administration Task Load Index score
NIOSH: National Institute for Occupational Safety and Health
PAPR: powered air-purifying respirator
PI: principal investigator
PPE: personal protective equipment
REDCap: Research Electronic Data Capture
SUS: System Usability Scale
WHO: World Health Organization

Protocol

Integrating Enhanced HIV Pre-exposure Prophylaxis Into a Sexually Transmitted Infection Clinic in Lilongwe: Protocol for a Prospective Cohort Study

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Abstract

Background: Pre-exposure prophylaxis (PrEP) reduces HIV acquisition risk by >90% and is a critical lever to reduce HIV incidence. Identifying individuals most likely to benefit from PrEP and retaining them on PrEP throughout HIV risk is critical to realize PrEP's prevention potential. Individuals with sexually transmitted infections (STIs) are an obvious priority PrEP population, but there are no data from sub-Saharan Africa (SSA) confirming the effectiveness of integrating PrEP into STI clinics. Assisted partner notification may further enhance STI clinic–based PrEP programming by recruiting PrEP users from the pool of named sexual partners of individuals presenting with an incident STI. However, the acceptability, feasibility, and effectiveness of these integrated and enhanced strategies are unknown.

Objective: This study aims to describe the implementation outcomes of acceptability, feasibility, and effectiveness (regarding PrEP uptake and persistence) of integrating an enhanced PrEP implementation strategy into an STI clinic in Malawi.

Methods: The enhanced PrEP STI study is a prospective cohort study enrolling patients who are eligible for PrEP (aged ≥15 years) who are seeking STI services at a Lilongwe-based STI clinic. Data collection relies on a combination of in-depth interviews, patient and clinic staff surveys, and clinic record review. All enrolled PrEP users will be screened for acute HIV infection and receive quarterly testing for *Neisseria gonorrhea*, *Chlamydia trachomatis*, and syphilis. Participants will be asked to name recent sexual partners for assisted notification; returning partners will be screened for PrEP eligibility and, if interested, enrolled into the cohort of PrEP initiators. We will also enroll patients who are eligible for PrEP but choose not to initiate it, from the STI clinic. Patient participants will be followed for 6 months; we will assess self-reported PrEP use, PrEP refills, sexual behaviors, perceived HIV risk, and incident STIs. Clinic staff participants will be interviewed at baseline and at approximately 6 months and will complete surveys examining the perceived acceptability and feasibility of the integrated and enhanced PrEP strategy.

Results: Enrollment began in March 2022 and is projected to continue until February 2023, with patient participant follow-up through August 2023. The results of this study are expected to be reported in 2024.

Conclusions: This study will generate important evidence regarding the potential integration of PrEP services into STI clinics in SSA and preliminary data regarding the effectiveness of an enhanced intervention that includes assisted partner notification as a strategy to identify potential PrEP users. Furthermore, this trial will provide some of the first insights into STI incidence

among PrEP users recruited from an STI clinic in SSA—critical data to inform the use of etiologic STI testing where syndromic management is the current standard. These findings will help to design future PrEP implementation strategies in SSA.

Introduction

Background

Daily oral pre-exposure prophylaxis (PrEP) reduces HIV acquisition risk by 90% [1-6]. HIV prevention policies in sub-Saharan Africa (SSA), including Malawi, increasingly include PrEP as an evidence-based intervention to decrease HIV incidence [7-9]. Identifying individuals most likely to benefit from PrEP and helping them to navigate complex, dynamic obstacles to uptake and retention are key to maximize HIV prevention. Ultimately, PrEP persistence (ie, continued engagement in PrEP care and drug adherence) for individuals at greatest risk of HIV acquisition is needed to maximize PrEP outcomes [10].

PrEP screening frequently uses epidemiologic risk profiles and relies on self-reported risk behaviors, such as sex work or identifying as a man who has sex with men, which are frequently stigmatized and underreported, particularly in SSA [11-18]. Risk scores may perform well in identifying individuals at high risk of HIV infection, but generally require self-identification as a member of a key population, which may limit their utility where these classifications are stigmatized. In contrast, an incident sexually transmitted infection (STI) is an indicator of unprotected sex and, in high HIV prevalence settings, a reasonable proxy for risk of HIV exposure. Incorporating PrEP with STI care is an efficient means of leveraging clinic infrastructure and an appealing opportunity to integrate related services while adding value for PrEP users [19]. Illustrating the importance of including STI screening with PrEP programs, multiple studies have observed high rates (>30%) of incident STIs while on PrEP [20,21], and there is mounting evidence that STI incidence increases after starting PrEP [22-27]. Although the World Health Organization (WHO) includes individuals with STIs as a priority PrEP population [28], no previous study has combined PrEP with existing STI clinics in SSA, and the acceptability and feasibility among patients at the STI clinic and clinic staff (ie, clinicians and counselors) regarding the integration of these services remains unknown.

Furthermore, partners of PrEP users, particularly PrEP users with a recently diagnosed STI, may benefit from PrEP services. Assisted partner notification (aPN) is a WHO-endorsed strategy in which HIV-infected index cases name recent sexual partners, who are subsequently contacted and offered HIV testing services [29]. This extremely effective and efficient strategy has historically been deployed specifically for targeted HIV case finding [30] or, more recently, among men who have sex with men in Kenya as a strategy to link HIV-uninfected partners of

individuals diagnosed with HIV to PrEP services [31]. Understanding the acceptability and feasibility of extending aPN as an approach to reach high-risk sexual networks of PrEP users who may not otherwise be linked to HIV prevention services could expand PrEP's reach and effectiveness.

Connecting individuals at high risk of HIV to PrEP is only the first step to improve PrEP effectiveness. Suboptimal adherence [20,32] and premature discontinuation despite ongoing HIV risk [33-40] drastically limits PrEP's prevention potential, with 50% to 90% of users stopping PrEP within 6 months [40-44]. Discrepancies between perceived and actual risk are well documented in Malawi, an east African country with a generalized HIV epidemic (adult HIV prevalence of approximately 9%) [45,46]. Integrating etiologic STI testing with PrEP affords providers and PrEP users an objective indicator of risk, thus facilitating tailored PrEP counseling that can address risk misperception and potentially helping to align *perceived* HIV risk with *actual* HIV risk to further optimize PrEP persistence [47,48-52]. Unfortunately, largely owing to resource constraints, Malawi, similar to most of SSA, currently does not offer STI testing, relying instead on syndromic screening for STIs, thereby missing a significant number of asymptomatic infections [53-57]. Understanding how or if incident STIs influence PrEP counseling, affect perceived risk, and possibly improve risk-aligned PrEP persistence is critical to refine PrEP management guidelines in the region.

Efficiently and effectively scaling up PrEP in Malawi requires identifying the right individuals to start PrEP (based on the risk of HIV acquisition) and developing strategies to improve PrEP persistence for as long as those individuals remain at increased risk of HIV. Local guidelines recommend that individuals seeking STI clinical services are appropriate for PrEP, presuming that they meet other eligibility criteria. The Malawi Ministry of Health (MOH) has recently started to offer PrEP at an urban STI clinic in Lilongwe, Malawi, one of the first times this integrated approach has been deployed in the region. Diversifying PrEP delivery models, including adjusting the location and associated service packages, may improve uptake of and persistence on PrEP [58-61].

Objectives

By recruiting participants from STI clinics, we will identify a PrEP-eligible population using objective evidence of recent sexual risk (STI), regardless of self-identification as a member of a key population, and explore the use of aPN as a strategy to recruit additional PrEP users. The overarching objective of this proposal is to examine the feasibility, acceptability, and effectiveness (ie, PrEP uptake and PrEP persistence) of

integrating PrEP into an STI clinic in Malawi, including an evaluation of enhanced PrEP services via recruitment of recent sexual partners for possible PrEP initiation and provision of etiologic STI testing alongside PrEP care.

Methods

Study Overview

In this prospective pilot cohort study, we will explore the feasibility, acceptability, and effectiveness of an enhanced PrEP implementation strategy integrated into an STI clinic in Lilongwe, Malawi. Our enhanced strategy pairs STI clinic–based PrEP distribution with aPN and etiologic STI testing. We will

enroll individuals initiating PrEP at the Bwaila District Hospital STI clinic. Bwaila STI is a public STI clinic in central Lilongwe, Malawi, with approximately 15,000 patient visits annually. In this study, we will follow incident STIs, self-reported risk behaviors, perceived HIV risk, and PrEP use for 6 months (Figure 1). These index participants will be asked to name and provide locator information about recent sexual partners. Partners who do not return to the clinic within 14 days will be traced and, if interested and eligible, will be offered PrEP and enrollment into the prospective cohort. We will also enroll a small subset of PrEP-eligible individuals seeking care at the STI clinic who decline PrEP, following similar biomedical and behavioral outcomes for 6 months.

Figure 1. Study flow diagram for persons seeking STI services.
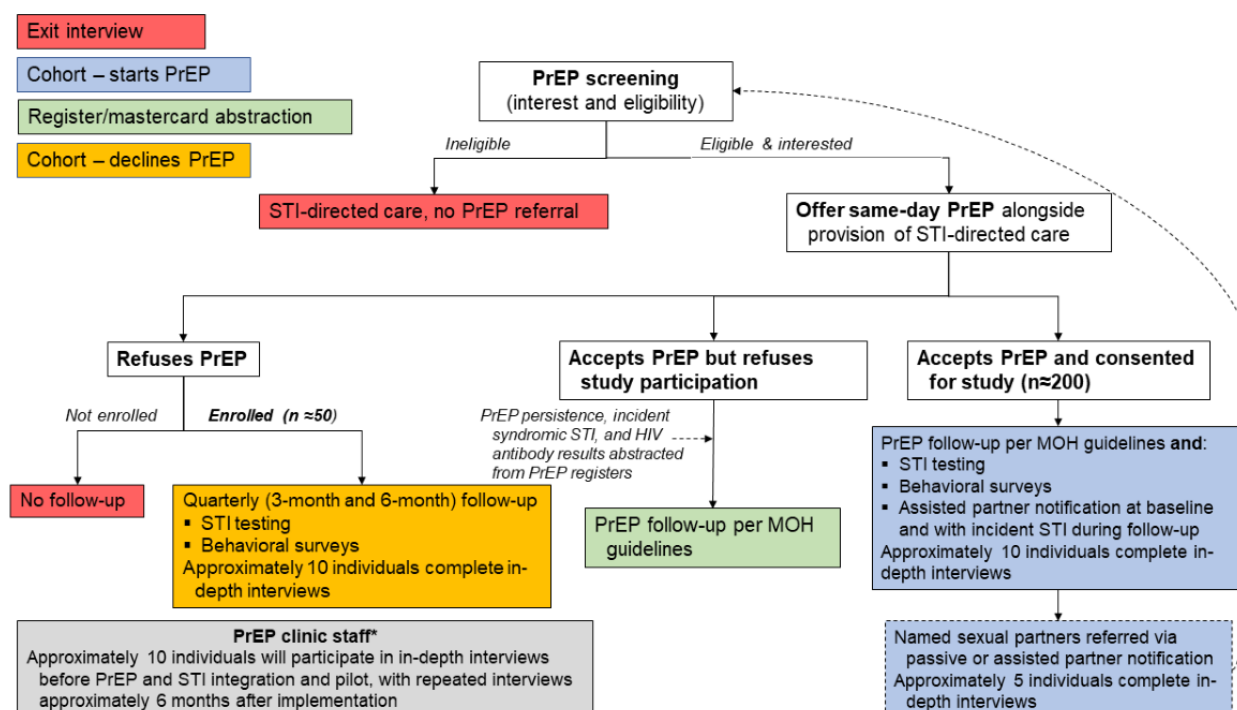
We will contextualize acceptability and feasibility outcomes through quantitative and qualitative analyses; specifically validated implementation outcome measures (Acceptability of Intervention Measure and Feasibility of Intervention Measure) [62]; and in-depth interviews with STI clinic staff involved in the provision of PrEP or related services (ie, aPN and STI testing), index patients, and referred partners. All basic PrEP services, including the PrEP medications, are provided by the Malawi MOH. Currently, the only approved PrEP in Malawi is daily tenofovir disoproxil fumarate and lamivudine or tenofovir disoproxil fumarate and emtricitabine—intermittent (so-called event driven) PrEP is not endorsed by Malawi guidelines. Our protocol was designed to easily adapt if other PrEP agents are approved or offered at the enrolling clinic, including long-acting injectable (LAI) PrEP. Findings of this

study will inform future implementation trials examining integrated services as an implementation strategy to improve PrEP uptake and persistence.

Study Populations and Eligibility Criteria

Participants in this study are of two types: (1) potential PrEP users (including referred sexual partners) and (2) STI clinic staff (Textbox 1). PrEP eligibility will be defined according to current Malawi guidelines (Textbox 2). If these guidelines change during the study, our eligibility will be updated to reflect the modified guidelines. Clinic staff members, including STI nurses, PrEP nurses, HIV counselors, and clinic management, who are engaged in the provision of PrEP (including screening and referral), aPN, or STI services will be eligible for feasibility and acceptability evaluations (Textbox 1).

Textbox 1. Eligibility criteria for sexually transmitted infection (STI) clinic patient (potential pre-exposure prophylaxis [PrEP] user) participants and clinic staff participants.

Inclusion criteria for potential PrEP user (patient)

- Aged ≥15 years

- Eligible for PrEP according to Malawi PrEP guidelines (refer to Textbox 2)

- Presenting for care at STI clinic (primary presentation or referral from partner based on STI or HIV exposure)

- Able to consent for study participation and willing to provide locator information for follow-up tracing

Exclusion criteria for potential PrEP user (patient)

- Current imprisonment or incarceration in a medical or psychiatric facility

Inclusion criteria for STI clinic staff

- Aged ≥18 years

- Involved in duties relevant to integration or provision of PrEP or assisted partner notification at STI clinic

Exclusion criteria for STI clinic staff

- Unable or unwilling to provide informed consent

Textbox 2. Malawi Ministry of Health—pre-exposure prophylaxis (PrEP) eligibility criteria.

- Aged ≥15 years

- HIV seronegative

- At substantial risk for HIV, with prioritization of the following individuals:

  - People who buy or sell sex

  - Key population (female sex workers, men who have sex with other men, and transgender individuals)

  - Vulnerable population including adolescent girls and young women aged 15-24 years

  - Clients with sexually transmitted infection

  - Serodiscordant couples including HIV-negative women who are pregnant or breast feeding or HIV-negative men or women for whom their HIV-infected partner is not on antiretroviral therapy (ART), is on ART for <6 months, has an unsuppressed or high viral load, or is nonadherent to ART

- Have ruled out acute HIV infection or defer PrEP initiation for anyone with signs or symptoms consistent with acute HIV infection

- Willingness to attend scheduled PrEP visits

- No contraindication to use of tenofovir disoproxil fumarate and lamivudine

- Bodyweight ≥30 kg

- Estimated glomerular filtration rate ≥60 mL/min (serum creatinine is recommended before PrEP initiation for individuals who are aged >50 years, have a history of hypertension and diabetes mellitus, have BMI <18.5 kg/m^2, are receiving nephrotoxic medications, or have any symptoms or signs suggestive of renal impairment)

- No known renal diseases

- No diabetes mellitus

Potential PrEP-User Participant Recruitment and Sample Size

Overview

We will enroll 250 PrEP-eligible individuals (aged ≥15 years) who are presenting to care at an urban STI clinic colocated on a district hospital campus in Lilongwe, Malawi. As a pilot study, no power calculations were pursued—sample size was determined based on expected recruitment feasibility. Among potential PrEP users, that is, individuals who are eligible for

PrEP according to MOH guidelines [63], there are three subgroups: (1) PrEP users who are initiated on PrEP at their index STI clinic visit; (2) patients who are eligible for PrEP, but decline PrEP at their index STI clinic visit; and (3) referred partners from group 1 who are eligible for and agree to initiate PrEP. Demographic information will be collected from referred partners who decline or are ineligible for PrEP, but they will not be enrolled in the study. All participant recruitment occurs on-site at the STI clinic by trained study nurses. All groups will be enrolled simultaneously.

Given the objectives of this pilot study, we will intentionally recruit participants to represent a mix of age (15-24 years vs ≥25 years) and sex. Groups 1 and 3 (PrEP initiators) will comprise approximately 200 participants in total. We expect that approximately 60% (120/200) of index PrEP users enrolled will be women, reflecting the historic demographics of the STI clinic population. We will attempt to have approximately 30% (60/200) of index PrEP users enrolled aged between 15 and 24 years at enrollment. There are no historical estimates for partner eligibility or uptake among index patients who are HIV-negative (one of the objectives of this study), but we estimate that approximately 75% (150/200) of the PrEP-user participants will be from group 1.

Group 1—PrEP-User Participant (Approximately 150 Participants)

All patients in the STI clinic will receive a brief overview of the study design and objectives during the standard educational session provided to all individuals queuing for STI services. All individuals seeking STI services proceed first to HIV testing and counseling services (HTSs), according to Malawi standard of care. As described in Figure 1, patients eligible for PrEP based on HIV status are then referred to the on-site PrEP provider, who confirms PrEP eligibility and can also provide necessary STI screening and treatment. Then, potential study participants are referred to the on-site study nurse, who conducts additional screening for study eligibility. If eligible (Textbox 1), participants will be offered study enrollment and will complete an informed consent form. Eligible individuals who choose not to participate will be referred by the study nurse and proceed with any additional standard clinical management for syndromic STIs. Eligible participants may choose to defer enrollment for up to 7 days from the date of their index STI clinic visit. In this case, upon their next presentation to the clinic, they are referred directly to the study nurse, who reverifies eligibility and proceeds with informed consent.

Individuals who initiate PrEP at their enrollment visit are not under any obligation to continue PrEP throughout the study period and may choose to stop and start PrEP at their discretion.

Group 2—Individuals Who Declined PrEP (Approximately 50 Participants)

We expect that most PrEP-eligible individuals seeking STI services will decline PrEP. We will recruit approximately 20% (50/250) individuals who decline PrEP at their STI clinic visit into the prospective cohort. Of note, these individuals may choose to initiate PrEP later in the follow-up period, but will remain in group 2, regardless of subsequent PrEP use. Individuals who decline PrEP will be referred by HTS counselors to the study nurse.

Group 3—Referred Partners (Approximately 50 Participants)

Tracing procedures for named sexual partners (named by group-1 participants) are described in the following sections. Upon presenting to the clinic, partners will undergo screening for both study and PrEP eligibility by the study nurse. Interested partners will receive HIV testing services. If confirmed to be eligible for PrEP (ie, HIV-uninfected), they will be offered PrEP

and enrollment into the study. Partners who are eligible for PrEP but decline it or those who are ineligible for PrEP will be dismissed from study participation. We expect that approximately 25% (50/200) of the PrEP-user participants will be from group 3; however, there is no formal cap for this enrollment. Enrolled partners will count toward the total enrollment goal of approximately 200 PrEP initiators (groups 1 and 3).

Partner Elicitation (aPN)

Overview

We will follow the established WHO and President's Emergency Plan for AIDS Relief protocols for eliciting sexual contacts [64,65] from individuals initiating PrEP; participants will be asked to provide the name and locator information for all sexual partners in the preceding 6 months. Participants will be asked to refer sexual partners to the clinic and will be provided with cards to distribute to their partners. Each card will request the recipient to report to the STI clinic with the card, and it will contain a number that links them back to the index participant. Counselors will encourage participants to distribute these cards to all individuals the participant has had sexual contact with in the preceding 6 months. In our surveys and in-depth interviews, we will explore preferences for four different aPN strategies:

1. Client referral—index clients will contact the partner and inform them that they should be screened or treated for STIs
2. Provider referral—the health care providers will contact the named partners directly and suggest they be screened for STIs, without telling them the index client's name (ie, this will be done anonymously)
3. Contract referral—the index client can contact the partner within a certain period (typically 7-14 days), after which the provider will contact the named partner directly if they have not returned for screening, again without telling the index client's name to the partner (ie, this will be done anonymously)
4. Dual referral—the provider can sit with the index client and their partner and support the client as they tell the partner about their STI

Sexual Partner Tracing

In accordance with the contract referral approach, if the named partners do not present to an STI clinic within 7 to 14 days, community outreach workers will use the tracing information (ie, phone number and address) to contact the partners and counsel them to visit the clinic. Contact may be made through telephone, SMS text message, or in person, as needed, and the name or identity of the index patient will not be disclosed.

Upon presentation to the clinic, sexual partners will be screened for PrEP eligibility and offered the opportunity to participate in the study. If they are eligible and agree to participate, they will receive the same enhanced PrEP services as index patients, including etiologic STI testing and partner referral. Partners who choose not to participate in the study will be offered STI screening and treatment services consistent with the standard of care for contacts of STI cases, including PrEP if interested and otherwise eligible. We will maintain a deidentified log of

PrEP eligibility and PrEP uptake for partners who do not participate in the study.

Data Collection

Overview

All study visits will be completed at the STI clinic, with study visits at enrollment and at 0, 1, 3, and 6 months aligning with the distribution of oral PrEP (Table 1). Group-2 participants will have visits at 0, 3, and 6 months.

Table 1. Schedule of events.

Evaluation	Baseline	Month		
		1[a]	3	6
PrEP[b] eligibility screening	✓	N/A[c]	N/A	N/A
Rapid HIV antibody test	✓	✓	✓	✓
Mastercard[d]/PrEP refill review	N/A	✓	✓	✓
Syndromic STI[e] assessment	✓	✓[f]	✓[f]	✓[f]
HIV RNA testing[g]	✓	+/−	+/−	+/−
STI testing (urine and blood)[h]	✓	N/A	✓	✓
Sexual partner elicitation	✓	✓	✓	✓
In-depth interviews[i]	✓	✓	✓	✓

[a]Month-1 visit is only for individuals who are initiated on PrEP at enrollment.

[b]PrEP: pre-exposure prophylaxis.

[c]N/A: not applicable.

[d]Mastercards are the paper-based medical record for each person who initiates PrEP at the clinic.

[e]STI: sexually transmitted infection.

[f]During follow-up visits, patients will be asked regarding any symptoms, and a physical examination will be conducted if symptoms are reported, with treatment provided according to presenting clinical symptoms and national guidelines.

[g]HIV RNA testing will be performed at baseline for all participants and at follow-up for anyone reinitiating PrEP, as defined by Malawi PrEP guidelines.

[h]Tests will be conducted for *Neisseria gonorrhea*, *Chlamydia trachomatis*, and syphilis (rapid plasma regain, with *Treponema pallidum* particle agglutination if rapid plasma regain titer is detectable) at each visit regardless of symptoms. If symptoms are reported by participants at the scheduled 1-month or patient-initiated interim study visit, specimens will also be collected for STI testing. Any infection detected by testing will be treated according to Malawi STI treatment guidelines.

[i]In-depth interviews may occur adjacent to any scheduled study visit.

Surveys

Surveys will be conducted among clinic staff and potential PrEP users via face-to-face interview. Clinic staff will respond to a Likert-scale survey evaluating the acceptability and feasibility of the integrated and enhanced PrEP strategies under investigation [62] at baseline and approximately 6-month follow-up visit (Multimedia Appendix 1).

Potential PrEP users (all groups) will respond to multiple tablet-based surveys at each visit, assessing perceived HIV risk, sexual behaviors (ie, partners and condom use), STI symptoms, PrEP adherence and side effects, PrEP refill (according to the documented clinic PrEP records), acceptability of PrEP receipt within the STI clinic setting, partner referral, and etiologic STI testing (Table 2). The visit timing aligns with the Malawi PrEP follow-up schedule [63].

Table 2. Patient and clinic staff participant survey content.

Outcome	Patient participants				Clinic staff	
	Baseline	1 month[a]	3 months	6 months	Baseline	6 months
Acceptability[b]	✓	N/A[c]	N/A	✓	✓	✓
Feasibility[b]	N/A	N/A	N/A	N/A	✓	✓
Appropriateness[b]	N/A	N/A	N/A	N/A	✓	✓
PrEP[d] use[e]	✓	✓	✓	✓	N/A	N/A
Contraception[f]	✓	✓	✓	✓	N/A	N/A
Perceived HIV risk	✓		✓	✓	N/A	N/A
Reasons for initiating (or declining) PrEP	✓	N/A		✓	N/A	N/A
Number of sexual partners[g]	✓	N/A	✓	✓	N/A	N/A
Condom use	✓	N/A	✓	✓	N/A	N/A
HIV status of partners	✓	N/A	✓	✓	N/A	N/A

[a]There is no month-1 visit for group-2 participants.

[b]Refers to acceptability, feasibility, and appropriateness specific to etiologic sexually transmitted infection testing, assisted partner notification, and integration of sexually transmitted infection and pre-exposure prophylaxis services.

[c]N/A: not applicable.

[d]PrEP: pre-exposure prophylaxis.

[e]Adherence to PrEP is asked to group-1 and group-3 participants and any group-2 participant who decides to initiate PrEP during the follow-up period. Reasons for discontinuation is asked to individuals with gaps in use or intended cessation of use.

[f]Asked only to female participants.

[g]At baseline, participants are asked about partners in previous 6 months; during follow-up visits, participants are queried about the number of partners since their previous visit (regardless of interval) and in the past month.

Individual In-depth Interviews

The content of the in-depth interview guides will be informed by Conceptual Model for Implementation Research by Proctor [66]. Clinic staff in-depth interviews will focus on experience with prescribing PrEP (ie, structural or clinic-specific challenges to distribution), experiences with eliciting partners for PrEP referral (ie, refusals, index preferences for provider-initiated referral, contract referral, or dual referral), perceptions regarding how PrEP is being used (ie, perceived patient adherence to PrEP, fluctuations in PrEP use, or barriers to ongoing engagement in PrEP care), perceptions regarding alternative PrEP formulations (eg, injectable and insertable), approach to HIV risk assessment, and communication strategies regarding risk. To better elucidate the possible pathways through which STI testing may facilitate PrEP persistence, we will explore how or if the presence of an STI in the PrEP user influences counseling. As clinicians and clinic staff are the primary implementing actors for the integrated STI+PrEP strategy, we will also evaluate the perceived barriers to or facilitators of provision of this new clinical service. Refer to Multimedia Appendices 1 and 2 for sample in-depth interview guides.

A subset of approximately 25 potential PrEP users will be recruited to participate in the in-depth interviews. The final number and distribution of interviews between each PrEP user group will depend on thematic saturation based on real-time review of transcripts. Topics include motivation for starting or stopping PrEP, perceived HIV risk, and perceived barriers to PrEP use, specifically when managed through an STI clinic.

Probes will be determined based on whether respondents accepted or refused PrEP initially. For example, among PrEP acceptors, we will elicit responses regarding how perceived risk influences PrEP use, thus providing additional depth to the survey questions. Interviews will also explore how or if the presence of a symptomatic or asymptomatic STI may influence their HIV risk perception and perceived need for PrEP. Finally, we will examine the preferences for nonoral PrEP formulations, including LAI PrEP, with all patient participants.

Clinic Record Review

We will extract data from existing clinic records to examine clinic-wide uptake and PrEP persistence. Source documents include an electronic medical record that captures basic demographics (age and sex) and critical clinical outcomes (HIV status) for each clinic encounter at the STI clinic; the PrEP register, which documents all individuals who are offered PrEP within the clinic and captures basic demographics (age, sex, and pregnancy status); and PrEP *mastercards*. Mastercards are the paper-based medical record for each person who initiates PrEP at the clinic; the document captures HIV risk (Textbox 2) and includes a PrEP readiness assessment documenting additional PrEP eligibility and a table corresponding to each PrEP visit in which HIV-negative serostatus is confirmed and STI screening, if done, is documented.

Anonymous Survey Among Individuals Not on PrEP

A convenience sample of individuals who are not initiated on PrEP will be asked to respond to a brief survey capturing age,

sex, whether they were offered PrEP, and reason for declining PrEP. The purpose of this survey is to help estimate the proportion of patients in the STI clinic who were not enrolled in the study but were offered PrEP, and among those offered PrEP, to understand the reasons for declining. Patients will be approached as they are checking out at the reception desk and asked to respond to the brief survey. Patients who are enrolled into the study will not be surveyed. Among individuals who are not offered PrEP, we will also record HIV status from the same-day HTS.

Laboratory Evaluations

According to the Malawian guidelines, all patients with STI at Bwaila STI undergo HIV testing via fingerstick blood collection using 2 rapid test protocols, unless a person has documentation of HIV infection [63]. Participants with newly diagnosed HIV infection or those who are not on antiretroviral therapy (ART) will be referred to the colocated HIV clinic for management.

Before PrEP initiation, patients will undergo any necessary screening tests to confirm the safety of PrEP, as provided by MOH PrEP programs. At the time of submission, same-day PrEP initiation is recommended, with discontinuation if baseline estimated glomerular filtration rate is <60 mL/min. Currently, hepatitis B testing is part of PrEP initiation tests offered through MOH; however, stockouts sometimes preclude testing; results obtained from rapid hepatitis B testing, if conducted, will be entered into appropriate study case report forms. Consenting patient participants in all 3 groups will undergo STI testing at baseline and follow-up visits (Table 1). Urine specimens will be tested for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* using Xpert CT/NG cartridge and GeneXpert System platform (Cepheid). Syphilis rapid plasma regain (RPR) titer (BD Macro-VUE; Becton, Dickinson and Company), with confirmatory *Treponema pallidum* particle agglutination (Serodia Fujirebio Inc), if RPR is positive, will be analyzed on blood specimens. Repeat RPR or *Treponema pallidum* particle agglutination will be conducted if the previous test was nonreactive at 3 months or if signs or symptoms of new syphilis infection are present. Repeat RPR titer will be conducted regardless of baseline RPR at the 6-month visit. Individuals initiating PrEP will be screened for acute HIV infection with HIV RNA testing using GeneXpert viral load cartridge (Cepheid). Anyone with detectable HIV RNA will be contacted immediately, and PrEP will be discontinued with prompt ART referral.

Study Outcomes

Our primary outcomes evaluate the acceptability, feasibility, and effectiveness of (1) PrEP integration into STI services and (2) the enhanced PrEP package (aPN and STI testing).

Acceptability and feasibility of PrEP integration into STI services is measured using patient and clinic staff surveys, contextualized by determinants of integration, as examined using qualitative interviews [66]. Effectiveness is defined in terms of PrEP uptake and persistence at 1, 3, and 6 months. We will examine PrEP initiations as a proportion of all STI clinic patient visits and reasons for declining PrEP among individuals eligible but not starting PrEP. Among individuals who initially

refuse PrEP, we will describe how many subsequently initiate PrEP. We will assess PrEP persistence according to clinic attendance, PrEP refills abstracted from mastercards, and self-reported PrEP adherence in study surveys, evaluating the frequency of appropriate PrEP refills and engagement with care. We will also evaluate PrEP persistence in the general clinic population using clinic record review among individuals who started on PrEP during the study recruitment period but who were not enrolled in the study. Finally, we will examine the reasons for PrEP discontinuation among individuals who terminate use during the study follow-up period.

Acceptability and feasibility of aPN as part of PrEP care is similarly assessed with patient and clinic staff surveys and qualitative interviews, examining preferences for aPN strategies from multiple perspectives. Effectiveness of the aPN strategy as a component of PrEP care is evaluated using partner referral outcomes and PrEP uptake among eligible partners. Specifically, referred partner metrics will include the following: number of partners referred per index, proportion of index participants naming ≥1 recent sexual partner, proportion who have ≥1 recent sexual partner returning to the clinic (with or without community tracing), and proportion of all returning partners who are eligible for and initiated on PrEP. To explore strategies that may enhance or improve aPN, we will describe participant preferences regarding the sex, age, and cadre (ie, health professional vs peer) of the person eliciting partners for naming and subsequent tracing.

Finally, acceptability and feasibility of etiologic STI testing is examined using patient and clinic staff surveys and qualitative interviews, exploring perceived barriers to and facilitators of integrating testing into usual care. Effectiveness of this strategy as a component of PrEP care will examine incident infections (including asymptomatic infections that would be otherwise missed by syndromic management among index and partner participants) and proportion of participants receiving appropriate STI treatment within 7 days of testing. An incident infection is defined as a new positive diagnosis based on follow-up testing (Table 1). If a patient had a positive result at their previous visit, we will distinguish between persistent versus incident infections based on whether the participant had received appropriate pathogen-directed treatment for their previous infection. All STI treatment will be offered in concordance with local management guidelines.

Secondary outcomes include fluctuations in HIV risk, including reports of unprotected encounters with sexual partners with unknown HIV infection status or known infection not on ART, multiple sexual partners without consistent condom use, and sexual partners who may have other partners. We ask patients to report any primary or casual partners in the month before the interview, and thus assess the rates of concurrency. Furthermore, by having primary partners *named* within our survey tool, we are able to query regarding any changes in primary partners during the 6-month follow-up period. Changes in HIV risk will be evaluated alongside reported perceived risk of HIV (assessed at each follow-up visit). We will examine partnership patterns within the cohort, including the proportion of participants who report no change or new partners throughout the follow-up period, and characterize partner switching among those with

multiple partners, including primary and casual partners. Finally, we will evaluate predictors of PrEP persistence at each time point (1, 3, and 6 months) and those factors that are associated with PrEP discontinuation.

Planned Statistical Analysis

Planned analyses are primarily descriptive in nature, summarizing participant characteristics, behaviors, and perceptions. We will examine differences between nonreferred participants who initiated PrEP (group 1) and those who did not initiate PrEP (group 3), with a particular focus on HIV risk behaviors, PrEP perceptions, and self-perceived HIV risk. Exact test by Fisher will be used to compare the differences in proportions between arms for categorical variables, and t tests will be used for continuous data ($a=.05$).

We will additionally evaluate longitudinal changes in HIV risk behaviors, perceived HIV risk, and PrEP use, both at the individual and population levels. To examine individual-level behavior changes, we will characterize each participant's behaviors and perceptions over the course of follow-up and compare patterns by PrEP initiation group. To examine population-level behavior changes, we will calculate predicted probabilities and 95% CIs for our behaviors of interest by visit, using generalized estimating equations to account for within-participant correlation. Both individual-level and population-level analyses will focus on partner type (primary or steady vs casual) and incident STIs, with comparisons among participant groups (group 1, group 2, and group 3).

We will explore risk factors associated with PrEP discontinuation using logistic regression among participants who start PrEP at enrollment or during the study follow-up period.

Planned Qualitative Analysis

For qualitative work, interviews will be transcribed in English from either English or local language audio recordings. Transcripts from users and clinic staff will be analyzed separately and reviewed for quality. Interview transcripts and field notes will be thematically analyzed using a combination of deductive and inductive analytic approaches. An initial codebook will be developed based on a priori concepts driven by the theoretical underpinnings used to develop the semistructured questionnaire, specifically the Conceptual Model for Implementation Research by Proctor [66]. Then, all textual data will be read thoroughly to summarize first impressions. Emerging themes will be incorporated into the codebook. Pre-existing codes may be modified based on interview transcripts. Transcripts will be coded iteratively in qualitative computer software programs. Researchers will code interviews separately to assess intercoder reliability. The codebook will be revised and updated. Analysis of the coded data will include investigation of relationships among codes, coding of matrices, and mapping of codes and themes. Identifying any hierarchical structure among themes also helps to determine how the codes fit together. Themes may be compared across groups by triangulating data.

Ethics Approval

This study has been approved by the University of North Carolina at Chapel Hill Biomedical Institutional Review Board (21-2457) and Malawi National Health Services Research Committee (21/09/2777). Potential participants will be provided up-to-date information, and they will provide consent before any study procedures. All research procedures will adhere to Malawi and US ethical standards for research involving human participants.

Malawi guidelines allow those aged ≥15 years to initiate PrEP if they meet other eligibility requirements. In the proposed study, we independently consent PrEP users aged between 15 and 17 years, without additional separate parental consent based on their legal right and eligibility to receive PrEP, the minimal risk posed by participating in the described study, and the potential for adolescents to directly benefit from the outcomes of this study. We provide adequate protection regarding the confidentiality of all study activities, including receipt of care, participation in interviews, and referrals for services, if needed. The study has been registered in ClinicalTrials.gov (NCT05307991).

Results

Enrollment began in March 2022 and is projected to continue until February 2023, with patient participant follow-up through August 2023. As of November 14, 2022, we have enrolled 78.8% (197/250) of the patient participants (group 1: 146/197, 74.1%; group 2: 29/197, 14.7%; and group 3: 22/197, 11.2%). The results of this study are expected to be reported in 2024.

Discussion

Overview

This study examines the acceptability, feasibility, and effectiveness of an enhanced PrEP package as part of a PrEP implementation strategy that integrates PrEP services with STI care in Lilongwe, Malawi. The efficiency and effectiveness of integrated services are at the core of this pilot study, leveraging the existing infrastructure and staff to recruit individuals already presenting for STI care. As PrEP availability expands around the world, including in SSA, novel delivery strategies are needed to recruit and retain the individuals at highest risk of acquiring HIV.

Linking individuals seeking care for STIs to PrEP is a logical approach to integrate complementary sexual health services [67-69]. Individuals seeking care at STI clinics are not only at increased risk of HIV but also almost universally eligible for PrEP under many national guidelines [70]; identifying eligible PrEP users at STI clinics may reach those with limited contact with the health care system [68,69,71-74]. In the United States, urban demonstration projects show high interest when PrEP is offered in STI clinics [75,76], with good uptake and adherence [77], and this integrated strategy may be more effective for reducing HIV incidence compared with community-based PrEP recruitment [78]. Our study fills a critical knowledge gap in SSA regarding the acceptability and feasibility from both patient and clinic staff perspectives of what has been shown to be a

promising integrated PrEP and STI implementation strategy elsewhere.

Our study expands on the integration of complementary services (PrEP and STI) by examining a novel application of an evidence-based intervention (aPN). A reliable workhorse for finding individuals previously unaware of HIV infection and linking them to ART, to the best of our knowledge, aPN has not previously been used as a strategy to identify potential high-risk PrEP beneficiaries besides individuals linked to PrEP based on sexual partners who have been newly diagnosed with HIV [31]. Our surveys collect detailed information regarding partnership patterns and associated HIV risk, characterizing partner switching, awareness of partner HIV status, and, as relevant, awareness of HIV treatment among HIV-infected partners. Coupled with our partner notification approach and insights regarding returning partners' HIV status and PrEP uptake, we will be uniquely positioned to explore dynamics of partner stability and HIV risk that may influence PrEP use.

Linkage of partners to PrEP and STI testing services may be particularly relevant when coupled with etiologic STI testing. Hardly a novel part of PrEP care in some parts of the world, evaluating the frequency of asymptomatic STIs among both PrEP users and their sexual partners could have important implications for STI management in much of SSA, where most countries continue to rely on less sensitive and less specific syndromic management. We are also exploring how or if PrEP counselors integrate STI test results into PrEP counseling and whether an STI diagnosis, with or without symptoms, influences perceived risk of HIV for individuals on PrEP. These more nuanced features of attitudes toward STI testing and their potential influence on PrEP use will be examined qualitatively.

Although 6 months of follow-up likely only captures a brief portion of the full *at-risk* period for PrEP initiators, this study will provide unique insights into fluctuations of HIV risk behaviors, perceived HIV risk, and PrEP use—including starting and stopping PrEP. Understanding the interplay between these 3 factors may help to inform PrEP distribution and counseling strategies in the setting of shifting risk behaviors. By prospectively monitoring changes in HIV risk, including biomarkers of risk (ie, incident STI), among a cohort of individuals seeking STI services, our outcomes may help to inform the development of *prevention-effective* PrEP use outcomes and programmatic objectives [79,80].

PrEP persistence is best considered in the context of contemporaneous HIV risk behaviors. Poor PrEP persistence, including suboptimal adherence [20,32] and discontinuation [33-40], threatens PrEP effectiveness when interruptions occur during periods of high HIV risk. In contrast, if PrEP persists in times of low HIV risk, users may experience unnecessary side effects, and scarce resources may be misallocated. The concept of PrEP use relative to sexual risk has been described previously [79], but few studies have considered the concept of alignment between PrEP use and risk perception or behavior in describing or interpreting PrEP persistence outside known serodiscordant partnerships [81]. Outcomes from this pilot study lay the foundation for a better understanding of these complex behavioral patterns that are at the core of defining and supporting appropriate and effective PrEP use.

Limitations

There are potential challenges associated with this pilot study; our observational design may limit conclusions regarding causality of, for example, etiologic STI testing and PrEP persistence. The retention of participants is likely enhanced as they are being provided transport incentive to participate in study activities and are traced via phone or in person for missed study visits. These efforts artificially increase retention in the study; however, ongoing PrEP use is not a requirement for participation. We are addressing this by comparing PrEP refill records and routine metrics of PrEP use among study participants and nonparticipants receiving PrEP at Bwaila during the study enrollment period. Our measurement of PrEP use is imperfect, relying on refill timing and self-reported use. This may overestimate or underestimate true adherence, and future studies may seek more objective measurements of PrEP exposure using urine, blood, or hair.

Another challenge is accurately capturing PrEP uptake at the clinic level, as PrEP may not be offered to all individuals who are eligible. We are approaching this challenge in two ways: first, we are collecting exit interviews for the first approximately 3 months of study enrollment, in which we will examine the proportion of patients in a convenience sample who self-report being offered PrEP; second, we are discussing PrEP eligibility, integrated services, and attitudes toward PrEP referral with clinic staff during qualitative interviews. We believe that these discussions can help to contextualize observed referral *rates* and inform future investigations that may seek to increase PrEP referrals.

There is potential measurement error surrounding our incident STI outcome, specifically if individuals seek treatment elsewhere for symptoms of an STI during the study follow-up period. We have tried to mitigate this by requesting patients to return to the clinic for any concerning symptoms. Our assessment of STIs is not exhaustive, with the notable omission of testing for trichomoniasis and herpes simplex virus. Physical examinations would help identify patients with any concomitant symptoms, and we will use these estimates in a sensitivity analysis to examine potential missed diagnoses. However, as we know that syndromic diagnosis is relatively insensitive (missing individuals who are asymptomatic) and, particularly for nonulcerative disease, not very specific, we may be underestimating incident STIs within this population.

Injectable PrEP, which requires every 8-week dosing rather than daily oral pills, is an exciting development, but may have different determinants of uptake within the STI clinic and among the clinic population. If LAI PrEP becomes approved for use in Malawi during the study period, this formulation can be offered to eligible participants, consistent with MOH eligibility and recommendations. Although the intention of this study is not to directly compare LAI with oral (daily) PrEP, our study design and the content of our in-depth interviews directly acknowledge this forthcoming technology, and we are equipped to examine relevant PrEP uptake and persistence outcomes for both oral *or* LAI.

Conclusions

Despite these limitations, this study lays a foundation for future large-scale evaluations of an integrated PrEP strategy—informing the feasibility of otherwise resource-intensive interventions such as partner tracing and STI testing. These preliminary data can be used to plan PrEP programs that address challenges in optimizing PrEP across the PrEP cascade—from identifying the appropriate candidates for PrEP to retaining these individuals in a *risk-aligned* manner, such that the need for PrEP and counseling on benefit of PrEP reflect HIV risk.

Data Availability

The data set anticipated to be generated during this study will be available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Clinic staff in-depth interview guide.
[DOCX File , 31 KB - resprot_v11i12e37395_app1.docx]

Multimedia Appendix 2
Patient in-depth interview guide.
[DOCX File , 33 KB - resprot_v11i12e37395_app2.docx]

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Abbreviations

aPN: assisted partner notification
ART: antiretroviral therapy

HTS: HIV testing and counseling service
LAI: long-acting injectable
MOH: Ministry of Health
PrEP: pre-exposure prophylaxis
REDCap: Research Electronic Data Capture
RPR: rapid plasma regain
SSA: sub-Saharan Africa
STI: sexually transmitted infection
UNC: University of North Carolina
WHO: World Health Organization

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Protocol

Nigerian and Ghanaian Young People's Experiences of Care for Common Mental Disorders in Inner London: Protocol for a Multimethod Investigation

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Abstract

Background: The Care Quality Commission published a review in 2018 in England titled "Are We Listening," which revealed that child and adolescent mental health services are not responsive to the specific needs of young Black people and other ethnic minorities even in areas with ethnically diverse populations. It found that commissioners and service planners failed to engage with these young people and their families to understand their needs and expectations.

Objective: The purpose of this study is to engage Nigerian and Ghanaian young people (NAGYP) with experiences of care for common mental disorders (CMDs) in London, to increase understanding of their needs, and to give voice to their views and preferences. Their parents', caregivers', and practitioners' views will also be sought for service improvement.

Methods: Three combined contemporary complementary methodologies—thematic analysis, interpretative phenomenological analysis (IPA), and intersectionality-based policy analysis (IBPA)—will be used across 3 comprehensive phases. First, a scoping review where relevant themes will be critically analyzed will inform further phases of this study. Detailed mapping of community and mental health care services in 13 inner London boroughs to investigate what professionals actually do rather than what they say they do. Second, IBPA will be used to scrutinize improving access to psychological therapies and other legislations and policies relevant to NAGYP to undertake an intersectional multileveled analysis of power, models, and constraints. Third, IPA will "give voice" and "make sense" of NAGYP lived experiences of CMDs via a representative sample of NAGYP participants' (n=30) aged 16-25 years, parents or caregivers' (n=20), and practitioners' (n=20) perspectives will be captured.

Results: The study has been approved by the UCL Institute of Education Research Ethics Committee (Z6364106/2022/02/28; health research) and University College London (Z6364106/2022/10/24; social research). Recruitment has begun in 13 inner boroughs of London. Data collection through observation, semistructured interviews, and focus groups are expected to be finalized by early 2024, and the study will be published by early 2025.

Conclusions: Combining multiple qualitative methodologies and methods will enable rigorous investigation into NAGYP's lived experiences of care received for CMDs in London. Findings from this study should enable a reduction in the negative connotations and harmful superstitions associated with mental health–related issues in this group, inform evidence-based interventions, and facilitate preventive or early access to interventions. There may also be an indirect impact on problems resulting from mental illness such as school dropout, antisocial behaviors, knife crimes, juvenile detention centers, and even death.

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KEYWORDS

Nigerian; Ghanaian; lived experience; common mental disorder; mental health; London; mental healthcare; mental disorder; ethnic; minority; racial; preference; perspective; patient need; qualitative; experience; content analysis; mental illness; phenomenological; phenomenology; policy analysis; United Kingdom; Great Britain; youth; pediatric; adolescent; adolescence; young person; young people

Introduction

Background

Since the 1970s, there have been concerns that the mental health system in the United Kingdom does not lend itself to the specific needs of Black people [1-3]. This may have led to the establishment of the Nafsiyat Intercultural Therapy Centre for ethnic minorities in London in 1983 [4,5]. Yet in 2018, the Care Quality Commission, an independent regulator, published its findings from a review of England's child and adolescent mental health services (CAMHSs) entitled "Are We Listening?" [6]. This revealed that, even in areas with ethnically diverse populations, CAMHSs are still not responsive to the specific needs of Black young people and other minorities. They found, "commissioners and service planners had failed to engage with...young people, families, and caregivers to understand their needs and expectations" [6]. Direct engagement with ethnic subgroups is a knowledge gap that this study aims to fill.

Thus, this study aims to engage a section of 2 underserved communities, Nigerian and Ghanaian young people (NAGYP), to increase understanding of their care needs for common mental disorders (CMDs) in inner London. The study will also engage with their parents or caregivers and practitioners to capture their views on CMDs and mental health care (MHC) models. It starts from the position that MHC needs to be reflective of cultural humility toward NAGYP as conceptualized in multicultural competencies [7,8].

This is the first study in the United Kingdom to explore NAGYP mental health experiences as part of the push against a one-size-fits-all approach to MHC [9-11]. In the domain of ethnic minorities, Lavis [9], Butt et al [10], and the London Assembly [11] highlight that paying specific attention to the needs of different subgroups and individualization is paramount. Vostanis et al [12] in their work on Indian adolescents in England argued, "rather than a blanket approach being applied to policy and service planning to meet the needs of diverse communities of young people, more specific evidence needs to be gained." Given the size of the NAGYP population in the United Kingdom, this NAGYP study will add to the body of evidence.

The 2011 Census analysis for ethnicity (as we wait for the 2021 Census, due to be published in early 2023 [13]) estimated that 312,000 Nigerian-born and 130,000 Ghanaian-born people live in the United Kingdom [14]. It also showed that around one-fifth of the foreign-born population of England and Wales was born in Africa (1.3 million, 17%). Those from Ghana and Nigeria had the highest proportion of Black or Black British (both 89%, 285,000) people [15]. London is the setting of this study, with a 2020 population of 9 million [16], and of the non-UK born, London has a Nigerian and Ghanaian population of 135,000 and 63,000, respectively [17]. These population sizes are much larger than those of the Jewish community (n=7770) in the City of Salford, Greater Manchester [18], or the Chinese community (n=14,000) in Northeast England [19], whose young people have already been the subject of research.

Prevalence of CMDs Varied by Ethnicity

The 2014 age-standardized data showed that on average, Black people are more likely to report a CMD: Black and Black British 23%, mixed and other 20%, Asian and Asian British 18%, White British 17%, and White other 14% [20,21]. For children and young people, the latest series (2017, 2020, and 2021) of mental health surveys sponsored by the Department of Health and Social Care did not show CMD prevalence by ethnicity. For all ethnic groups, CMD rates were higher in girls (10%) than boys (6.2%) in 5- to 19-year-olds [22,23]. The data for ethnicity was on general mental disorders; among 6- to 23-year-olds, White British, mixed or other, Asian or Asian British, and Black or Black British people were estimated at 18.9%, 22.5%, 8.4%, and 8.3%, respectively [23].

There are a few issues to consider regarding the lack of data and its inconsistencies. First, the data for CMD prevalence by ethnicity is grossly limited. There is evidence of variation in CMD prevalence and symptom presentation among ethnic subgroups [24,25]. The London Assembly [11] was unequivocal that nuanced data on ethnic subgroups "simply does not exist." When the nature and scale of the demand for mental health services are not known, it inhibits policy makers' and service planners' responses. The Assembly emphasized the frustration of funding and commissioning services with little or no knowledge of the demand for those services.

Second, the data suggest links between poor mental health, youth, and gang violence [26-28]. This has led to young Black people being wrongly associated with a criminal proclivity, rather than this being acknowledged as the result of structural inequalities. A practitioner participant in Fitzpatrick et al's [29] study said, "When I became a consultant [...] I saw Black people..., not being given the more respectable diagnoses but the more derogatory ones, those that carry punishment instead of therapy."

Definition of Common Mental Disorder

The British Psychological Society and The Royal College of Psychiatrists recognize "depression" (including subthreshold disorders) and "anxiety" (including generalized anxiety disorder, panic disorder, phobias, social anxiety disorder, obsessive-compulsive disorder, and posttraumatic stress disorder) as CMDs [30]. In some works of literature, depression and anxiety disorders are recognized and are often grouped together as "emotional disorders" as a more restrictive definition of CMDs [9,11,31,32]. CMDs has been chosen as the acronym or term in this protocol to align with the National Collaborating

Centre for Mental Health and National Institute for Health and Clinical Excellence definitions.

Study Aims and Objectives

The primary aim is to investigate the NAGYP experiences of MHC for CMDs in inner London in order to give voice to their views and preferences for service improvement. The study has 5 key objectives:

1. To identify the care and treatment options available for NAGYP in London living with CMDs
2. To evaluate how culturally appropriate and potentially adaptable the Positive Practice Guide of Improving Access to Psychological Therapy (PPG-IAPT) is for NAGYP service users, which is the first line of treatment for CMDs
3. To investigate the lived experience of NAGYP of care for CMDs in inner London and the views of their parent or caregiver on the construct of CMDs
4. To ascertain how practitioners use models in their repertoire to care for NAGYP
5. To understand how NAGYP's views, preferences, and expectations could inform care and practice design

Methods

Combining Thematic Analysis, Interpretative Phenomenological Analysis, and Intersectionality-Based Policy Analysis

This study has chosen 3 contemporary complementary methodologies to achieve the research objectives at different

phases. This choice stems from the consideration of CMDs as a phenomenon and their impact on the NAGYP social world. These philosophical underpinnings reflect the personal and professional background of the lead researcher as a Black man and a social worker, and the sensitive nature of the phenomenon, both in terms of cultural stigmatization [11,25] and institutional mistrust [33] that characterizes NAGYP's reality.

While thematic analysis (TA) will focus on NAGYP's lived experiences in terms of what a CMD as a phenomenon "looks like," interpretative phenomenological analysis (IPA) [34] will focus on what it "feels like" [35]. In context, TA will culminate in "deeper-level analysis relating to power and communities" [35], and on the other hand, IPA will "give voice" to and "make sense" [36] of NAGYP's own accounts. In addition, intersectionality-based policy analysis IBPA [37] will focus on intersectional issues, particularly how NAGYP social identities related to race, culture, religion, status, and so forth, and dispositions intersect with shared social structures and context [38,39]. IBPA will be used to scrutinize the PPG-IAPT for NAGYP constituents in order to expose the assumptions that characterize policy formulation in the absence of robust direct engagement with those for whom the policies are intended [40,41]. The study will be undertaken in 3 comprehensive phases, see Figure 1.

Figure 1. Research design for NAGYP London. CMD: common mental disorder; IBPA: intersectionality-based policy analysis; IPA: interpretative phenomenological analysis; MHC: mental health care; NAGYP: Nigerian and Ghanaian young people; PPG-IAPT: Positive Practice Guide of Improving Access to Psychological Therapy; TA: thematic analysis.
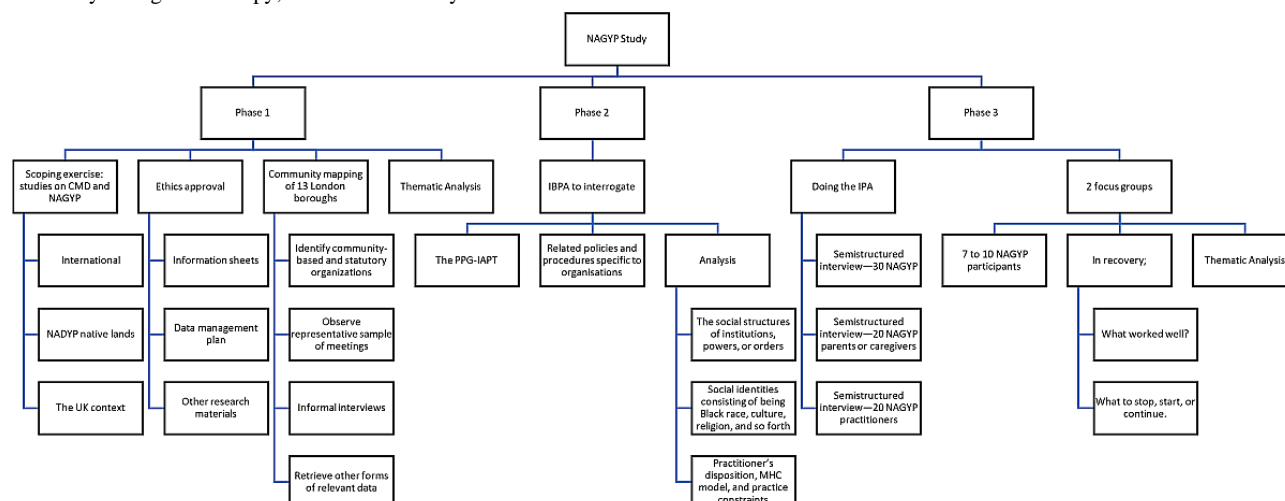
Phase 1: Scoping Exercise and Community Mapping

Scoping Exercise

In the United Kingdom and England in particular, there is a body of work on CMDs in relation to ethnic minority children and young people [29] (eg, [42-46]). However, little is known about Black or African people specifically [25] (eg, [47,48]), and very little or nothing is known about the individual or combination of this study's subgroups (Nigerian and Ghanaian),

geographical location (London), and their relationship with the phenomenon (CMDs). Thus, this phase will review literature that examines elements of NAGYP and Black African people with experiences of CMDs. Boote and Beile [49] suggest that for topics about which little or nothing has been written, the reviewer may need to "broaden the search" to explore related topics. Therefore, the principles of a scoping review will be used to "determine the scope or coverage" [50]. Cooper [51] argues that "coverage" is the most distinct element of a literature review. Thus, the coverage will include NADYP native lands

and UK studies, though with a particular focus on London as the primary geo-socio-political context of this study. Relevant themes will be critically analyzed and will inform further phases of this study.

Studies on the CMD Construct Related to the NAGYP Domain Globally

The rationale and understanding of the impact of CMDs on Black African young people at a global level will be important to place our UK findings in context. Attention will be given to the location and social context from which samples were drawn.

Studies in NAGYP Native Countries

Relevant studies undertaken in Nigeria and Ghana will be synthesized. Findings from NAGYP homelands will increase understanding of the perceptions of NAGYP, their general disposition, and what they make of CMDs. This is crucial because when people migrate, they do so with the health perceptions and cultural and religious beliefs developed within their country of origin.

Studies in the United Kingdom

In the United Kingdom, since health is a devolved matter across the constituent countries, relevant literature will have a national spread across England, Scotland, Wales, and Northern Ireland. However, the literature from England, specifically London, will, where possible, have primacy in informing further stages. London is the primary social, political, and environmental context of this study, where the researcher will engage in multimethod research activities with NAGYP, parents or caregivers, and practitioners.

Databases

The selected databases and libraries include International Bibliography of the Social Sciences, Applied Social Sciences Index and Abstract, Web of Science, SCOPUS, UCL Explore, Google Scholar, and Academic Search Complete (via London Senate House Library). These databases host a rich variety of social science peer-reviewed literature with international coverage. In addition, studies will be added through snowballing from the included studies' reference lists [52].

Ethics Approval

Ethical approval has been granted by the UCL Institute of Education Research Ethics Committee (Z6364106/2022/02/28; health research) and University College London (UCL) (Z6364106/2022/10/24; social research). We are waiting for approval from the National Health Service (NHS) Health Research Authority Ethics Committee.

Community Mapping

Rigorous community mapping will be undertaken in these inner London boroughs: Camden, Greenwich, Hackney, Hammersmith and Fulham, Islington, Kensington and Chelsea, Lambeth, Lewisham, Southwark, Tower Hamlets, Wandsworth, Bexley, and Westminster. These have been chosen from among London's 32 boroughs because they are home to a sizable NAGYP population [53]. There are 5 objectives in community mapping within London boroughs. They are (1) to identify community-based organizations delivering specific MHC services to NAGYP or Black African people or minority groups within them, (2) to ensure voluntary and statutory organizations with departments providing such services are included within them, (3) to attend a representative sample of meetings where relevant care is being discussed or delivered, (4) to conduct an informal interview with a representative sample of practitioners, and (5) doing TA with a framework approach.

The objective is to investigate the ways and extents to which MHC and elements of models are actually adapted by practitioners to meet the specific mental health needs of NAGYP. Contacts will be made directly with these departments or teams. Permission will be sought to attend and observe selected meetings, at least one from each borough, where care plans are discussed, as well as workshops or sessions where care is delivered in action. The ones deemed appropriate will be attended to with due regard to full ethical and governance requirements. If permission is not granted, data from the relevant service websites would be analyzed instead. Some practitioners (n=20-25) will also be invited for an informal interview at this stage.

Informal Interviews

Various spontaneous, unscheduled interviews will be undertaken with practitioners after meetings or observed sessions, either to clarify or better understand certain approaches or practices. These informal interviews are meant to complement what the researcher observes as part of ethnographic interviews [54]. This has the potential to validate what is discussed in meetings, adding to the authenticity of the data. The interview content will be written in a field notebook as soon as possible, as it may not have been recorded due to the spontaneous nature of the interview [54]. Informants may provide different amounts of information depending on what the researcher needs to know. To manage bias, the information collected will be incorporated as field note data rather than interview data.

Doing TA With a Framework Approach

The qualitative data generated in this phase will be analyzed using the framework approach. Framework matrices (called charts) enable the analysis of data from a wide variety of sources, such as websites, PDFs, audio or video recordings, blog posts, field notes, memos, and transcripts generated from informal interviews. The approach allows all data to be collected before analysis begins. The data will be imported into NVivo (QSR International), where it will be summarized in charts according to predetermined themes [55]. The reporting for TA is normally written in a descriptive list, as "careers" or journeys through time or place, or as a typology. This study will be written in a descriptive list format to ensure that findings are communicated in a concrete (rather than more conceptual) manner that is understandable to wider audiences [35]. The process is illustrated in Figure 2.

Figure 2. Stages of the framework approach [35].
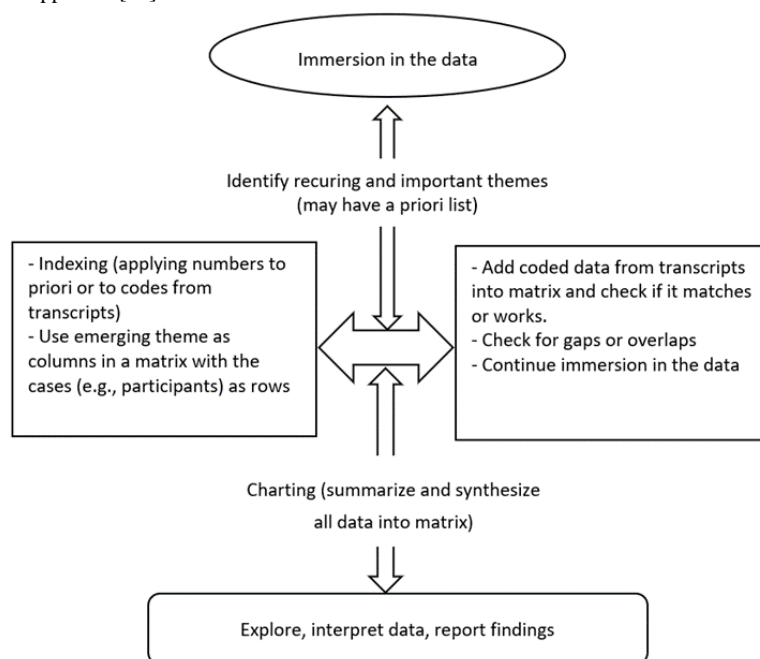
Phase 2: Interrogating the PPG-IAPT for Black People and Ethnic Minorities

The IBPA will be used to scrutinize the PPG-IAPT as the main MHC national policy, as well as other organizational internal policies and procedures for NAGYP and its constituents with CMDs. IBPA is an "equity-promoting public policy analysis" framework [37] that will be used to perform a multileveled intersectionality analysis. The analysis will emphasize the simultaneous interplay and triangulation between:

1. The social structures of institutions, powers, or orders on one strand
2. Social identities consisting of being Black race, culture, religion, and so forth, as the second strand
3. Practitioner's disposition, MHC model, and practice constraints as the third strand

The aim is to ascertain the PPG-IAPT and the related policy of its cultural adaptiveness and appropriateness to the specific needs of NAGYP service users. The 2 core components of IBPA will be used. They are (1) a set of guiding principles (see Figure 3) and (2) a list of 12 overarching questions (see Textbox 1) [37] with a set of subquestions [56].

The design is for the principles to be used with the questions (including the subquestions) simultaneously. Each question will be asked and answered in a manner that would depict explicit intersectionality-informed analysis. The aim is to draw attention to those assumptions that characterize policy formulation without robust direct engagement with those whom the policies are intended for [40,41].

The 12 questions are divided into 2 categories; the first 5 are termed "descriptive." This will expose the critical background information about the problem in the PPG-IAPT and its related policies for ethnic minorities. This phase will pay particular attention to how the problems the policy is meant to ameliorate are identified, deconstructed, and then addressed. For example, only 1 Nigerian and no Ghanaian people were involved in the focus group in the formulation of the PPG-IAPT. This will bring to light the assumptions as well as the inequities or privileges, if any, that inundate the policy position. The remaining 7 questions are termed "transformative." These are intended to help identify alternative policy responses or proffer suitable solutions that could provoke social and structural change. Phase 1 will play a fundamental role in this. The overarching goal of IBPA is to reduce inequities, if not completely eradicate them, and ultimately to promote equity and social justice [37].

Hankivsky et al [37] argued that "simplicity and flexibility are key features of the Framework." All 12 questions may not be relevant to this study. For this study, some of the questions may be prioritized and given more consideration than others due to the context and approaches to implementation adopted by individuals or teams. What is critical is that the questions are rooted in key intersectionality principles subsumed in structure and politics [39]. The combined effect of these categories of questions on the PPG-IAPT for minority groups as a national policy position and its related policies and procedures unique to individual organizations would transform how its associated problems and processes are understood.

Figure 3. Guiding principles of intersectionality-based policy analysis [37].
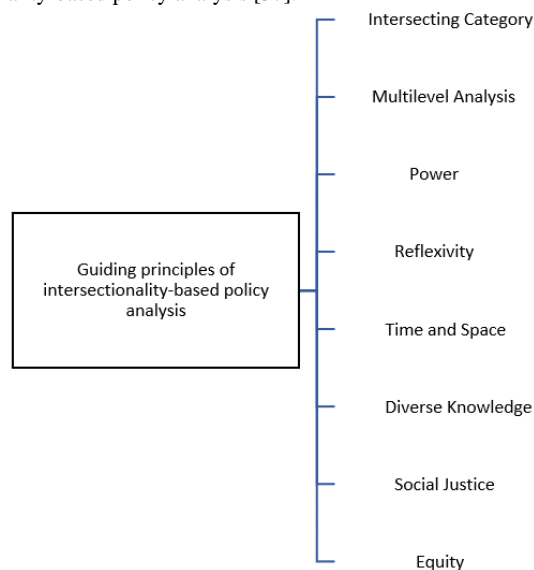
Textbox 1. Descriptive and transformative questions of intersectionality-based policy analysis. Adapted from Hankivsky et al [37].

Descriptive questions

1. What knowledge, values, and experiences do you bring to this area of policy analysis?

2. What is the policy "problem" under consideration?

3. How have representations of the "problem" come about?

4. How are groups differently affected by this representation of the "problem"?

5. What are the current policy responses to the "problem"?

Transformative questions

1. What inequities actually exist in relation to the "problem"?

2. Where and how can interventions be made to improve the "problem"?

3. What are the feasible short-, medium-, and long-term solutions?

4. How will proposed policy responses reduce inequities?

5. How will implementation and uptake be assured?

6. How will you know if inequities have been reduced?

7. How has the process of engaging in an intersectionality-based policy analysis transformed:

    - Your thoughts on relations and structures of power and inequity?

    - The way you and others engage in policy development, implementation, and evaluation?

    - Broader conceptualizations, relations, and effects of power asymmetry in the everyday world?

Phase 3: Engaging With NAGYP, Parents, and Practitioners

This is the core of the study and provides, through semistructured interviews, an in-depth understanding of the lived experiences of NAGYP on the MHC received for CMDs. Their parents' and practitioners' views are a key part of this. The focus of this is to use IPA to "give voice" and "make sense" [36] of NAGYP's experiences in their own words, terms, and accounts without affiliation to any existing theory or concept [34].

Semistructured Interviews

Semistructured Interview: NAGYP

Around 25 to 30 NAGYP participants in the age range of 16-25 years will be identified and recruited from the phase 1 exercise. In addition, participants will be recruited through local gatekeepers such as notable voices, faith and community leaders, local associations, and voluntary service providers within the community. The interview will explore themes related to the following topics:

- Meaning and perception of CMDs
- Experience during therapy

- Views, preferences, and expectations
- Anything particularly helpful in MHC
- What to stop, start, or continue

Semistructured Interview: NAGYP Parents or Caregivers

This is aimed at capturing about 15-20 NAGYP parents' views and perceptions of the CMD and MHC constructs. Topics will aim to enable the following:

- Reducing the negative connotations and harmful superstitions of CMDs that characterize NAGYP communities
- A more liberal understanding of CMDs
- Improving access to early intervention or professional help

Parents and caregivers will be interviewed because the meaning they attach to CMD discourses, negative or positive, is often passed on to their young people due to the strong family ties that exist among Black parents, children, and young adults resulting from their cultural dispositions of the family unit [57,58].

Semistructured Interview: NAGYP Practitioners

The interviews will be designed to elicit the practitioner's practical knowledge of MHC models. They are aimed at practitioners in the selected London areas who have delivered MHC to NAGYP. Up to 15-20 participants will be identified from phase 1. One practitioner will be included in an embedded pilot. The knowledge generated from this research activity would be used to categorize the different practitioners' understandings

of MHC models relating to the services they provide for NAGYP as well as the options available within and across disciplines. The dimensions of the categorization will be substantiated in the domain of MHC models in existing literature, as currently understood. However, their preference for modification or for new MHC models for NAGYP will be benchmarked against the medical and social models of disability [59] and Eurocentric and Afrocentric MHC. The interview topic guide includes:

- The most prevalent CMD diagnosis for NAGYP service users
- Own experience as a therapist supporting NAGYP
- Professional training received in response to meeting the needs of NAGYP, or Black young people in general
- Perception of the most suitable model of intervention
- Effective ways of integrating the model with the PPG-IAPT
- Challenges and key determinants of success in providing MHC to NAGYP
- Potential examples of positive practice
- The future of MHC for NAGYP

Doing the IPA

This phase will culminate in the IPA protocol. The most recent changes to the terminology of IPA will be adopted in the analysis. For example, the usual emergent themes and superordinate themes will be called experiential statements and personal experiential themes, respectively [60,61]. The following steps in Textbox 2 will be adhered to.

Textbox 2. Steps in doing interpretative phenomenological analysis. Adapted from Smith et al [61].

Step 1: Starting with the first case: reading and rereading, be immersed in the transcript. This is to make sure the respondent becomes the focus of the analysis. Similar to thematic analysis.

Step 2: Exploratory noting: disentangling semantic content, language, and conceptual comments with an open mind, noting everything of interest, and developing an avowedly interpretative statement relating to context. This will be reviewed with my supervisor.

Step 3: Constructing experiential statements: the process of consolidating and crystallizing the exploratory notes. This process represents 1 manifestation of the hermeneutic circle, that is, "the me" and the lived experiences of the participant in collaborative (cocreating) efforts. Tied within local instances in the transcript.

Step 4: Searching for connections across experiential statements: clusters of statements can be organized through different possibilities, using flexibility.

Step 5: Naming the personal experiential themes (PETs), consolidating, and organizing them in a table. Not tied within local instances but within the transcript as a whole.

Step 6: Continuing the individual analysis of other cases: steps 1-5 will be repeated for other cases in their own terms and individuality, in keeping with IPA's idiographic commitment.

Step 7: Working with PETs to develop group experiential themes (GETs) across cases: drawing links between each PET to create GET.

Focus Group

To pay greater attention to the views and preferences of NAGYP toward CMDs and MHC to inform care and practice design, focus groups will be used to engage with NAGYP. Participants will be recruited through the established contacts from phase 1. In the focus group discussion, 7 to 10 NAGYP participants in the age range of 16 to 25 years will be involved. The topic guide will be informed by the data collected so far; 2 sessions are anticipated. The activities will be documented and analyzed using standards for handling data from multiple voices [62,63]. The focus groups will explore the experiences of MHC; the

experiences that play a substantial role in recovery; what worked well; and what to stop, start, or continue.

Results

The study has been approved by the UCL Institute of Education Research Ethics Committee (Z6364106/2022/02/28; health research) and UCL (Z6364106/2022/10/24; social research). Recruitment has begun in the 13 inner boroughs of London. Data collection through semistructured interviews and focus groups is expected to be finalized by early 2024, and the study will be published by early 2025.

Discussion

The study aims to investigate NAGYP's lived experiences of care for CMDs in inner London. The study anticipates identifying the care and treatment options available; the cultural appropriateness of the PPG-IAPT for NAGYP service users, which is the first line of treatment; and parents' views and practitioners' dispositions on models of care. We hope the outcomes of this study will contribute to providing a response to the London Assembly's recognition of mental disorders as a peculiar problem being faced by young Londoners, particularly from minority ethnic subgroups. The Assembly acknowledged how this could negatively impact their well-being and economic capacities [12]; some impacts may lead to antisocial behaviors and fatalities [26,27]. We also expect the findings to be consistent with the recommendations in the joint Green Paper published by the Department of Health and Social Care and Department for Education [64]. The Green Paper captured the views and expectations of 65 respondents from Black or minority ethnic backgrounds and LGBT+ communities, or those who have a disability; all were younger than 25 years. Their expectations were unequivocal, including creating a welcoming environment, training the CAMHS workforce to gain cultural competence skills, providing bespoke MHC, improving service awareness, and providing out-of-term time support [65]. These expectations highlighted in the Green Paper have not yet been met; a report published in February 2022 by the NHS Race and Health Observatory body found evidence of ethnic inequalities in every area reviewed [65].

The NHS Race and Health Observatory is an independent expert body given the responsibility of examining health inequalities experienced by minority ethnic groups in England, of which NAGYP is a major constituent. Their main findings in a review revealed that Black people's fear and distrust of mental health services form "clear barriers to seeking help" [66]. Thus, a key strength of this study is in the bottom-up and transparent methodological choices. For example, while TA interrogates NAGYP's lived experiences of what CMD as a phenomenon looks like and how it feels like, IPA allows idiographic accounts in participants' own words and terms to allow the very essence of the phenomenon to reveal itself in its primordial form [36]. Then, NAGYP's social identity and context are explored within the precepts of IBPA.

The main potential limitation, while also a richness, is that qualitative methods are focused mainly on participants' experiences [67,68] and seek to gain access to participants' social worlds. As a result, Smith et al [66] acknowledge that IPA researchers might strongly influence the interpretation of the respondent's world. According to Larkin et al [36], the wide range of interpretative frameworks available for IPA constitutes a practical problem. Cromby and Nightingale [69] noted that the part of the participant's world that the researcher would want to make real or relative may be typically dependent on choices shaped by the researcher's "moral, political or pragmatical precepts" instead of epistemological choice. Larkin et al [36] put it succinctly that "we can never fully escape the 'preconceptions' that our world brings with it," thus, transparency is key. Therefore, Larkin and Thompson [70] and Smith et al [61] recommended that a meticulous, detailed, organized, plausible, and transparent account of the analytical process must be kept. This study will do so.

With respect to the overarching aim of this pragmatic study, which centers on equitable MHC, Article 1 of the 1992 United Nations' Minorities Declaration expects the state to protect a minority's existence [71]. In the United Kingdom, the Equality Act [72] places a statutory duty on public sectors and wider society to promote racial equality, including in MHC. The process of improving this research population's MHC may positively impact them, their friends and associates, and their involvement in street and knife crimes in the future; it might combat stigma and reduce the negative connotations and harmful superstitions of mental health–related issues that characterize these communities; and it might contribute to a more liberal understanding that could elicit access to early intervention or the seeking of professional help. The findings of this study are expected to be published in 2025.

Data Availability

The data sets collected and analyzed for the duration of this study will be made available from the corresponding author upon reasonable request.

Authors' Contributions

AI had the original idea and is the key contributor. CR and GS supervised the project.

Conflicts of Interest

None declared.

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Abbreviations

CAMHS: Child and Adolescent Mental Health Service
CMD: common mental disorders
IBPA: intersectionality-based policy analysis
IPA: interpretative phenomenological analysis
MHC: mental health care
NAGYP: Nigerian and Ghanaian young people

NHS: National Health Service
PPG-IAPT: Positive Practice Guide of Improving Access to Psychological Therapy
TA: thematic analysis
UCL: University College London

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Protocol

Postoperative Sigmoidoscopy and Biopsy After Elective Endovascular and Open Aortic Surgery for Preventing Mortality by Colonic Ischemia (PSB-Aorta-CI): Protocol for a Prospective Study

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Abstract

Background: Endovascular aortic repair is considered the standard procedure in treating patients diagnosed with pathologies of the abdominal aorta with suitable anatomy. Open surgery remains an option mostly for patients not suitable for endovascular surgery. Colonic ischemia is an important and life-threatening postoperative complication of these procedures.

Objective: The aim of this study is to evaluate the clinical value and safety of performing a planned sigmoidoscopy and biopsy for detection of colonic ischemia in patients undergoing elective aortic surgery. We also aim to develop prediction scores which could identify patients at risk for colonic ischemia and facilitate their timely treatment.

Methods: The trial is designed as a prospective study. The decision for aortic surgery and eligibility for these procedures will be ascertained according to current guidelines. Afterward, screening of the patient for the remaining inclusion and exclusion criteria will occur. If eligibility for study inclusion is confirmed, the patient will be informed about the aims of the study and all study-specific procedures (sigmoidoscopy and biopsy) and asked to provide informed consent.

Results: The primary end point is the proportion of patients diagnosed endoscopically with subclinical and clinically relevant colonic ischemia among all patients undergoing aortic surgery. Patient recruitment started on June 2021. The final patient is expected to be treated by the end of June 2023. Institutional Review Board review has been completed at the University of Halle (Saale; reference #052-2021).

Conclusions: this shows that sigmoidoscopy can be performed safely and is effective for the timely diagnosis of colonic ischemia in these patients, this could result in its routine implementation in both elective and emergency settings.

Trial Registration: German Clinical Trials Register DRKS00025587; https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00025587

International Registered Report Identifier (IRRID): DERR1-10.2196/39071

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Introduction

Endovascular aortic repair (EVAR) is considered the standard procedure in treating patients diagnosed with abdominal aortic pathologies and suitable anatomy. Open surgery remains an option mostly for patients not suitable for endovascular surgery. Colonic ischemia is known as a severe complication after both open and endovascular aortic surgery. Its incidence is well described, and even with modern treatment options, colonic ischemia carries a high mortality rate. One of the assumed causes of colonic ischemia after aortic surgery is reduced blood flow via the inferior mesenteric artery. The origin of the vessel is either ligated during open repair (OR) or excluded from antegrade perfusion during EVAR. Reimplantation is rarely performed during OR and not possible during EVAR. Moreover,

stenosis or occlusion of the inner iliac arteries may contribute to ischemia of the distal colon and rectum.

When compared to OR, EVAR is associated with reduced invasiveness, less general anesthesia, shorter operation times, less blood loss, and lower postoperative pain. Two meta-analyses showed lower short-term mortality in patients undergoing EVAR when compared to OR [1,2]. Nevertheless, there are no advantages in terms of long-term mortality [3]. In the emergency setting, no advantages for EVAR in terms of short- or long-term outcomes could be found [4-7]. Because of the evidence and experience from the last 30 years, most vascular surgeons now consider EVAR as the treatment of choice in the elective and emergency context, leaving OR for individual cases with anatomic unsuitability for EVAR, mycotic abdominal aortic aneurysms, conversion after early or delayed failure or infection of EVAR, or patient preferences (Figure 1).

Figure 1. Flowchart of surgical procedures. AAA: adominal aortic aneurysm; bEVAR: branched endovascular aortic repair; fEVAR: fenestrated endovascular aortic repair; OR: open repair.
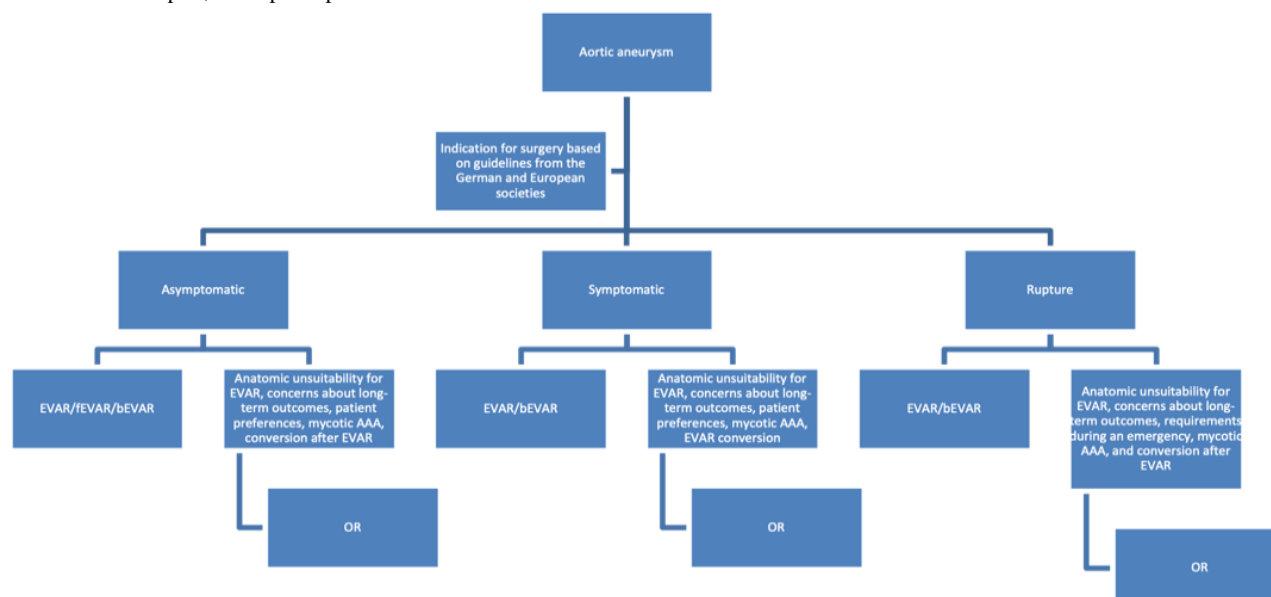
As already stated, the risk of developing colonic ischemia is present in both endovascular on open treatment of aortic aneurysms. In a meta-analysis involving 13 studies reporting outcomes of colonic ischemia after elective aortic repair comprising 162,750 patients (78,151 EVAR and 84,599 OR), all studies found a higher risk of colonic ischemia for OR than for EVAR (2.1%-3.6% vs 0.5%-1%; combined odds ratio 2.7, 95% CI 2.0-3.5) [8].

Other studies highlight the low incidence but high fatality of colonic ischemia. Lowe et al [9] reported in a systematic review and meta-analysis including 5 cohort studies and 3 case reports with 6184 infrarenal elective EVARs an, incidence of colonic ischemia of 0.5% to 2.8%. In these patients, fatality ranged from 35% to 80%. The authors highlight the importance of identifying risk factors and establishing prophylactic measures in patients with an increased risk of developing these severe complications after infrarenal EVAR. In a database analysis from the United States on 89,967 patients who underwent aortic surgery, the overall incidence of colonic ischemia was 2.2%. The patients who developed colonic ischemia were at increased risk for

mortality (37.8% vs 6.7%) [10]. Studies reporting on the use of colonoscopy for identifying patients at risk for colonic ischemia have been published, mostly regarding patients in an emergency context. In both patient collectives—elective and emergent—high mortality rates have been reported. In a study by Champagne et al [11] that included 88 patients who underwent emergent aortic reconstruction because of ruptured aortic aneurysm, colonoscopy was performed in 62 patients who survived for more than 24 hours. Bowel ischemia was documented in 35% of patients. Of these, 16 patients had grade I or grade II ischemia and repeat endoscopy. Grade I ischemia was defined as mucosal ischemia; grade II ischemia was characterized by involvement of the mucosa and the muscularis layers; and grade III ischemia was described by transmural ischemia, gangrene, and perforations. Nine patients needed bowel resection because of grade III ischemia; two procedures were performed because of worsening ischemia discovered at repeat colonoscopy. In another meta-analysis, the accuracy of routine endoscopy in diagnosing colonic ischemia after abdominal aortic aneurysm repair was analyzed. In all, 718

patients were included (44% underwent elective, 56% emergent, and 6% endovascular repair). Among all patients, 20.8% were identified with colonic ischemia (6.5% grade III). The pooled diagnostic odds ratio for all grades of colonic ischemia on endoscopy was 26.6 (95% CI 8.86-79.88) [12]. In a study from Germany, the incidence of colonic ischemia among patients who underwent aortic surgery was 2.4%. Colonic ischemia was predominantly diagnosed by endoscopy (74%). In-hospital mortality was increased in the colonic ischemia group (26.7% vs 2.9%; $P<.001$) [13].

The aim of this study is to evaluate the clinical value and safety of performing a planned sigmoidoscopy and biopsy for detection of colonic ischemia in patients undergoing elective aortic surgery. We also aim to develop prediction scores which could identify patients at risk for colonic ischemia and facilitate their timely treatment. If this study shows that sigmoidoscopy can be performed safely and is effective for diagnosing colonic ischemia in these patients, this could result in its routine implementation in both elective and emergency settings.

Methods

Study Design

The trial is designed as a prospective study. The decision for aortic surgery and eligibility for these procedures will be ascertained according to the current guidelines from the German and European societies (Deutsche Gesellschaft für Gefäßchirurgie [DGG; German Society of Vascular Surgery and Vascular Medicine], Society of Vascular Surgery [SVS], and European Society of Vascular Surgery [ESVS]) [14-16]. Afterward, screening of the patient for the remaining inclusion and exclusion criteria will occur. If eligibility for study inclusion is confirmed, the patient will be informed about the aims of the study and all study-specific procedures and asked to provide informed consent. This will take place prior to the planned aortic surgery.

End Points

The primary end point is the proportion of patients diagnosed endoscopically with subclinical and clinically relevant colonic ischemia among all patients undergoing aortic surgery.

The secondary end points are the proportion of patients requiring surgery for colonic ischemia after aortic surgery, the proportion of patients requiring stoma formation for colonic ischemia, perioperative in-hospital morbidity and mortality measured according to the Clavien-Dindo classification of surgical complications, length of hospital stay, and frequency of reoperation.

Study Population

The inclusion criteria are the following: elective open or endovascular surgery for abdominal aortic aneurysm (Figure 1), provision of written informed consent prior to any study-specific procedures and willingness to comply with treatment and follow-up, and age ≥18 years.

The exclusion criterion is any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with the patient's safety, provision of informed consent, or compliance with study procedures.

Number of Trial Participants

We assume that the rate of colonic ischemia diagnosed by sigmoidoscopy within 48 hours after the operation would be 10% in asymptomatic patients. In the current literature, the incidence of colonic ischemia diagnosed by clinical suspicion only in symptomatic patients is approximately 5%. This rate plus 10% of the 95% of asymptomatic patients results in an overall rate of patients with signs of colonic ischemia of 14.5%. In turn, this results in a 1-armed binomial distribution with 120 cases to be compared to the incidence reported in the literature (5%; α=5%; 1-β [power]=80%) [17].

Analysis of End Points

Analysis of the primary end point will occur as soon as all patients have undergone aortic surgery and sigmoidoscopy and are discharged from the hospital. The primary end point will be presented as a proportion with a 95% CI.

Secondary end points (proportion of patients proceeding to surgery for colonic ischemia after aortic surgery, perioperative in-hospital morbidity, and mortality measured according to the Clavien-Dindo classification of surgical complications) will also be analyzed once the patient has been discharged from the hospital after the respective procedure. The incidence of complications will be presented as a proportion with a 95% CI stratified by the highest Clavien-Dindo grade of all complications that occurred in each patient.

Recruitment

Participants will be recruited at the institution carrying out the study. Dedicated screening for trial participation will be performed when open and endovascular aortic surgery for the patient is discussed by the interdisciplinary vascular board. If the patient is selected to undergo open or endovascular surgery, informed consent will be presented to the patient by a physician within 24 hours before surgery.

Trial Implementation and Enrollment

Trial Procedures

All relevant trial procedures are displayed in Table 1. The computed tomography (CT) scan is not a study-specific procedure, as every patient who undergoes open or endovascular aortic surgery will receive a preoperative CT scan as routine care.

Table 1. Time and events table.

Required measures	Screening/trial entry	Aortic repair	Sigmoidoscopy 24-48 h after aortic repair
Verification of inclusion and exclusion criteria	✓		
Informed consent	✓		
Computed tomography	✓		
Ascertainment of data as detailed in Evaluation and Follow-up	✓	✓	✓
Ascertainment of primary end point			✓
Follow-up exams at the discretion of the treating physician			
Surgery		✓	

Sigmoidoscopy

A standard sigmoidoscopy (from the rectum to the transition of the sigmoid to the descending colon) will be performed. The macroscopically visible ischemia will be graded according to the following scheme: grade I = mucosal ischemia; grade II = involvement of the mucosa and the muscularis layers; and grade III = transmural ischemia, gangrene, and perforations.

A biopsy should be always performed, when possible, in macroscopically suspicious areas. When no macroscopic suspicion is present, a biopsy should be taken in the sigmoid colon. Biopsy should differentiate between normal mucosa, the nongangrenous type of ischemia (mucosal atrophy, edema, hyperemia, mild acute inflammation), and the gangrenous type of ischemia (acute wall necrosis).

Evaluation and Follow-up

Trial Entry

Upon trial entry, the following information will be assessed: date of birth and sex; date of diagnosis; diagnosis; symptoms or clinical history of chronic mesenteric ischemia; in case of aneurysm, the maximal transversal diameter; the length of aneurysm neck; history of cardiovascular diseases; CT findings (patency of abdominal branches: superior mesenteric artery, inferior mesenteric artery and celiac artery, lumbar arteries, hypogastric arteries); Eastern Cooperative Oncology Group (ECOG) performance status; and American Society of Anesthesiologists (ASA) status.

Surgery

At the time of surgery, the following information will be assessed: date of surgery; type of procedure; duration of surgery; intraoperative complications according to the Clavien-Dindo-classification [18]; blood results at the time of or directly before the procedure, including C-reactive protein, lactate, leukocytes, glomerular filtration rate, creatinine, and hemoglobin; intraoperative hypotension; intraoperative blood loss; and aortic clamp time.

Sigmoidoscopy

At the time of sigmoidoscopy, the following information will be assessed and documented in a protocol: date of sigmoidoscopy; examination time; sigmoidoscopy findings (grade I: mucosal ischemia; grade II: mucosa and the muscularis layers; grade III: transmural ischemia, gangrene, and perforations; if grade III ischemia is detected, no biopsy will be performed); complications of the sigmoidoscopy; blood results, including C-reactive protein, lactate, leukocytes, glomerular filtration rate, creatinine, and hemoglobin; and a checklist to assess the degree of clinical suspicion of colonic ischemia filled out by the surgeon (if the checklist does not indicate a suspicion of colonic ischemia this will be defined as subclinical).

At the time of biopsy result, the following information will be assessed and documented in a protocol: date of result, biopsy findings differentiating ischemia in nongangrenous type (mucosal atrophy, edema, hyperemia, mild acute inflammation), and gangrenous type (acute wall necrosis), and ischemia grade.

Independent observers, blinded to the macroscopical findings of the sigmoidoscopy and the clinical course of the patient, will assess the results of the biopsy.

The tissue will be preserved for immunohistochemistry and RNA analysis of ischemia markers (eg, fatty acid binding protein).

Discharge or Death of the Patient

In-hospital mortality and complications will be documented according to the Clavien-Dindo classification. For any operations performed due to a complication, details will be recorded (type of procedure, stoma formation etc).

Ethics Approval

The study has been approved by the Ethical Committee of the Medical Faculty of the Martin-Luther University Halle-Wittenberg (application #2021-052).

Results

The primary end point is the proportion of patients diagnosed endoscopically with subclinical and clinically relevant colonic ischemia among all patients undergoing aortic surgery. Patient recruitment started on June 2021. The final patient is expected to be treated by the end of June 2023. For each participant, the duration of the trial will be a treatment phase from recruitment into the trial until hospital discharge. The primary end point will be ascertained at the time of obtaining sigmoidoscopy and biopsy results. The total duration of the trial is expected to be 48 months.

Discussion

This prospective study will provide insight into the clinical value and safety of performing routine sigmoidoscopy and biopsy for the detection of colonic ischemia in patients undergoing elective aortic surgery and further help determine whether the use of sigmoidoscopy in patients after an aortic surgery is safe. It will be conducted according to the presented protocol. The expected results will support health care professionals and patients with aortic aneurysms undergoing endovascular and open surgery in their decision-making concerning a planned sigmoidoscopy after the procedure. Specifically, we expect the results to provide sufficient data to develop risk scores for these patients. If this study shows that sigmoidoscopy can be performed safely and is effective in diagnosing colonic ischemia in these patients, it could be implemented routinely in both elective and emergency settings.

After due consideration, all participating investigators are convinced that the trial has a favorable risk-benefit ratio. The study has been approved by the Ethical Committee of the Medical Faculty of the Martin-Luther University Halle-Wittenberg. The innovative prospective design of this study in this context is also relevant for providing new knowledge in an international research context because, so far, only retrospective studies have been conducted on the given research topic. Colonic ischemia after aortic surgery is a relatively rare condition, with an incidence of approximately 5%. However, it bears severe clinical consequences with an in-hospital mortality of 26.7%-37.8% [9,10,13]. Colonoscopy and sigmoidoscopy have been proven to be sensitive and specific in diagnosing this pathology in the aortic surgery scenario [10-12] and are already a diagnostic standard when there is clinical suspicion [19]. Furthermore, based on the current data, no precise and evidence-based clinical, laboratory, or radiographic instruments that recognize colonic ischemia are available. Sigmoidoscopy has been described as a safe procedure with complication rates of 0.08%, with most complications being of mild severity [20]. However, these complication rates relate to a general population and not to patients after aortic surgery with possible colonic ischemia, in whom the risk for endoscopy-related complications is unclear and might be higher. Nonetheless, the additional risk posed to trial participants by sigmoidoscopy is estimated to be low according to the available cohort studies [20].

We state that according to the currently available evidence, the value of sigmoidoscopy and biopsy after endovascular and open surgery should be investigated to develop prediction scores that could identify patients at risk for colonic ischemia and facilitate their timely treatment. Patients with a delayed diagnosis of the condition have a high mortality. If a patient is diagnosed with subclinical ischemia, follow-up will be offered. All complications, both arising from sigmoidoscopy and the other aspects of the patients' treatment, will be documented and reported to the principal investigator (AR). He can interrupt the trial at any point or, in accordance with the ethical committee, implement changes to the study protocol.

The study is being conducted in accordance with the applicable version of the declaration of Helsinki. Prior to study initiation, approval from the relevant ethical committee has been sought. Before enrolment into the trial, patients will be informed in writing and verbally about the nature and implications of the trial and especially about the possible benefits and risks to their health. Patients will document their consent by signing the informed consent form. Patients can leave the trial at any point without providing a reason for doing so. In such a case, treatment of the patient will continue according to the individual judgment of the treating physicians. Given that open aortic surgery and sigmoidoscopy are considered routine surgical and diagnostic treatments and given that the trial evaluates the value of sigmoidoscopy as a novel diagnostic sequence, there is no requirement for trial-specific patient insurance. Trial participants will be insured by the hospital's insurance covering inpatient treatments. The trial has been registered in a publicly available repository (German Clinical Trials Register; DRKS00025587) for clinical trials prior to initiation. All planned substantial changes will be submitted for approval to the relevant ethical committees in writing as protocol amendments.

Concerning our dissemination plan, we aim to publish results from this trial in the form of one or several manuscripts in international medical journals. The principal investigator (AR) will review all manuscripts to prevent forfeiture of patent rights to data not in the public domain. The authorship list will be agreed on by the principal investigator prior to publication. Investigators from the participating departments will be offered authorship on manuscripts. Publication of the first manuscript reporting study results is planned to take place as soon as possible after analysis of the primary end point. Efforts will be made to ensure that the pertinent manuscript will not be submitted later than 6 months after the results are available.

Data Availability

The data sets generated during this study will be available from the corresponding author (AR) on reasonable request.

Authors' Contributions

Conflicts of Interest

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Abbreviations

ASA: American Society of Anesthesiologists
CT: computed tomography
DGG: Deutsche Gesellschaft für Gefäßchirurgie
ECOG: Eastern Cooperative Oncology Group
ESVS: European Society of Vascular Surgery
EVAR: endovascular aortic repair
OR: open repair
SVS: Society of Vascular Surgery

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Protocol

Clinical Utility of the OmniGraf Biomarker Panel in the Care of Kidney Transplant Recipients (CLARITY): Protocol for a Prospective, Multisite Observational Study

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Abstract

Background: Death with a functioning allograft has become the leading category of graft loss in kidney transplant recipients at all time points. Previous analyses have demonstrated that causes of death in kidney transplant recipients are predominated by comorbidities strongly associated with immunosuppressant medications. Adverse drug events (ADEs) have been strongly associated with nonadherence, health care utilization, and graft loss; clinicians face a difficult decision on whether making immunosuppressant adjustments in the face of ADEs will improve symptomology or simply increase the risk of acute rejection. Clinicians also face a treatment quandary in 50% of kidney transplant recipients with stage 3 or worse chronic kidney disease at 1 year post transplantation, as progressive decline in renal function has been strongly associated with inferior allograft survival.

Objective: The primary objective of the CLinical Utility of the omnigrAf biomarkeR Panel In The Care of kidneY Transplant Recipients (CLARITY) trial is to evaluate change in renal function over time in kidney transplant recipients who are undergoing OmniGraf monitoring in conjunction with monitoring of their medication-related symptom burden (MRSB). A secondary objective of this study is to identify the impact of OmniGraf use in conjunction with patient-reported MRSB as part of clinical care on patients' self-efficacy and quality of life.

Methods: CLARITY is a 3-year prospective, multisite, observational study of 2000 participants with a matched control, measuring the impact of real-time patients' MRSB and the OmniGraf biomarker panel on change in renal function over time. Secondary outcome measures include the Patient-Reported Outcomes Measurement Information System (PROMIS) Self-Efficacy for Managing Chronic Conditions–Managing Medications and Treatment–Short Form 4a; the PROMIS-29 Profile (version 2.1); the PROMIS Depression Scale, hospitalizations—subcategorized for hospitalizations owing to infections; treated rejections, MRSB, and proportion of participants with overall graft survival at year 3 post transplantation; graft loss or death during the 3-year study follow-up period; and change in provider satisfaction.

Results: The primary outcome measure of the study will be a comparison of the slope change in estimated glomerular filtration rate from baseline to the end of follow-up between study participants and a matched control group. Secondary outcome measures include changes over time in PROMIS Self-Efficacy for Managing Chronic Conditions–Managing Medications and Treatment–Short Form 4a, the PROMIS-29 Profile (version 2.1), and PROMIS Depression Scale in the study group, as well as a comparison of hospitalizations and causes, rejections, and graft and patient survival compared between participants and a matched cohort. The anticipated first enrollment in the study is October 2022 with data analysis and publication expected in October 2027.

Conclusions: Through this report, we describe the study design, methods, and outcome measures that will be utilized in the ongoing CLARITY trial.

Trial Registration: ClinicalTrials.gov NCT05482100; https://clinicaltrials.gov/ct2/show/NCT05482100

International Registered Report Identifier (IRRID):   PRR1-10.2196/41020

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Introduction

The survival benefits of kidney transplantation in the United States are well documented [1,2]. Improvements in immunosuppression, better antimicrobial agents, and other aspects of ancillary care have resulted in significant improvements in short-term outcomes; however, there has been little improvement in long-term graft loss [3,4]. While the most recent Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients Annual Data Review [5] shows that death-censored allograft failure has been improving at all time points, death with a functioning allograft has remained stable and is now responsible for more than half of graft losses at each time point. A multicenter analysis of specific causes of kidney allograft loss demonstrated that causes of death were predominated by comorbidities with strong associations with immunosuppressive medications, including cardiovascular and infectious diseases and cancers [6]. Further, a more recent analysis [7] found that 65% of kidney transplant recipients seeking hospital readmission had adverse drug events (ADEs) that were considered contributory, and ADE-associated readmissions had a significantly higher hazard of graft loss and death than readmissions without an ADE. ADEs have also been identified as a predictive factor for medication adherence in a large multicenter study. Couzi et al [8] also found that physicians significantly underestimated the prevalence of adverse events when compared to patient self-reporting. While assessments of the impact of real-time knowledge of adverse events on mutability of readmissions and outcomes are lacking, a randomized controlled trial [9] of a mobile health intervention that included real-time ADE tracking demonstrated significant reductions in hospitalizations and grade 3 or higher ADEs. Even with knowledge of ADEs, clinicians may be reluctant to adjust immunosuppressive medications owing to concerns of rejection risk during the period of medication adjustment.

Clinicians also find themselves in a clinical quandary when faced with patients with poor graft function. According to the most recent Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients Annual Data Review [5], 50% of kidney transplant recipients have stage 3 chronic kidney disease (CKD) or worse at 1 year post transplantation. A large international analysis by the Patient Outcomes in Renal Transplantation investigators demonstrated that patients with stage 3b CKD or lower at 1 year post transplantation were at a significantly higher risk of graft failure by 10 years post transplantation—a risk that increased with a decrease in the estimated glomerular filtration rate (eGFR) [10]. Clinicians are aware of this, but they must also consider the risk of acute rejection that increases whenever immunosuppression is altered.

The OmniGraf biomarker panel (Transplant Genomics, Inc) includes the TruGraf peripheral blood expression profile and the Viracor TRAC donor-derived cell-free DNA test, which have demonstrated a strong ability to identify immune quiescence in stable patients post kidney transplantation, with a negative predictive value of 94% when both tests are negative and a positive predictive value of 89% for subclinical rejection when both tests are positive [11,12].

Because of the strong "rule out" capabilities of OmniGraf, it would be an ideal complement to real-time ADE knowledge and eGFR awareness to help guide clinicians' decisions to adjust (or not) the immunosuppressive regimen and help provide a dialogue between patients and clinicians on the risk-benefit of medication adjustments. With its ability to both "rule out" and "rule in" subclinical rejection, it would also be an ideal tool to help monitor patients during and after medication adjustments. Allowing patients to express their ADEs and the impact they have on their lives, along with frank discussions with clinicians and risk-benefit of medication adjustments, may help increase patient engagement and activation. This is a key goal to help minimize the burden of symptoms and increase life participation [13].

Therefore, the aim of this study is to evaluate change in renal function over time in kidney transplant recipients who are undergoing OmniGraf monitoring in conjunction with patients' medication-related symptom burden (MRSB) monitoring.

Methods

Study Design

CLARITY is a 3-year prospective, multisite, observational study of 2000 participants with a matched control, measuring the impact of real-time patients' MRSB and the OmniGraf biomarker panel on change in renal function over time. Approximately 50 sites will be targeted to enroll participants. The targeted sites will include transplant centers and large community nephrology practices with large populations of kidney transplant recipients who fall within the time line of 3 months to 2 years post transplantation. Sites will be limited to 200 participants to limit center effects in our outcomes.

Ethical Considerations

The study is under review by the Central Institutional Review Board (Pro00067364) as well as local institutional review boards (IRBs) at some sites (depending on local IRB requirements) and conforms to the ClinicalTrials.gov guidelines.

Aims

The primary objective is to evaluate change in renal function over time in kidney transplant recipients who are undergoing OmniGraf monitoring in conjunction with MRSB monitoring.

A secondary objective of this study is to identify the impact of OmniGraf use, in conjunction with patient-reported MRSB, as part of clinical care on patient quality of life and patient and graft survival.

Recruitment, Screening, and Enrollment Procedures

Adult (≥18 years old) kidney transplant recipients between 3 months and 2 years post transplantation, who meet the study eligibility criteria will be identified in accordance with local site IRB-approved practices and approached by research personnel for consideration for participation. Potential participants will be required to go through an informed consent process and complete an informed consent document to ensure they understand the goals, risks, and potential benefits of the study before any research-related activities are carried out.

Eligibility

Inclusion Criteria

Participants must be adult (≥18 years of age) recipients of a primary or subsequent kidney transplant, between 3 months and 2 years post transplantation, selected by their provider to undergo OmniGraf testing as part of posttransplantation care, and provide written informed consent and Health Insurance Portability and Accountability Act authorization.

Exclusion Criteria

Patients who are recipients of a combined organ transplant with an extrarenal or islet cell transplant, previous recipients of a nonrenal solid organ or islet cell transplant, those known to be pregnant, those infected with HIV, those who have active BK nephropathy, those who have nephrotic range proteinuria, or those who are participating in other biomarker clinical trials at the time of assessment will be excluded from participation.

Statistical Analysis

Sample Size Requirements

Sample size was determined using an SAS macro program, %GFR_Slope_Power, developed by Vonesh et al [14] specifically for the purpose of determining sample size or power estimates for comparing slopes between 2 treatment groups based on the linear spline mixed-effects model. An Assumption of eGFR slope change over 3 years in standard care was adopted in accordance with Vincenti et al [15]. Collectively, it is estimated that a sample of 450 patients per protocol would be required to detect a minimum total slope difference at 1.08 mL/minute/1.73 m^2/year with 84% power, assuring that the study will be powered for a clinically meaningful difference of 5 mL/minute/1.73 m^2/year. Conservatively assuming a 50% dropout rate and 50% loss to follow-up or missing data for end of follow-up, for this analysis, a sample size of 2000 participants should be sufficient to demonstrate a clinically significant difference in the primary outcome. Annual and as-needed review by an advisory board will halt enrollment when it is predicted that the sample size will be met.

Primary Analysis

The primary outcome variable defined is a change in the slope of eGFR in participants enrolled in the study compared to that of a matched cohort. Matching variables will include sex, race, time from transplant, living or deceased donor, and baseline eGFR.

eGFR will be summarized using descriptive statistics by study visit. Plots will be used as a general guideline to assess the functional relationship of eGFR over time for modeling purposes. Change in eGFR across time will be modeled using a linear mixed-effects (random intercept random slope) model.

Secondary Analysis

Secondary outcomes include continuous outcomes, categorical outcomes, and time-to-event outcomes. Categorical outcomes will be evaluated using a chi-square test or the Fisher exact test, when appropriate. Death-censored graft loss will be evaluated using a Cox cause-specific hazards model. A cumulative incidence curve will be used as with 95% CIs using the cumulative incidence function. Graft and patient survival will be estimated using the Kaplan-Meier method. Factors associated with the risk of graft loss and patient death will be evaluated using a Cox extended hazards model. The effect of TruGraf test results and TRAC test results on the risk of graft loss and patient death will be incorporated in the model as time-varying covariates. Patient-reported outcome measures will be assessed using scoring tools from the Patient-Reported Outcomes Measurement Information System (PROMIS) group. Cut point methods will be used descriptively for each time point based on thresholds known by the PROMIS group at that time or linkages to legacy measures, when appropriate. Comparison across time points will be carried out using Meaningful Change Methods for each PROMIS measure based on information and guidance from the PROMIS group.

Resources and Biomarker Testing

Participants will be provided with access to a method of reporting real-time MRSB via smartphone app or the internet and instructed to answer the MRSB questionnaire whenever they are experiencing ADE or prior to clinic visits (Textbox 1). The MRSB questionnaire is based on side effects that have been considered in previously validated side effect measures and is based on a questionnaire used in a mobile health analysis that was found to reduce hospitalizations and grade 3 or higher ADEs [9].

Physicians will have access to a portal that will include an easy-to-read report of responses, simultaneously prioritizing frequent MRSB that the participant considers at least moderately troubling. Participants will also undergo OmniGraf biomarker testing based on the frequency of their standard of care laboratory testing (Table 1). Laboratory testing data are not mandated and will be collected and entered into the electronic case report forms if available in the patient record.

Textbox 1. Medication-related symptom burden questionnaire.

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1. Do you have trembling hands?

- Not at all
- Very little
- Sometimes
- Often
- All the time

1A. How troublesome is it?

- Not at all
- Very little
- Moderately troubling
- Very troubling
- Extremely troubling

2. Do you have trouble falling or staying asleep?

- Not at all
- Very little
- Sometimes
- Often
- All the time

2A. How troublesome is it?

- Not at all
- Very little
- Moderately troubling
- Very troubling
- Extremely troubling

3. Are you having trouble with unplanned changes in weight?

- Not at all
- Very little
- Sometimes
- Often
- All the time

3A. How troublesome is it?

- Not at all
- Very little
- Moderately troubling
- Very troubling
- Extremely troubling

4. Do you have loss of interest in or the ability to perform sex?

- Not at all
- Very little
- Sometimes

- Often
- All the time

4A. How troublesome is it?

- Not at all
- Very little
- Moderately troubling
- Very troubling
- Extremely troubling

5. Do you have nausea?

- Not at all
- Very little
- Sometimes
- Often
- All the time

5A. How troublesome is it?

- Not at all
- Very little
- Moderately troubling
- Very troubling
- Extremely troubling

6. Do you have diarrhea?

- Not at all
- Very little
- Sometimes
- Often
- All the time

6A. How troublesome is it?

- Not at all
- Very little
- Moderately troubling
- Very troubling
- Extremely troubling

7. Do you have mood changes or feelings of depression?

- Not at all
- Very little
- Sometimes
- Often
- All the time

7A. How troublesome is it?

- Not at all
- Very little

- Moderately troubling

- Very troubling

- Extremely troubling

8. Do you have nervousness or anxiety?

- Not at all

- Very little

- Sometimes

- Often

- All the time

8A. How troublesome is it?

- Not at all

- Very little

- Moderately troubling

- Very troubling

- Extremely troubling

9. Do you have difficulty concentrating or remembering to do things?

- Not at all

- Very little

- Sometimes

- Often

- All the time

9A. How troublesome is it?

- Not at all

- Very little

- Moderately troubling

- Very troubling

- Extremely troubling

10. Do you have feelings of anger or irritability?

- Not at all

- Very little

- Sometimes

- Often

- All the time

10A. How troublesome is it?

- Not at all

- Very little

- Moderately troubling

- Very troubling

- Extremely troubling

11. Do you have headaches?

- Not at all

- Very little

- Sometimes

- Often

- All the time

11A. How troublesome is it?

- Not at all

- Very little

- Moderately troubling

- Very troubling

- Extremely troubling

Table 1. Schedule of assessments.

Enrollment or months post enrollment		Baseline visit (days –90 to 0)	3	6	9	12	15	18	21	24	27	30	33	36	Unscheduled visit	At workup for referral to transplant center
Visits	Details															
Informed consent	Prior to any study-related procedures	✓														
Assessment inclusion or exclusion criteria		✓														
Participant's demographics	Date of birth, sex, race, height, weight, and date of transplant	✓														
Transplant information	Donor type and cause for renal failure	✓														
Chemistry panel	Serum creatinine	✓	SOC[a]	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC
Immunosuppression medications	Name and changes in dose or medication		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Assessment of clinical events	Rejections, infections, graft Loss, and death	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
OmniGraf results	TruGraf and TRAC test results (if SOC laboratory tests are performed)	✓ (day 0)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Patient's medication-related symptom burden		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Biopsy information	Surveillance and for-cause: in case of rejection, type and grade		SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC
Patient-reported outcomes	PROMIS[b]-29, PROMIS Self-Efficacy, and PROMIS Depression Scale	✓				✓				✓				✓		
Provider satisfaction		✓				✓				✓				✓		

[a]SOC: standard of care.

[b]PROMIS: Patient-Reported Outcomes Measurement Information System.

Physicians can use the MRSB and OmniGraf results as they see fit, along with other clinical laboratory tests and information; however, they will be provided with a potential framework for integrating the information into their practice (Figure 1). In short, clinicians will see participants and review the MRSB portal and clinical laboratory tests, including OmniGraf. If the clinician notes that the participant has less than ideal renal function or has an MRSB that is troubling him/her, a discussion can be had between the clinician and participant. A clinical workup for the renal function or ADE can be performed to identify other treatable causes. If it is determined that the ADE (including renal function) is caused by or exacerbated by medications that the participant is taking, the laboratory findings and OmniGraf biomarker results can be used within the clinician-participant discussion to help determine the risks and benefits of adjusting medications to mitigate the ADE. OmniGraf results can also provide additional information to clinicians regarding participants who do not have a low eGFR or ADE, assisting in their clinical decision-making or identifying participants who may be at risk of subclinical inflammation.

Figure 1. Suggested framework for integrating OmniGraf and patients' medication-related symptom burden monitoring into clinical care. AMR: antibody mediated rejection; CKD: chronic kidney disease; TCMR: t-cell mediated rejection; Txp: transplant.
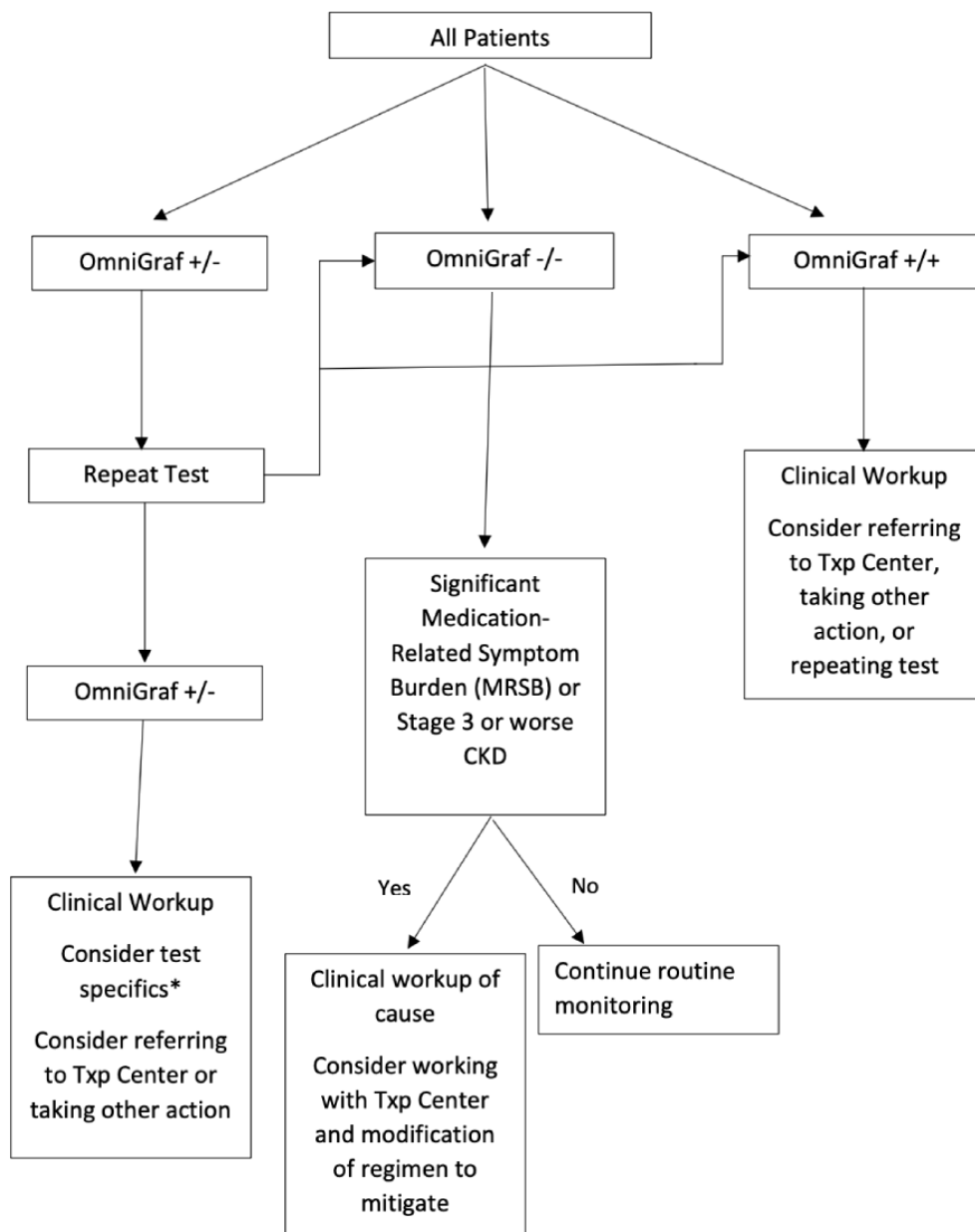
*TruGraf was developed against subclinical rejection biopsies and has shown better specificity for TCMR

TRAC is a marker of any injury specific to the allograft, immunologic or non, and has shown better specificity for AMR

Results

Results Overview

The primary outcome measure of this study will be the slope change in renal function over time in kidney transplant recipients who are undergoing OmniGraf monitoring in conjunction with MRSB monitoring. Secondary outcome measures include the PROMIS Self-Efficacy for Managing Chronic Conditions–Managing Medications and Treatment–Short Form 4a; the PROMIS-29 Profile (version 2.1); the PROMIS Depression Scale, hospitalizations—subcategorized for hospitalizations owing to infections; treated rejections, MRSB, and the proportion of participants with overall graft survival at year 3 post transplantation; graft loss or death during the 3-year study follow-up period; and change in provider satisfaction.

Study Endpoint Definitions and Assessment Plan

The following will be used to define and assess events within this study.

The primary endpoint is a comparison of the slope change in eGFR from baseline to the end of follow-up between the study participants and a matched control group. eGFR will be calculated using the 4-variable Modification of Diet in Renal Disease equation [16], with a sensitivity analysis performed using the Chronic Kidney Disease Epidemiology Collaboration equation [17]. Routine serum creatinine concentrations, which are measured as a part of usual care, will be utilized to estimate the GFR at baseline and at months 12, 24, and 36 post enrollment for assessments. The slope in eGFR change will be calculated for the entire follow-up for the primary outcome, with subanalyses performed between the other described time points. The matched control group will be a propensity-matched cohort from the US Medicare database.

Furthermore, we will compare the PROMIS Self-Efficacy for Managing Chronic Conditions–Managing Medications and Treatment–Short Form 4a scores at the end of follow-up relative to baseline [18]. This will measure changes in self-efficacy within the participant population—the belief that one can carry out a behavior necessary to reach a desired goal, even when a situation contained unpredictable and stressful elements. The study coordinator will provide access to the survey at baseline and at months 12, 24, and 36 post enrollment. Subanalyses will be performed among all time points.

We will then compare the PROMIS-29 Profile (version 2.1) scores at the end of follow-up relative to baseline [19]. This will measure changes in overall quality of life and satisfaction. The study coordinator will provide access to the survey at

baseline and at months 12, 24, and 36 post enrollment. Subanalyses will be performed among all time points.

This will be followed by a comparison of the PROMIS Depression Scale scores at the end of follow-up relative to baseline [20]. This will measure changes in symptoms of depression. The study coordinator will provide access to the survey at baseline and at months 12, 24, and 36 post enrollment. Subanalyses will be performed among all time points.

Hospitalizations, subcategorized for hospitalizations resulting from infections, will be compared between study participants and a matched control group. Study coordinators will obtain information on hospitalizations and causes at all follow-up events. This will be compared to hospitalizations and causes documented within the US Medicare database for a propensity-matched control group. Hospitalizations will be defined as admission to hospital with at least one overnight stay. Length of hospital stay will also be recorded.

MRSB, as defined as the change in the number and severity of ADE self-reported by study participants, will be recorded from the end of follow-up relative to baseline.

Overall graft failure, defined as return to chronic dialysis, transplant nephrectomy, retransplantation, or death, will also be recorded. The study coordinator capturing clinical event data will review the medical record at intervals in accordance with the schedule of evaluations to determine if a study participant has developed graft failure. The timing and cause of each graft loss will be recorded for comparative analysis with the propensity-matched external cohort. Patient death will be captured in a similar manner, with timing and cause recorded as well.

The anticipated first enrollment of participants in the study is October 2022, with data analysis and publication expected in October 2027.

Discussion

Owing to the comorbidities and toxicities associated with posttransplantation care, including immunosuppressive medication regimens, the care of kidney transplant recipients is highly complex and fraught with clinical conundrums. Founded on data demonstrating high rule-out capabilities, we hypothesize that the use of OmniGraf in conjunction with patients' MRSB monitoring will provide a promising and innovative approach to improving posttransplantation renal function. The ultimate goal of the research is to demonstrate how patients, clinicians, and biomarkers can work harmoniously to optimize and personalize posttransplantation care.

Conflicts of Interest

All authors are full-time, paid employees of Transplant Genomics, Inc.

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Abbreviations

ADE: adverse drug event
CKD: chronic kidney disease
CLARITY: CLinical Utility of the omnigrAf biomarkeR Panel In The Care of kidneY Transplant Recipients
eGFR: estimated glomerular filtration rate
IRB: institutional review board
MRSB: medication-related symptom burden
PROMIS: Patient-Reported Outcomes Measurement Information System

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Protocol

The Japan Registry for Adult Subjects of Spinal Muscular Atrophy (jREACT-SMA): Protocol for a Longitudinal Observational Study

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Abstract

Background: Spinal muscular atrophy (SMA) is an autosomal recessive genetic neuromuscular disorder with progressive muscle weakness and atrophy, mainly caused by lower motor neuron degeneration resulting from decreased levels of the survival motor neuron protein. Recently, 3 disease-modifying therapies for SMA (nusinersen, onasemnogene abeparvovec, and risdiplam) were approved in Japan that are expected to improve the prognosis of patients with SMA. Long-term clinical follow-up of adult patients treated with disease-modifying therapies and the natural history of SMA are essential to assess the real-world effectiveness of available treatments. Until recently, nusinersen was the only treatment option for patients with SMA in Japan; however, because Japanese approval of nusinersen was based on global clinical trials in infants and children aged 0-15 years with SMA, the effectiveness of nusinersen in adult patients has not been fully assessed in Japan. In addition, longitudinal clinical data of adult patients have not been systematically collected in Japan.

Objective: This longitudinal observational study of adult patients with SMA who have been diagnosed with 5q-SMA in Japan aims to gain a better understanding of the natural history of SMA, as well as the long-term effectiveness of disease-modifying therapies. Here, we describe the protocol for the study.

Methods: The Japan Registry for Adult Subjects of Spinal Muscular Atrophy (jREACT-SMA) study is a longitudinal (prospective and retrospective) observational study with a 60-month prospective follow-up being conducted at 19 investigational sites using the newly established jREACT-SMA registry. Patients aged ≥18 years with genetically confirmed 5q-SMA were planned to be enrolled in the registry from December 2020 to May 2022. The planned enrollment was 100 patients. The protocol was approved on September 28, 2020 (approval 2020-0289) by the ethical review committee of Nagoya University. Registration, demographics, genetic diagnosis, motor functions, patient-reported outcomes/quality-of-life outcomes, and other clinical data have been or will be collected.

Results: As of May 2022, 113 patients had been enrolled, and the completion of patient registration has been extended from May 2022 to December 2022. Data at registration and during the follow-up period were and will be prospectively collected at least once a year until November 2025 (maximum 60 months). Data analyses will be conducted when all data have been collected. Results are expected to be available in 2026 and the study is expected to be completed by March 2027.

Conclusions: This jREACT-SMA study will provide longitudinal prospective follow-up data in adult patients with SMA in Japan, including data on the natural history of the disease and data on the long-term effectiveness of disease-modifying therapies.

Trial Registration: University Hospital Medical Information Network Center Clinical Trials Registry UMIN000042015; https://rctportal.niph.go.jp/en/detail?trial_id=UMIN000042015

Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive genetic neuromuscular disorder with progressive muscle weakness and atrophy mainly caused by lower motor neuron degeneration resulting from decreased levels of the survival motor neuron (SMN) protein [1,2]. The *SMN* gene is an SMA-determining gene mapped to chromosome 5q13 [3]. Patients with 5q-SMA have the loss of *SMN1* or an *SMN1* point mutation and at least one copy of the highly homologous gene, *SMN2* [3,4]. *SMN2* differs from *SMN1* by only 11 nucleotides (7 in intron 6, 2 in intron 7, 1 in coding exon 7, and 1 in noncoding exon 8) [3,5-7], resulting in the alteration of splicing regulation and exclusion of exon 7 [5]. *SMN2* produces lower levels of the full-length *SMN* transcript [8], whereas *SMN* exon 7–skipped mRNA produces unstable protein, which is rapidly degraded [9].

SMA is one of the rare diseases affecting patients across a broad age range that is designated as an intractable disease [10] and a specific pediatric chronic disease [11]. The incidence of infantile-onset SMA (type I SMA) in Japan is 0.27 per 10,000 live births, and the number of Japanese patients with SMA is assumed to be approximately 1500 [12].

Before 2017, no disease-modifying therapy was available that could influence the clinical course of SMA [13]. Because patients with a higher copy number of *SMN2* tend to develop SMA with later onset and/or show relatively milder symptoms [9,14], increasing the level of full-length functional SMN protein from *SMN2* is expected to alleviate symptoms in patients with SMA [15]. Nusinersen is an antisense oligonucleotide drug that selectively corrects the splicing of *SMN2* pre-mRNA to produce increased amounts of functional SMN protein [15,16]. The efficacy and safety of nusinersen were demonstrated in clinical trials (some including Japanese patients) in infants and children aged 0-15 years with SMA [17-21]. A clinical trial to assess the efficacy of an investigational higher dose of nusinersen in patients with SMA, including patients aged ≥18 years, is also ongoing (ClinicalTrials.gov NCT04089566). In Japan, nusinersen was approved for the treatment of infantile-onset type I SMA in July 2017, and subsequently, its indications were expanded to later-onset types II, III, and IV SMA. In addition, onasemnogene abeparvovec, a gene replacement therapy, was approved in March 2020 for patients with SMA aged under 2 years old, and risdiplam, an oral, once-daily splicing modifier, was approved in June 2021 for patients aged 2 months or older.

The natural history of SMA has changed over the last decade due to improvements in care; in particular, the survival of critically ill infants with type I SMA has increased [22,23]. In addition, these new treatments are expected to improve the prognosis of SMA, suggesting that the number of adult patients with SMA will possibly increase. Neuromuscular symptoms, including muscle weakness, progress more slowly in adult patients with later-onset SMA compared with patients with infantile-onset SMA [24,25]. Therefore, long-term clinical follow-up of treated patients and the natural history of SMA are essential to assess the effectiveness of the treatment, particularly the improvement and/or maintenance of motor functions. Registry and multicenter observational studies of SMA that include adult patients have been reported or are ongoing in several countries [26-30]. At the planning and launch stage of this research, nusinersen was the only treatment option for patients with SMA in Japan. However, the administration regimen of nusinersen for later-onset SMA is different between Japan and other countries. In Japan, the treatment regimens used in the ENDEAR study [18] (4 loading doses and once every 4 months for the maintenance dose with adjustment for age) and in the CHERISH study [19] (3 loading doses and once every 6 months for the maintenance dose) have been approved for infantile-onset SMA and later-onset SMA, respectively. However, in other countries, only the ENDEAR treatment regimen has been approved for all types, including later-onset SMA. As such, the effectiveness of nusinersen in adult patients has not been fully assessed in Japan in both clinical trials and clinical practice. Therefore, it is important to systematically collect longitudinal clinical data, including the natural history of SMA in adult patients. As more treatment options have become available, we expect to gain a better understanding of the pathophysiology of SMA and clinical data to support treatment decisions obtained from long-term clinical follow-up in adult patients with and without treatment.

Here, we describe the protocol for a longitudinal observational study in adult patients with SMA who have been diagnosed with 5q-SMA, which is being conducted with the aim of establishing a new registry (Japan Registry for Adult Subjects of Spinal Muscular Atrophy [jREACT-SMA]). The study will lead to a better understanding of the natural history of SMA, as well as the long-term effectiveness of disease-modifying therapies in Japan.

Methods

Study Design

The jREACT-SMA study is a longitudinal (prospective and retrospective) observational registry study with a 60-month prospective follow-up being conducted at 19 investigational sites in Japan, including university hospitals, specialist centers, and tertiary hospitals (Figure 1). Patient data are collected from multiple centers because treatment for SMA is not centralized in Japan. The planned number of patients was 100, which takes into consideration the feasibility of enrolling patients; however, registration of additional patients is permitted (Textbox 1).

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Figure 1. Collaborative investigational sites of the jREACT-SMA study in Japan. The star indicates the principal investigational site (Nagoya University). The other collaborative investigational sites are indicated by circles. jREACT-SMA: Japan Registry for Adult Subjects of Spinal Muscular Atrophy.

Principal investigational site: Nagoya University

(Investigational sites)

1. National Hospital Organization Hokkaido Medical Center
2. Tohoku University
3. National Hospital Organization Sendai Nishitaga Hospital
4. National Hospital Organization Niigata Hospital
5. University of Tsukuba
6. National Hospital Organization Shimoshizu National Hospital
7. University of Tokyo
8. Tokyo Medical and Dental University
9. National Center of Neurology and Psychiatry
10. Yokohama City University
11. Yokohama City University Medical Center
12. University of Yamanashi
13. Kyoto University
14. National Hospital Organization Osaka Toneyama Medical Center
15. Kobe University
16. Tottori University
17. Kagoshina University
18. National Hospital Organization Okinawa National Hospital
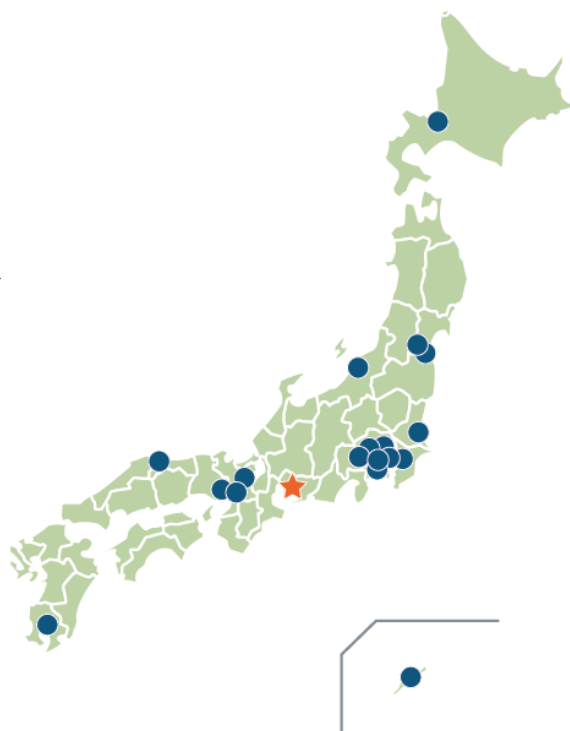
Textbox 1. Study plan.

Study design

- Multicenter, prospective and retrospective, and observational study

Study population

- Patients aged ≥18 years, with diagnosed spinal muscular atrophy (SMA) and genetically confirmed deletion or mutations of the *survival motor neuron* (*SMN1*) gene (5q-SMA) as well as at least 1 copy of the *SMN2* gene

Planned number of patients

- 100

Data to be collected

- Motor functions
- Measurement of motor abilities
- Physiological test (eg, respiratory function test)
- Blood test
- Patient-reported outcome and quality of life

Registration period (patient registration was planned to end in May 2022 and has been extended to December 2022)

- From December 2020 to May 2022 (18 months)

Prospective follow-up period

- From December 2020 to November 2025 (60 months)

Sample Selection

Patients who fulfill the following inclusion criteria are eligible for enrollment (Textbox 1): diagnosed with SMA, as defined by the Diagnostic Criteria of the Research Committee for Spinal Muscular Atrophy from the Ministry of Health, Labour and Welfare of Japan [31]; aged ≥18 years; genetically confirmed deletion or mutations of the *SMN1* gene (5q-SMA), as well as at least 1 copy of the *SMN2* gene; able to attend the investigational sites at least once a year during the follow-up

period; and able to understand the purpose of the study and provide written informed consent. Patients who had any condition (such as psychiatric disorders) that would make it difficult to comply with study requirements and patients who were deemed by the investigators to be unsuitable for study enrollment are excluded.

Patients will be enrolled regardless of treatment status. The requirement for treatment is decided by the investigators independently from the study, taking into account each patient's preference and medical condition. Disease-modifying therapies are administered according to the approved administration regimen.

Measurements and Planned Outcomes

Motor function scales and patient-reported outcomes (PRO)/quality-of-life (QOL) outcomes are the primary end points of the study. By partly referring to the TREAT-NMD SMA Registries Core Dataset [32], registration, demographics, genetic diagnosis, motor functions, PRO/QOL data, and other clinical data have been or will be collected (Table 1, data that are highly encouraged to be collected are shown in italics). All data have been or will be obtained from medical records or at regular visits. Further details and the schedule of data collection are shown in Table 1, and free-text columns are available for investigators to collect data other than those listed. Any adverse events for patients treated with each of the disease-modifying therapies are to be reported according to the standard safety report procedures in the respective all-case surveillance studies.

Table 1. Schedule of data collection. Highly encouraged data to be collected are expressed in italics.

Data to be collected (categories)	Variables	Retrospective observation period (from first visit)	Baseline (at registration; day −30 to registration)	Follow-up period (prospective observation period; registration to 60 months)
Informed consent	• *Date of registration* • *Date of informed consent* • *Registration number*		✓	
Inclusion/exclusion criteria	• N/A[a]		✓	
Demographics	• *Age at registration* or date of birth • *Sex*		✓	
Survival status	• *Survival status (age at death and causes of death if applicable)*			✓
Genetic diagnosis[b]	• *Name of genetic testing center* • *Genetic test results* (SMN1[c]*exon 7/exon 8 copy number*, SMN1 *deletion/mutation, and* SMN2 *exon 7/exon 8 copy number*)	✓	✓	
Clinical findings	• *Age at symptom onset* • *SMA[d] type (I, II, III, or IV)* • *Body weight* • Height	✓[e]	✓	✓[e]
Scoliosis	• *Presence or absence (surgical history, age, and surgical procedure at the first surgery if applicable)*		✓	
Motor functions ("able to do" or "unable to do" for each function)	• *Maintaining head upright without support* • *Rolling to side* • *Sitting without support* • *Crawling on hands and knees* • *Standing with support* • *Standing without support* • *Walking independently* • *Walking 10 m independently* • *Going up the stairs* • *Using whole hands* • *Raising hands overhead in a sitting position* • *Raising hands to mouth in a sitting position*	✓	✓	✓
Wheelchair use	• *Wheelchair use (age started if applicable)*	✓	✓	✓
Nutrition	• *Tube feeding (age started if current; age ended if previous)*	✓	✓	✓
Artificial ventilation[f]	• *Invasive/noninvasive ventilation (age started, hours/day if applicable)*	✓	✓	✓

Medications	• *Medications for SMA* (if applicable, collect the information below)
	  • Name of drugs (nusinersen sodium, onasemnogene abeparvovec, risdiplam, sodium valproate, or others)
	  • Age started medication
	  • Date started medication
	  • Dosage per administration and administration date if nusinersen
	  • Age at discontinuation and reasons for discontinuation
		✓	✓	✓

Data to be collected (categories)	Variables	Retrospective observation period (from first visit)	Baseline (at registration; day −30 to registration)	Follow-up period (prospective observation period; registration to 60 months)
Hospitalizations (except medication purpose) and comorbidities	• *Hospitalization in last 12 months from registration and between the previous visit and the latest visit during follow-up period (date of hospitalizations and name of disease if applicable)* • *Comorbidities diagnosed in last 12 months from registration and between the previous visit and the latest visit during follow-up period, other than diseases that are reasons for hospitalization (age at onset of comorbidities or age fully recovered if applicable)*	✓[g]	✓	✓
Clinical trials	• *Clinical trials for SMA (name of investigational drugs and age participated if applicable)*	✓	✓	✓

Measurement of motor abilities	• *2MWT[h] (m)[i]*
	• *6MWT[j] (m)[i]*
	• *HFMSE[k] (total score)*
	• *RULM[l] (higher score of left/right)*
	• Pinch strength (kg)
	• Grip strength (kg)
	• Tongue pressure (kPa)
	• MRC[m] score (higher score of left/right, grade 0, 1, 2, 3, 4, 5)
	  • Iliopsoas muscle
	  • Deltoid muscle
	  • Biceps brachii muscle
	  • Triceps brachii muscle
	  • Quadriceps femoris muscle
	  • Cervical flexor muscle
	  • Hamstring muscle
	  • Tibialis anterior muscle
	  • Gastrocnemius muscle
		✓	✓	✓

X-ray examination	• Quantitative bone mineral test • Skeletal muscle mass by DXA[n] (kg)	✓	✓	✓

Physiological test	• Nerve conduction test
	  • Ulnar nerve CMAP[o] (mV or uV)
	• Respiratory function test
	  • *FVC[p]*
	  • *VC[q]*
	  • *% VC*
	  • *FEV1.0[r]*
	  • *FEV1.0%[s]*
	  • Peak cough flow
		✓	✓	✓

Blood test	• *Creatine kinase* • *Creatinine* • *Creatine* • *Cystatin C*	✓	✓	✓

Data to be collected (categories)	Variables	Retrospective observation period (from first visit)	Baseline (at registration; day −30 to registration)	Follow-up period (prospective observation period; registration to 60 months)
PRO[t]/QOL[u]	• *mSMAFRS[y] (total score)* • ALSFRS-R[w] (total score) • MFI-20[x] (total score) • SDQ[y] (total score) • *CGI-S[z]* • *CGI-I[aa]* • *TGI[ab]* • *mRS[ac]* • Other validated PROs	✓	✓	✓
Rehabilitation	• *Rehabilitation (age started if current or age ended if previous)*	✓	✓	✓

[a]N/A: not applicable.

[b]Confirmed at registration.

[c]SMN: survival motor neuron.

[d]SMA: spinal muscular atrophy.

[e]Weight only.

[f]Collected data over time.

[g]Collected data for the last 12 months from registration.

[h]2MWT: 2-minute walk test.

[i]Highly encouraged to assess either one for ambulant patients.

[j]6MWT: 6-minute walk test.

[k]HFMSE: Hammersmith Functional Motor Scale–Expanded.

[l]RULM: Revised Upper Limb Module.

[m]MRC: Medical Research Council.

[n]DXA: dual-energy X-ray absorptiometry.

[o]CMAP: compound muscle action potential.

[p]FVC: forced vital capacity.

[q]VC: vital capacity.

[r]FEV1.0: forced expiratory volume in 1 second.

[s]FEV1.0%: forced expiratory volume % in 1 second.

[t]PRO: patient-reported outcome.

[u]QOL: quality of life.

[v]mSMAFRS: Modified SMA Functional Rating Scale.

[w]ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised.

[x]MFI-20: Multidimensional Fatigue Inventory-20.

[y]SDQ: Swallowing Disturbance Questionnaire.

[z]CGI-S: Clinical Global Impressions–Severity scale.

[aa]CGI-I: Clinical Global Impressions–Improvement scale.

[ab]TGI: Total Global Impression.

[ac]mRS: modified Rankin Scale.

Data Collection

The jREACT-SMA study uses the Research Electronic Data Capture system, operated by the ARO Data Coordinating Center, Department of Advanced Medicine, Nagoya University Hospital (Nagoya, Japan) and the Department of Neurology, Nagoya University Graduate School of Medicine (Nagoya, Japan), to register patients and collect/centralize data. The Research Electronic Data Capture system can be accessed securely by the investigators and study-related personnel only.

Information that can identify patients is anonymized at data entry. Anonymized data are labeled with an identifying code to reidentify patients. The identifying codes linking patients with their anonymized data are securely stored at each investigational site. The investigators are responsible for saving source data and ensuring the quality of data at each investigational site.

Data Analysis

Demographics at baseline and clinical characteristics at first visit will be summarized. Time-to-event outcomes (survival status and time to tracheostomy) will be analyzed using the Kaplan-Meier method. Continuous variables will be summarized by descriptive statistics, including arithmetic mean, standard deviation, minimum, 25% quartile, median, 75% quartile, maximum, and proportion of missing values. Categorical variables will be analyzed using Wilcoxon signed-rank test with the number and percentage in each category. Additional analyses referring to specific research questions may be conducted and will be described in a statistical analysis plan. The statistical analysis plan will be completed by database lock. Interim and final analyses are planned.

Ethics and Dissemination

The study is being conducted in compliance with the Declaration of Helsinki, Ethical Guidelines for Medical and Health Research Involving Human Subjects, and the Act on the Protection of Personal Information. Written informed consent has been or will be obtained from all patients, including agreement for publication. If patients withdraw informed consent, the patients' data will be excluded from the data set as much as possible. The study is registered at the University Hospital Medical Information Network Center Clinical Trials Registry (UMIN000042015). Collaborative investigational sites must obtain approval from their own relevant ethics committees before starting the study. Prior to patient screening, a contract research organization (Mebix, Inc.), funded by Biogen Japan Ltd, reviewed study responsibilities with the investigators and study-related personnel.

Ethics Approval

The study is led by Nagoya University, and the protocol was approved on September 28, 2020 (approval 2020-0289) by the ethical review committee of Nagoya University.

Results

Patient registration started in December 2020 and was planned to end in May 2022 (Textbox 1 and Figure 2). As of May 2022, 113 patients had been enrolled, and patient registration has been extended to December 2022. Data from the first visit (first visit at the investigational site regardless of diagnosis, with or without treatment; data before diagnosis could be inputted) to registration were and will be retrospectively collected. Data at registration and during the follow-up period were and will be prospectively collected at least once a year until November 2025 (maximum 60 months). Data analyses will be conducted when all data have been collected. Results are expected to be available in 2026 and the study is expected to be completed by March 2027 (Figure 2).

Figure 2. Study design. The study started and the first patient was registered in December 2020. Patient registration was planned to end in May 2022 and has been extended to December 2022. Retrospective data from their first visit to registration will be collected from medical records, and prospective data will be collected at regular visits until November 2025. Data analyses are planned after data collection is complete, and the study is expected to end in March 2027. FPI: first patient in (date of the first patient registration).
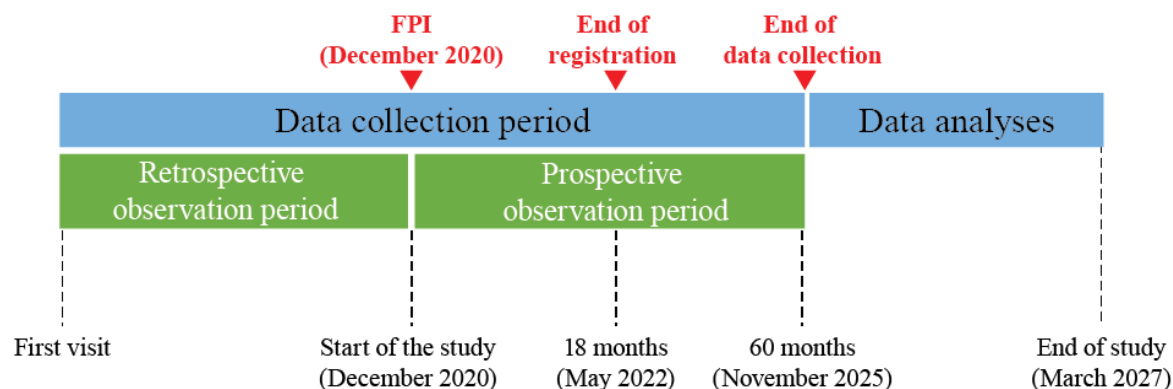
Discussion

Expected Findings

This protocol is for the first longitudinal (prospective and retrospective) observational study in Japanese adult patients with SMA, regardless of treatment status, with the aim of establishing a new registry named jREACT-SMA. Using the results from the jREACT-SMA study, we expect to gain a better understanding of the pathophysiology of SMA and clinical data to support treatment decisions for overcoming potential therapeutic limitations in adult patients with SMA.

Outside of Japan, other registry or observational studies have been or will be reporting real-world clinical data—including motor function scales such as the 6-minute walk test, the Hammersmith Functional Motor Scale–Expanded, and the Revised Upper Limb Module—in adult patients with SMA [26-30]. In addition, some of these studies will provide PRO and sociodemographic data [28]. However, data in Japanese patients with SMA are still required because the administration regimen of nusinersen for later-onset SMA is different between Japan and other countries. Several registries of patients with SMA are currently in operation in Japan, but no data have been reported yet. The Spinal Muscular Atrophy Research & Treatment Consortium [33] has been established for patients with SMA and health care professionals to share information regarding new clinical trials and investigator-initiated trials promptly and to help conduct the trials efficiently. The Rare Disease Data Registry of Japan [34] has been established to centralize clinical information and biological samples from the

Japan Agency for Medical Research and Development [35] and the intractable disease research groups of the Ministry of Health, Labour and Welfare. Distinct from these registries in Japan, the jREACT-SMA study will provide longitudinal prospective and retrospective follow-up data in adult patients with SMA, including both adult patients who transitioned from pediatric SMA and patients with adult-onset SMA.

In this jREACT-SMA study, patients who do not wish to receive active treatments are registered, as well as patients who have been or are being treated with disease-modifying therapies. Longitudinal observation of SMA in Japanese adult patients is limited [36], and the inclusion of untreated patients in jREACT-SMA will provide valuable information about the natural history of adults with SMA. In addition, because nusinersen was approved in Japan based on the results of clinical trials in infants and children with SMA who were aged ≤9 years at screening [17-19], the effectiveness of nusinersen in adult patients has not been fully assessed in Japan. As mentioned above, the administration regimen of nusinersen in Japan differs from other countries. The number of loading doses and the administration interval were defined by a pharmacokinetics simulation using data from patients with types II and III SMA. Therefore, information on patients treated with the Japan-approved administration regimen may provide further important insights into the optimization and validation of therapeutic protocols for Japanese adult patients with SMA. The comprehensive analyses from the jREACT-SMA study will allow us to address current gaps in our knowledge of the natural history of SMA, as well as the long-term effectiveness of disease-modifying therapies in adult patients.

Strengths and Limitations

The jREACT-SMA study is the first multicenter, long-term, longitudinal observational study to establish a registry for Japanese adult patients, which will better reflect real-world clinical settings. Most core hospitals that provide specialized treatment for SMA in Japan were included in the study. The only patients who will be excluded are those who have any condition that would make it difficult to comply with the study requirements and those who are deemed by the investigators to be unsuitable for study enrollment. A broad range of data will be collected, including patient background, clinical characteristics, and clinical measures such as motor functions and PRO/QOL, as well as physiological and blood tests. Only adult patients are eligible for the study; this allows examination of the clinical course of the disease in this population of patients with SMA, whose numbers are expected to increase as pediatric

patients survive longer. In addition, both patients treated with disease-modifying therapies and untreated patients have been enrolled, which will enable a better understanding of the natural history of SMA and the long-term effectiveness of the therapies during adulthood.

However, several limitations of the study need to be considered. First, we are not able to include all Japanese patients with SMA. Of note, the number of untreated patients to be registered may not be proportionate to their population in Japan because they make fewer hospital visits and are therefore less likely to be enrolled. Second, we cannot identify patients who have not yet been diagnosed with SMA, which makes it difficult to understand the full context of SMA in Japan from the jREACT-SMA study. Third, we may not be able to obtain information longitudinally if patients change hospitals during the data collection period (eg, if a patient moves from a participating hospital to a nonparticipating hospital, we are not able to obtain complete prospective data). Fourth, the baseline of the outcome measures may not be assessed appropriately or could be partly missing in the case of participants who started disease-modifying therapies before enrollment, meaning that data were collected retrospectively. Additionally, follow-up data could be partly missing in the case of participants who stopped regular visits. Fifth, the planned number of patients, especially untreated patients, is small; therefore, it may be difficult to analyze the effectiveness of disease-modifying therapies compared with the natural history of SMA. Sixth, although PRO/QOL are some of the primary end points, it is difficult to demonstrate that benefits in PRO/QOL result from intervention because of the absence of an age- and SMA type–matched control group in the study and the potential for response bias. Seventh, respiratory management (requirement for invasive/noninvasive ventilatory support) is proposed by physicians based on their treatment policy, knowledge, and experience, and the final decision is made by patients/caregivers. Therefore, outcomes relating to artificial ventilation should be carefully interpreted. Finally, the quantity of data (ie, number of patients with data in each category) may vary for different variables because although data collection is highly encouraged or optional, it is not mandatory.

Conclusions

The jREACT-SMA study will contribute to a better understanding of the natural history of the disease and the long-term effectiveness of disease-modifying therapies with the aim of establishing a database of Japanese adult patients with SMA.

The contents were presented at the 62nd Annual Meeting of the Japanese Society of Neurology, May 19-22, 2021, Kyoto, Japan and the 39th Annual Meeting of the Japanese Society of Neurological Therapeutics, October 28-30, 2021, Mie, Japan.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

All authors participated in the interpretation of study results and in the drafting, critical revision, and approval of the final version of the manuscript. KS, AH, MC, AS-N, and MK were involved in the study design. KS and MK are investigators. KS, YK, and MA collected the data in the study. KS, YK, and MA conducted the statistical analyses.

Conflicts of Interest

KS and MK have received research funding from Biogen Japan Ltd and lecture fees from Biogen Japan Ltd and Chugai Pharmaceutical Co, Ltd. AH has received lecture fees from Takeda Pharmaceutical Company Limited. MC and AS-N are former employees of Biogen Japan Ltd. All other authors declared no other conflicts of interest.

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Abbreviations

jREACT-SMA: Japan Registry for Adult Subjects of Spinal Muscular Atrophy
PRO: patient-reported outcome
QOL: quality of life
SMA: spinal muscular atrophy
SMN: survival motor neuron

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Protocol

Exploring Stakeholder Requirements to Enable the Research and Development of Artificial Intelligence Algorithms in a Hospital-Based Generic Infrastructure: Protocol for a Multistep Mixed Methods Study

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Abstract

Background: In recent years, research and developments in advancing artificial intelligence (AI) in health care and medicine have increased. High expectations surround the use of AI technologies, such as improvements for diagnosis and increases in the quality of care with reductions in health care costs. The successful development and testing of new AI algorithms require large amounts of high-quality data. Academic hospitals could provide the data needed for AI development, but granting legal, controlled, and regulated access to these data for developers and researchers is difficult. Therefore, the German Federal Ministry of Health supports the Protected Artificial Intelligence Innovation Environment for Patient-Oriented Digital Health Solutions for Developing, Testing, and Evidence-Based Evaluation of Clinical Value (pAItient) project, aiming to install the AI Innovation Environment at the Heidelberg University Hospital in Germany. The AI Innovation Environment was designed as a proof-of-concept extension of the already existing Medical Data Integration Center. It will establish a process to support every step of developing and testing AI-based technologies.

Objective: The first part of the pAItient project, as presented in this research protocol, aims to explore stakeholders' requirements for developing AI in partnership with an academic hospital and granting AI experts access to anonymized personal health data.

Methods: We planned a multistep mixed methods approach. In the first step, researchers and employees from stakeholder organizations were invited to participate in semistructured interviews. In the following step, questionnaires were developed based on the participants' answers and distributed among the stakeholders' organizations to quantify qualitative findings and discover important aspects that were not mentioned by the interviewees. The questionnaires will be analyzed descriptively. In addition, patients and physicians were interviewed as well. No survey questionnaires were developed for this second group of participants. The study was approved by the Ethics Committee of the Heidelberg University Hospital (approval number: S-241/2021).

Results: Data collection concluded in summer 2022. Data analysis is planned to start in fall 2022. We plan to publish the results in winter 2022 to 2023.

Conclusions: The results of our study will help in shaping the AI Innovation Environment at our academic hospital according to stakeholder requirements. With this approach, in turn, we aim to shape an AI environment that is effective and is deemed acceptable by all parties.

International Registered Report Identifier (IRRID): DERR1-10.2196/42208

KEYWORDS

Introduction

Background

The advancement and development of artificial intelligence (AI) in health care hold several promises, such as the heightened quality of diagnosis and treatment [1-4], improvements for clinical workflow processes [5], and a reduction of costs [3,6]. These hopes also apply to health systems' reactions to global health emergencies, such as the COVID-19 pandemic or future challenges [7]. For the purpose of this research, we used the definition by He et al [8], who define AI as a "branch of applied computer science wherein computer algorithms are trained to perform tasks typically associated with human intelligence" [8].

Although AI development and research are conducted in many countries nowadays [5], a report from the Joint Research Centre of the European Commission [9], as well as original research, shows that AI development and implementation in the European Union and in Germany are still in their early stages [10,11]. In part, this could be explained by the low availability of the data needed for the development of AI tools [12,13] and by regulatory and legal uncertainties [10]. In its efforts to support the further development of AI tools within the country, the German government deemed the following aspects as especially important: (1) data sovereignty, (2) patients' protection-worthy interests, (3) patients' rights, and (4) compliance with ethical requirements for the protection of sensitive health data [14].

Both patients' interests and their rights concerning the use of their routine medical data have been studied before. In a systematic review, Aitken et al [15] synthesized the results of qualitative research on data sharing for the purpose of health research. They identified overall widespread conditional support for this purpose. The conditions for support included, inter alia, the assurance of individuals' confidentiality, a preference for the anonymity of data, and assurances of data security [15]. However, it is unclear whether these results and conditions can be applied to AI—a fundamentally new general-purpose technology. A study by McCradden et al [16] aimed to generate insights into public perceptions on using health data for AI research. They concluded that the general views about AI in their studied sample of the general population were mostly negative. Still, the participants were able to describe the potential benefits for health research that could be gained through the use of AI. Important conditions for supporting the use of health data for AI research were consent, the transparency of AI use, and assurances of data privacy [16]. These findings were based on a sample from the general population in Canada. It is plausible to assume that these preferences and opinions could vary among different cultural contexts and between the general population and current patients. Hence, we decided to involve patients in the first part of our project, even though they will not be direct users or beneficiaries of our generic infrastructure. To facilitate later discussions on patient and public involvement

in research, the Guidance for Reporting Involvement of Patients and the Public [17] framework will be used.

The availability of large quantities of structured, high-quality data is fundamental to the development of AI tools [4,18]. Hospitals and other health care facilities inherently store the large amounts of data needed for AI development, but access to these data can pose legal and ethical challenges [12,13]. Besides that, legal certainty for the (partly) automized testing of routine medical data against a defined gold standard is missing [19]. Therefore, databases for the development and testing of new AI algorithms are often assembled manually. This requires high efforts from hospitals and product developers and slows down development and evaluation processes. In turn, patients can only benefit from new innovations after significant delays.

These problems and questions are addressed by the Protected Artificial Intelligence Innovation Environment for Patient-Oriented Digital Health Solutions for Developing, Testing, and Evidence-Based Evaluation of Clinical Value (pAItient) project, which aims to establish the AI Innovation Environment as a proof-of-concept extension of the already existing Medical Data Integration Center [20] at the Heidelberg University Hospital. The project partners include the German Cancer Research Center, the German Research Center for Artificial Intelligence, and Mint Medical GmbH (Heidelberg, Germany).

We also propose that knowledge of the requirements and needs of stakeholders, such as patients, health care providers, and industry partners, regarding the planned, generic infrastructure is an important antecedent for high acceptance and usefulness. This infrastructure is a novel concept and thus warrants a close analysis of factors influencing stakeholder acceptance.

Aims

This paper presents the protocol for our study, which aims to explore stakeholders' requirements for developing AI in partnership with an academic hospital and granting AI experts access to anonymized personal health data.

Methods

We designed a multistep mixed methods study, combining qualitative and quantitative measures. This approach will allow us to gain in-depth insights into stakeholders' opinions and quantify our findings.

Stakeholders and Participants

Study participants were recruited from the following six stakeholder groups: (1) researchers from a biomedical research institute, (2) researchers from an AI research institute, (3) employees from start-up companies in the field of AI development, (4) employees from an AI imaging company, (5) patients at the Heidelberg University Hospital, and (6)

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physicians actively working in inpatient or outpatient health care.

Participant Recruitment

Potential study participants from groups 1 to 4 were invited via email, following a snowball sampling approach. Patients (group 5) were recruited through a purposive sampling approach. Recruitment took place in different departments (the Department of Obstetrics and Gynecology, the Department of Internal Medicine, and the outpatient department at the National Center for Tumor Diseases Heidelberg) at the Heidelberg University Hospital, which is one of Europe's largest medical centers [21]. Patients were approached by a study team member and invited to participate. In addition, informational materials, such as leaflets containing information on the study and the contact data

of the study team, were provided. Recruitment procedures for physicians (group 6) are described elsewhere [22].

The inclusion criteria for groups 1 to 4 and group 6 were employment or the conduction of research activities in one of the defined areas. To be able to participate, patients had to report either a self-defined chronic disease or at least 3 visits to the hospital or an ambulatory health care provider in the last 3 months. The exclusion criteria were persons aged under 18 years and persons whose command of German or English was not sufficient for conducting an interview.

Data Collection

The following paragraphs describe the qualitative and quantitative methods that were used for data collection (Figure 1 depicts an overview). The methods used for data analysis are described in their respective paragraphs.

Figure 1. Study design overview. AI: artificial intelligence.
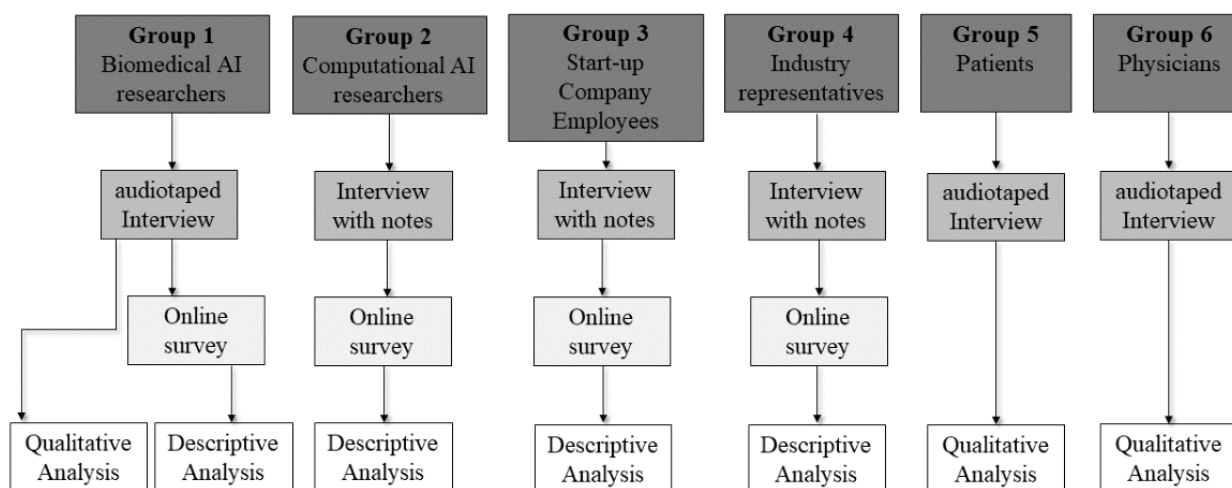
Qualitative Measures

Within an interprofessional team of researchers from the fields of health services research and medical informatics, semistructured interview guidelines were developed. The guidelines for professional interview partners were structured in 3 sections. The first section asked participants to briefly describe the projects they are currently working on. The second section contained questions concerning data usage, such as questions about the kinds of data that participants need for their projects. In the third section, participants were asked to elaborate on how an academic hospital could support them in their work. Translated versions of the interview guides can be found in Multimedia Appendix 1. A translated version of the interview guide for physicians was published elsewhere [22].

For patients, the interview guidelines followed a different approach. They included questions about general thoughts and expectations surrounding AI and the use of data for the development of AI. As these topics are complex and can be difficult to understand for patients, case vignettes were used for the patients' interview guidelines.

Interviews with AI researchers, start-up company employees, and industry representatives were individually scheduled and were conducted by a researcher with a professional background

in medical informatics. A researcher with profound experience in qualitative research methods was present during the interviews to facilitate data collection and to take notes.

Interviews with patients and physicians were conducted by researchers from the field of health services research. All interviews were performed via a videoconferencing tool. Participants were informed about the aims of the study before the interviews and were asked to give their informed consent. Interviews with participants from the biomedical research institute, patients, and physicians were audiotaped, pseudonymized, and transcribed verbatim, following appropriate transcription guidelines. These data were transcribed, managed, and analyzed with MAXQDA 2020 (VERBI Software GmbH). Participants from these groups were also asked to provide sociodemographic data, such as age and gender, on a separate form. After the data collection was completed, the data analysis was conducted according to thematic analysis procedures [23].

Interviews with participants from the remaining groups were documented through field notes. These were reviewed and used as the basis for developing the quantitative instrument.

Quantitative Measures

Web-based surveys were created based on the interview guidelines and field notes from the interviews. The

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questionnaires followed the same structure for all participant groups, but items varied and were tailored to each participant group. Within its base structure, the questionnaires included questions on the software, hardware, and types of data necessary for AI development. Additionally, participants were asked to rate experienced barriers and advantages of working with academic hospitals on Likert scales. REDCap (Research Electronic Data Capture; Vanderbilt University; hosted at the Heidelberg University Hospital) was used for study data collection and management. REDCap is a secure, web-based software platform that was designed to support data capture for research studies [24,25]. Potential participants were invited to fill in the survey via email. The survey results will be analyzed descriptively.

Ethics Approval

The design for the stakeholder requirements analysis study was approved by the Ethics Committee of the Heidelberg University Hospital (approval number: S-241/2021) in March 2021.

Results

The pAItient project received funding from the German Federal Ministry of Health in August 2020. We conducted 18 interviews, which enabled us to design a tailored survey instrument for participant groups 1 to 4. For the quantitative part of the study, 21 surveys were filled. Data collection concluded in summer 2022. Data analysis is planned to start in fall 2022. We plan to publish the results in winter 2022 to 2023.

Discussion

The aim of our study is to explore stakeholders' requirements for developing AI in partnership with an academic hospital and granting AI experts access to anonymized personal health data. We planned to include perspectives from a multitude of stakeholders, such as patients, physicians, AI researchers, and industry employees. We believe that following our 2-step mixed methods approach will allow us to identify the stakeholders' priorities and will enable them to make important suggestions. We will be able to include these priorities and suggestions into the development process and into the technical infrastructure of the proposed AI Innovation Environment at our institution.

Data collection posed a significant challenge to our study. We faced difficulties in recruitment, especially for the group of patients. We believe that this may have been due to the complexity of the topic—AI—and a resulting low interest in research participation, which has been identified as a barrier before [26]. Hence, we redesigned the invitational leaflets, introduced a small financial compensation for participation, and had different members of the study team approach patients at different times of the day and in different departments. However, patient recruitment remained challenging. In order to comply with the agreed timelines for the overall project and to be able to start developing the AI Innovation Environment, participant recruitment had to be concluded in summer 2022.

Data Availability

The data sets that have been generated during the study are not publicly available due to privacy regulations but are available from the corresponding author on reasonable request.

Authors' Contributions

LW and MK drafted and prepared the original manuscript. OH was the overall principal investigator of the study. LW was responsible for the study design and study protocol. LW, MK, GS, and OH contributed to the concept and design of the study and to the preparation of the manuscript. All authors approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Translated interview guide.
[PDF File (Adobe PDF File), 97 KB - resprot_v11i12e42208_app1.pdf]

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Abbreviations

AI: artificial intelligence
pAItient: Protected Artificial Intelligence Innovation Environment for Patient-Oriented Digital Health Solutions for Developing, Testing, and Evidence-Based Evaluation of Clinical Value
REDCap: Research Electronic Data Capture

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Protocol

The Evaluation of a Clinical Decision Support Tool Using Natural Language Processing to Screen Hospitalized Adults for Unhealthy Substance Use: Protocol for a Quasi-Experimental Design

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Abstract

Background: Automated and data-driven methods for screening using natural language processing (NLP) and machine learning may replace resource-intensive manual approaches in the usual care of patients hospitalized with conditions related to unhealthy substance use. The rigorous evaluation of tools that use artificial intelligence (AI) is necessary to demonstrate effectiveness before system-wide implementation. An NLP tool to use routinely collected data in the electronic health record was previously validated for diagnostic accuracy in a retrospective study for screening unhealthy substance use. Our next step is a noninferiority design incorporated into a research protocol for clinical implementation with prospective evaluation of clinical effectiveness in a large health system.

Objective: This study aims to provide a study protocol to evaluate health outcomes and the costs and benefits of an AI-driven automated screener compared to manual human screening for unhealthy substance use.

Methods: A pre-post design is proposed to evaluate 12 months of manual screening followed by 12 months of automated screening across surgical and medical wards at a single medical center. The preintervention period consists of usual care with manual screening by nurses and social workers and referrals to a multidisciplinary Substance Use Intervention Team (SUIT). Facilitated by a NLP pipeline in the postintervention period, clinical notes from the first 24 hours of hospitalization will be processed and scored by a machine learning model, and the SUIT will be similarly alerted to patients who flagged positive for substance misuse. Flowsheets within the electronic health record have been updated to capture rates of interventions for the primary outcome (brief intervention/motivational interviewing, medication-assisted treatment, naloxone dispensing, and referral to outpatient care). Effectiveness in terms of patient outcomes will be determined by noninferior rates of interventions (primary outcome), as well as rates of readmission within 6 months, average time to consult, and discharge rates against medical advice (secondary outcomes) in the postintervention period by a SUIT compared to the preintervention period. A separate analysis will be performed to assess the costs and benefits to the health system by using automated screening. Changes from the pre- to postintervention period will be assessed in covariate-adjusted generalized linear mixed-effects models.

Results: The study will begin in September 2022. Monthly data monitoring and Data Safety Monitoring Board reporting are scheduled every 6 months throughout the study period. We anticipate reporting final results by June 2025.

Conclusions: The use of augmented intelligence for clinical decision support is growing with an increasing number of AI tools. We provide a research protocol for prospective evaluation of an automated NLP system for screening unhealthy substance use

using a noninferiority design to demonstrate comprehensive screening that may be as effective as manual screening but less costly via automated solutions.

Introduction

The COVID-19 pandemic has exposed major gaps in health care delivery with limited resources and staffing. In 2020, deaths related to drug overdose reached an all-time high with a record 93,000 deaths nationwide during the pandemic year [1]. The number of substance use–related hospital visits outpaces visits for heart disease and respiratory failure [2]. Despite the recommendations from the US Preventive Services Task Force for Unhealthy Drug Use Screening [3], hospital screening rates remain low, with detection rates around 50% [4]. Manual screening efforts within busy hospital settings impose staffing requirements and administrative burdens, with the corresponding missed opportunities to prioritize care for the most vulnerable patients.

The prevalence of unhealthy substance use (nonmedical use of opioids or benzodiazepines, illicit drugs, or alcohol) in hospitalized patients is estimated to be 15% to 25%, far exceeding that of the general population, and the hospital setting is an important touchpoint for engaging patients [5,6]. Hospitals currently screening for unhealthy substance use need better approaches to identifying and treating patients, with less than a quarter of patients with a substance use disorder receiving treatment [7]. During the COVID-19 pandemic, screening efforts became even more challenging with changes in workflow and the reallocation of resources that further reduced manual screening rates [8]. Meanwhile, substance misuse ranks second among principal diagnoses for unplanned 7-day hospital readmission rates [7,9].

As of 2017, over 80% of hospitals in the United States have adopted an electronic health record (EHR) system [10]. Clinical decision support (CDS) and intelligent data-driven alerts are now part of federal incentive programs for meaningful use [11]. With access to EHR data and financial incentives to improve quality care, hospitals are increasingly well equipped to leverage computational resources to improve screening efforts via automated solutions [12,13]. The potential in digital phenotyping for substance use identification and treatment is real [14], but few pragmatic studies have been implemented to examine their effectiveness. Prior studies have demonstrated that the EHR contains information needed to identify cases of substance use [15,16]. However, leveraging data-driven methods with artificial intelligence (AI) and automating screening approaches remain in their infancy [17].

Although information about substance use is routinely recorded in providers' intake notes in the EHR, it is neither organized nor prioritized during routine care for CDS [18]. Automated, data-driven solutions with natural language processing (NLP) can automatically extract important risk factors from clinical notes [19]. The computational methods of NLP derive semantic features from clinical notes, from which machine learning models can predict substance misuse. We previously published and made publicly available an NLP screening tool for different types of substance misuse [8]. During the validation of the algorithm, we achieved sensitivity and specificity greater than 85% using a convolutional neural network (CNN) from clinical notes with a false negative rate of less than 5% to screen for unhealthy alcohol use, unhealthy opioid use, and unhealthy nonopioid drug use (ie, cocaine and amphetamines).

In the advent of the digital era of AI in medicine, machine learning classifiers and AI-driven models are now being developed at an exponential pace. However, very few NLP systems have been translated into real-world clinical contexts with rigorous evaluation [20]. We provide a study protocol on one of the first NLP-driven solutions using our validated algorithm with the hypothesis that we can achieve a comprehensive and automated screening system that reduces workforce resources without compromising effectiveness. To test our hypothesis, we plan to examine health outcomes in a noninferiority design coupled with a cost-effectiveness analysis. More specifically, we propose a pre-post segmented regression analysis to evaluate the effectiveness of the automated screening tool in maintaining or increasing (1-tailed test) the proportion of patients who screened positive and received any of a composite group of interventions compared to usual care (eg, interviewer-administered screening).

Methods

Setting and Study Design

The study will be implemented at Rush University Medical Center (RUMC) across the surgical and medical hospital inpatient wards. This prospective evaluation will target all adult (18-89 years of age) hospitalizations over a 24-month period (12 months of usual care with manual screening and 12 months under the implementation of automated screening) and an additional 6-month follow-up period for secondary outcomes. We will use pre-post segmented regression analysis with noninferiority hypothesis testing to evaluate the impact of the substance misuse classifier compared to usual care. The trial is registered at ClinicalTrials.gov (NCT03833804).

Preintervention Period: Usual Care With Manual Screening

In 2017, RUMC launched a multidisciplinary Substance Use Intervention Team (SUIT) to address the opioid epidemic through a universal screening and Screening, Brief Intervention, and Referral to Treatment (SBIRT) program in the hospital [21]. Screening, intervention flow sheets, and consult order sets were built into EHR-driven workflows for inpatient nurses and social workers. Leveraging the EHR infrastructure, the manual screening by nurses and social workers was driven by four key components: (1) a single workflow that connects the nursing and social work navigators and allows both disciplines to document screening information into a common flowsheet in the EHR; (2) a status column in the unit patient list where the social work team indicates the current stage of the intervention for each patient; (3) a consult order to addiction medicine that operates within a work queue managed by the SUIT; and (4) a flowsheet for the SUIT to document the details of the intervention. Specifically, if patients reported positive to the universal manual screening during the rooming process, an indicator in the substance use column would update to signal a social worker to conduct a full manual screening with the Alcohol Use Disorders Identification Test (AUDIT) and/or Drug Abuse Screening Tool (DAST). As part of usual care and in the preintervention period, RUMC will perform an initial 2-question universal screening for alcohol (5 or more drinks for men and 4 or more drinks for women) and drugs (any illicit drug use in the past year). Those who screen positive will receive a full screening with the 10-item AUDIT [22] or 10-item DAST [23]. Once completed, the social worker may provide a brief motivational interviewing intervention for an AUDIT score above 4 or DAST score above 1. For higher risk scores, the social worker may recommend a consult to the SUIT for addiction services. Alternatively, primary teams will be able to consult the SUIT directly, at which time, AUDITs and DASTs will be performed by the SUIT themselves. The consulting team determines with the patient whether to initiate medication and linkage to outpatient services upon discharge. If ready, patients may begin medication and, upon discharge, receive individual and group psychotherapy, case management, and continued medication treatment at an outpatient addiction medicine clinic.

Postintervention Period: AI-Assisted Screening

We previously published a substance misuse screening tool using NLP and machine learning from the clinical notes, Substance Misuse Algorithm for Referral to Treatment using Artificial Intelligence (SMART-AI) [8]. SMART-AI was developed on hospitalized RUMC patients between October 1, 2017, and December 31, 2019, with temporal validation between January 1, 2020, and December 31, 2020. In hospitalized patients, the SMART-AI CNN used the first 24 hours of EHR notes to identify and screen for multiple types of unhealthy substance use (unhealthy alcohol use, unhealthy opioid use, and unhealthy nonopioid drug use). Temporal validation of the classifier during the COVID-19 pandemic demonstrated a mean area under the receiver operating characteristic curve of 0.97 (95% CI 0.96-0.98) and a mean area under the precision-recall curve of 0.69 (95% CI 0.64-0.74) for the different types of unhealthy substance use. The number needed to evaluate (NNE)

on positive screenings to identify a true positive was 1.5 for unhealthy alcohol use, 1.3 for unhealthy opioid use, and 2.6 for unhealthy nonopioid drug use. This created 39, 26, and 16 alerts per 1000 hospitalized patients for each group, respectively. This was deemed an acceptable workload by the SUIT clinical care team. In the intervention period, the manual screening performed by nurses and social workers will be replaced with SMART-AI.

The EHR system at RUMC is provided through Epic (Epic Systems Corporation). We designed an approach to collect notes from the first 24 hours of hospitalization from Epic, which is how SMART-AI was originally developed and validated [8]. With an average time of 1.6 days from a patient's admission to receipt of a SUIT consultation during usual care, we anticipate this is sufficient time for the automated screener to operate and clinical interventions to occur after admission notes are collected.

During the postintervention period, an alert will run every 24 hours after a nightly data extraction from the front-end EHR (Epic) into the back-end data warehouse (Clarity) at RUMC. SMART-AI will operate using the daily EHR notes collected in the data warehouse that are preprocessed through an NLP engine and fed into the SMART-AI machine learning model in a Microsoft Azure cloud computing environment. The output classifications for screen-positive cases will be published as reports routed through a secure environment for viewing. At RUMC, the patients who flagged positive for substance misuse will be reported with an encrypted email routed to the SUIT provider each morning, after the server is refreshed with the last 24 hours of data.

NLP Pipeline

Linguistic preprocessing of the EHR to extract clinical information from unstructured text will be managed via an open-source software called the Clinical Text and Knowledge Extraction System (cTAKES; version 4.0) [24]. cTAKES processes clinical notes; identifies types of clinical named entities such as drugs, diseases/disorders, signs/symptoms, anatomical sites, and procedures; and maps them to concepts from the National Library of Medicine's Universal Medical Language System (UMLS) Metathesaurus. cTAKES is a modular pipeline that first breaks the EHR note into tokens and sentences. Next, it annotates the word tokens with parts-of-speech tags (eg, noun and adjective). Third, candidate phrases are formed and matched to a dictionary of medical concepts sourced from the UMLS. Mappings convert the raw text to standardized medical terminologies such as SNOMED CT and RxNORM, using concept codes from the UMLS called Concept Unique Identifiers (CUIs). The text spans from the EHR notes are ultimately transformed into sequences of CUIs representing UMLS-named entity mentions (diseases, symptoms, anatomy, and procedures). For instance, "heroin use" is assigned "C0600241" as its CUI and is a separate CUI from "history of heroin use," which is "C3266350."

The sequences of CUIs from the notes collected in the first 24 hours of hospitalization are concatenated into a single document and converted into sequences of dense vectors known as CUI embeddings, which in turn serve as the input layer to SMART-AI, a multilabel CNN. All SNOMED CT and

RxNORM CUIs mapped from the notes are available to the model as 300-dimensional CUI embeddings. There is no limitation to the number of CUIs to be fed into the model, which is an advantage over pretrained language model transformers that commonly have a token limitation. SMART-AI will provide the final output classification for screen-positive cases for unhealthy alcohol, opioid, and/or nonopioid drug use. We will use a cutoff of 0.05 on the predicted probabilities for each substance use label because this provided the best test characteristics in the validation study [8]. The previously trained and validated CNN model for SMART-AI is available on Github [25], and more technical details about the model are detailed in the development and validation study [8]. No changes were made to the implementation of this protocol.

Data Collection and Management

The clinical SUIT has previously established outcome data collection methods using the EHR [26,27]. Specific to this study,

flowsheets within the EHR have been updated with hospital operations to capture additional SUIT consult parameters (Table 1). Preconsult information includes the consult modality (inpatient screen, prior patient of SUIT, ad hoc, and emergency department–initiated), the consult reason (evaluation for treatment initiation, continuity for medication-assisted treatment [MAT] maintenance, and acute care adjustment of MAT), and inpatient screen exemption reason (intoxication/overdose, withdrawal, and related physical ailment). Additionally, the post-SUIT consult disposition (complete consult, patient refusal, and incomplete consult) will be another recorded parameter within the EHR. Beginning in the preintervention period, the data will be extracted monthly from the EHR to monitor quality and completeness and will be presented biannually at scheduled Data Safety Monitoring Board (DSMB) meetings.

Table 1. Components of the intervention electronic health record data capture.

Component	Description
Composite outcome	
Brief intervention/motivational interviewing	A social worker provides a brief intervention using motivational interviewing for alcohol or stimulant use
Naloxone dispensing	Prescription, free kit from clinic, or order for home kit
MAT[a]	Buprenorphine, methadone, or naltrexone (OUD[b]); acamprosate, gabapentin, or disulfiram (AUD[c])
Addition consult	Consultation team includes specialists from emergency medicine, psychiatry, toxicology, social work, and pharmacology
Referral to outpatient treatment	Individual or group psychotherapy, case management, and continued MAT
Consult characteristics	
Consult modality	Inpatient screen, established patient, ad hoc, and emergency department–initiated
Consult reason	Evaluation for initial treatment, MAT maintenance, MAT adjustment, not substance use–related, and non-MAT disposition planning
Inpatient screen exemption	Intoxication/overdose, withdrawal, and related physical ailment (endocarditis, alcoholic cirrhosis, and acute psychosis)
SUIT[d] provider role	Consultant, supporting other service, and curbside
Disposition	Incomplete, patient refusal, patient discharged, and completed consult

[a]MAT: medication-assisted treatment.

[b]AUD: alcohol use disorder.

[c]OUD: opioid use disorder.

[d]SUIT: Substance Use Intervention Team.

Primary and Secondary Outcomes

The primary outcome is the count of patients who had an addiction consult and received the composite intervention of any of the following: (1) naloxone dispensing (prescription, free kit from clinic, or order for home kit); (2) MAT (buprenorphine, methadone, naltrexone, acamprosate, gabapentin, or disulfiram); (3) referral to outpatient treatment; and/or (4) brief intervention/motivational interviewing for substance misuse. Each component will be indicated separately in the EHR flowsheet for the hospital encounter (Table 1).

The secondary outcome is all-cause rehospitalizations following 6 months from the index hospital encounter. Further exploratory outcomes include each component of the primary outcome analyzed separately: naloxone dispensing, MAT, referral to outpatient treatment, and brief intervention/motivational interviewing for unhealthy substance use. We will also characterize the time to consult and discharge rates against medical advice (AMA).

Analysis Plan

Descriptive statistics will be reported for demographic and clinical variables stratified by pre- and postintervention periods. Outcomes will be compared by time period (pre- vs

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postintervention) using generalized linear mixed effects models (GLMMs), which will allow for appropriate modeling of the different dependent variables, including continuous, count, or categorical, and to include random effects to account for correlated data due to patients with multiple index hospitalizations. For the primary end point, we will first plot the proportion of hospitalized patients who received any component of the composite outcome by the month of index hospitalization to examine seasonality, trends, and outlying values. The piecewise GLMM will be used to model the composite outcome. The primary explanatory variable will be a dichotomous variable for the time period (preintervention vs postintervention), and the covariates will include age, sex, race/ethnicity, and payor status. This model will take the form of:

where p_{ij} is the probability of the composite outcome for patient i at hospitalization j, α is the overall intercept, β is the coefficient for time period, X_{ij} is the design matrix of covariates, u_i is the patient-level random intercept, and $_{ij}$ is the random error term. Additional variables will be considered including season/month, primary diagnosis, and the unit, with fit statistics (Akaike information criterion [AIC] and Bayesian information criterion [BIC]) used to guide model selection. A similar GLMM will be specified to predict rehospitalization for the secondary end point.

For the exploratory end point of time to consult, among the subset receiving the composite outcome, a Poisson mixed-effects regression model will regress time to consult on time period (preintervention vs postintervention) and covariates. The rate of discharge AMA will be modelled similarly to the primary end point with mixed-effects logistic regression. Finally, the addition of interaction terms to the primary GLMM (eg, payor by intervention period) will be performed to test if some subgroups of patients may be more or less likely to experience the composite end point after the implementation of SMART-AI.

Our hospitalization-level analysis plan assumes the degree of seasonality and autocorrelation in this design will be minimal. If the assumption holds true, mixed-effects regression, which is flexible regarding outcome variable distribution and can account for both fixed effects (covariates) and random effects (nesting), is preferable to time-series approaches, which directly model the aggregated data. We believe this assumption is reasonable as we found a white noise model using 3 years of prior SUIT data (August 2018 to July 2020), which demonstrated negligible autocorrelation (AR$_{1,1}$=0.04, SD 0.22; P=.86) and required no differencing to achieve stationarity (constant mean and constant variance over time). We will verify whether this assumption holds for the study period, and an interrupted time-series approach using autoregressive integrated moving average (ARIMA) models will be applied should autocorrelation be substantial [28]. In this case, a transformation will be applied to stabilize the variance over time if the data are heteroscedastic. Differencing will be applied to induce stationarity, such as a difference to account for linear trend (d=1,

degree of nonseasonal differencing), and autocorrelation functions (ACFs) will be plotted to verify stationarity. After differencing, ACFs and partial ACFs will be used to determine the orders of autoregression or moving average that will correct the remaining autocorrelation. We will formally test if the intervention will promote a step change (binary indicator for a level shift when intervention begins) and a ramp effect (the variable takes the value of 0 before the intervention and increases by 1 for each month following the beginning of the intervention). Fit statistics (AIC and BIC) and residual analysis (Ljung-Box test for white noise) will be used to identify a parsimonious and appropriate model based on ARIMA orders, differencing assumptions, and parameters for intervention impact (step, pulse, or ramp).

Cost-Benefit Analysis

In the cost-benefit analysis, both costs and consequences of alternatives are measured in monetary units [29]. We will conduct in-depth interviews with SUIT personnel and brief interviews with RUMC staff (nurses and social workers) to query about the fixed and variable costs associated with establishing and implementing substance misuse screening during the usual care with manual screening and AI-assisted screening periods. During both periods, we will ask about the time cost of staff receiving training and administering the universal screening (not applicable during the intelligence-assisted screening period), secondary screening, and brief intervention/motivational interviewing for unhealthy substance use, which is not a billable service within a hospitalization context. The time cost of staff and resources dedicated to building EHR infrastructure to support manual and AI-assisted screenings will also be calculated (Multimedia Appendix 1). Costs associated with the index hospitalization, including naloxone dispensing, MAT, other treatments, and same-hospital rehospitalizations, will be extracted from the EHR and administrative billing records. The cost-benefit analysis will be conducted using the health system perspective and within the hospitalization episode. We will use a mixed-effects generalized linear model with log link function and gamma distribution to calculate the adjusted cost or saving per index hospitalization during the preintervention and postintervention periods. Our analysis will adjust for patient-level sociodemographic and clinical characteristics and include random intercepts to account for multiple index hospitalizations per patient. We will repeat the analysis with and without the cost of same-hospital rehospitalizations. Results from the regression analysis will be combined with data collected from the interviews to calculate the incremental cost or saving per index hospitalization receiving substance misuse screening and the incremental cost or saving per index hospitalization receiving any component of the composite outcome during the manual screening period compared to the AI-screening period. We will also calculate the average cost of the SBIRT program per patient and the average cost of composite outcome per patient during each intervention period. The Hospital Care component of the Personal Health Care Price Index published by the Centers for Medicare and Medicaid Services will be used to adjust costs to analyze cost per year in US dollars [30].

Sample Size Calculations

In 2020, on average, approximately 2400 (SD 250) patients were hospitalized each month with 94 (SD 9) SUIT consults performed at RUMC. Overall, a median of 3.9% (IQR 3.5%-4.2%) of hospitalized patients received a SUIT consult during each month of 2020 (Figure 1). This period of time was chosen to inform power as it represents a "new normal" for SUIT practices in the era of COVID-19. We hypothesize that additional components of the composite outcome will lead to a new preintervention outcome rate of 4.8% of hospitalized patients. For the primary end point, the null hypothesis is that the difference in the proportion receiving the composite outcome

P_2 (postintervention) and P_1 (preintervention) is less than or equal to a noninferiority difference $D0$ of 0.5% such that H_0: $P_2 - P_1 \le D0$. This corresponds to the SMART-AI time period intervention rate of 4.3% or less under the null hypothesis of inferiority. A total sample size of 60,000, or 30,000 hospitalizations per time period, will have 82% power to detect a 0% difference using a 1-sided Z test and $\alpha=.025$ (Table 2). Power is slightly attenuated in the setting for mixed-effects logistic regression with covariates compared to the simple Z test; however, we expect a minimal correlation between time period and covariates, or R-squared close to zero (Figure 2).

Figure 1. Monthly SUIT consults from 2018-2020. SUIT: Substance Use Intervention Team.
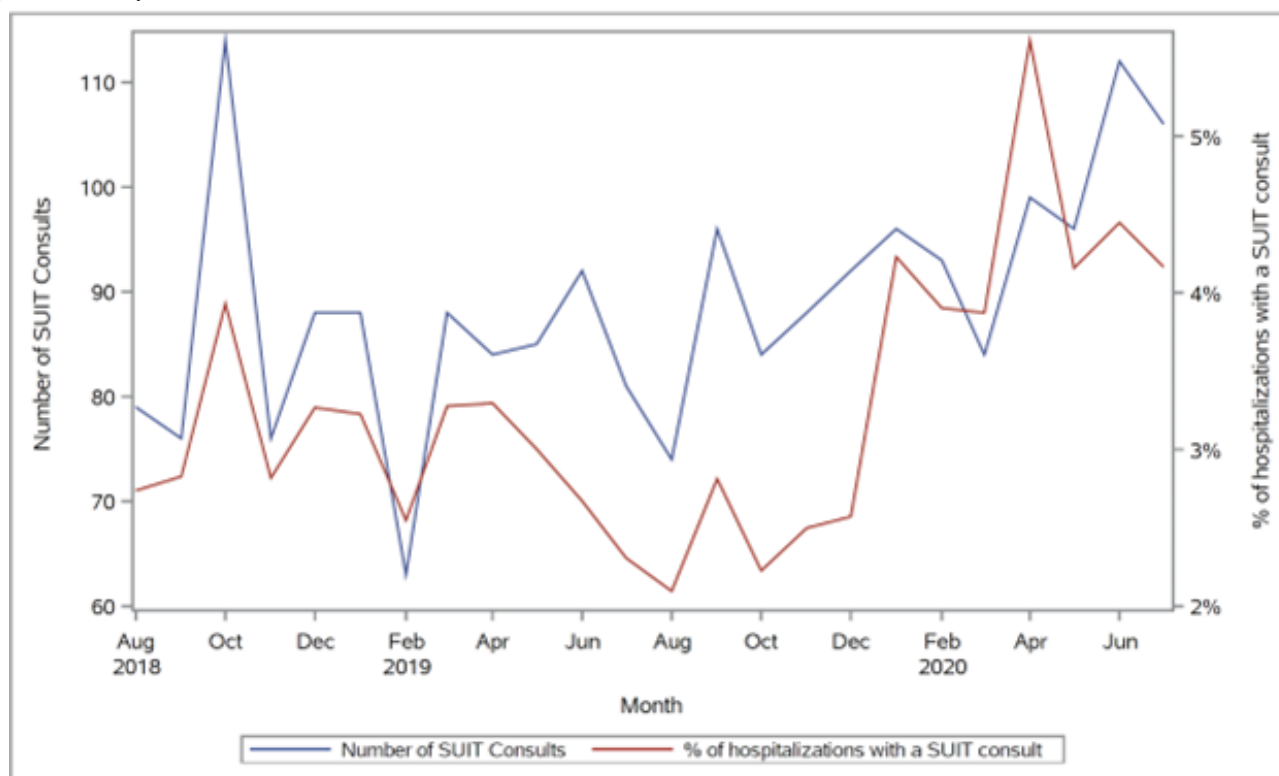
Table 2. Power estimates for a noninferiority hypothesis[a].

Setting	Proportion with outcome		Noninferiority difference	Difference at which power is calculated	Power for 2 proportions
	Preintervention	Postintervention			
1	0.048	0.046	−0.005	−0.002	41%
2	0.048	0.047	−0.005	−0.001	63%
3	0.048	0.048	−0.005	0.000	82%
4	0.048	0.049	−0.005	0.001	93%
5	0.048	0.050	−0.005	0.002	98%

[a]Assumptions: $\alpha=.025$, n=60,000 (50% per time period).

Figure 2. Power curve for covariate-adjusted logistic regression analysis. r-sq: R-squared.
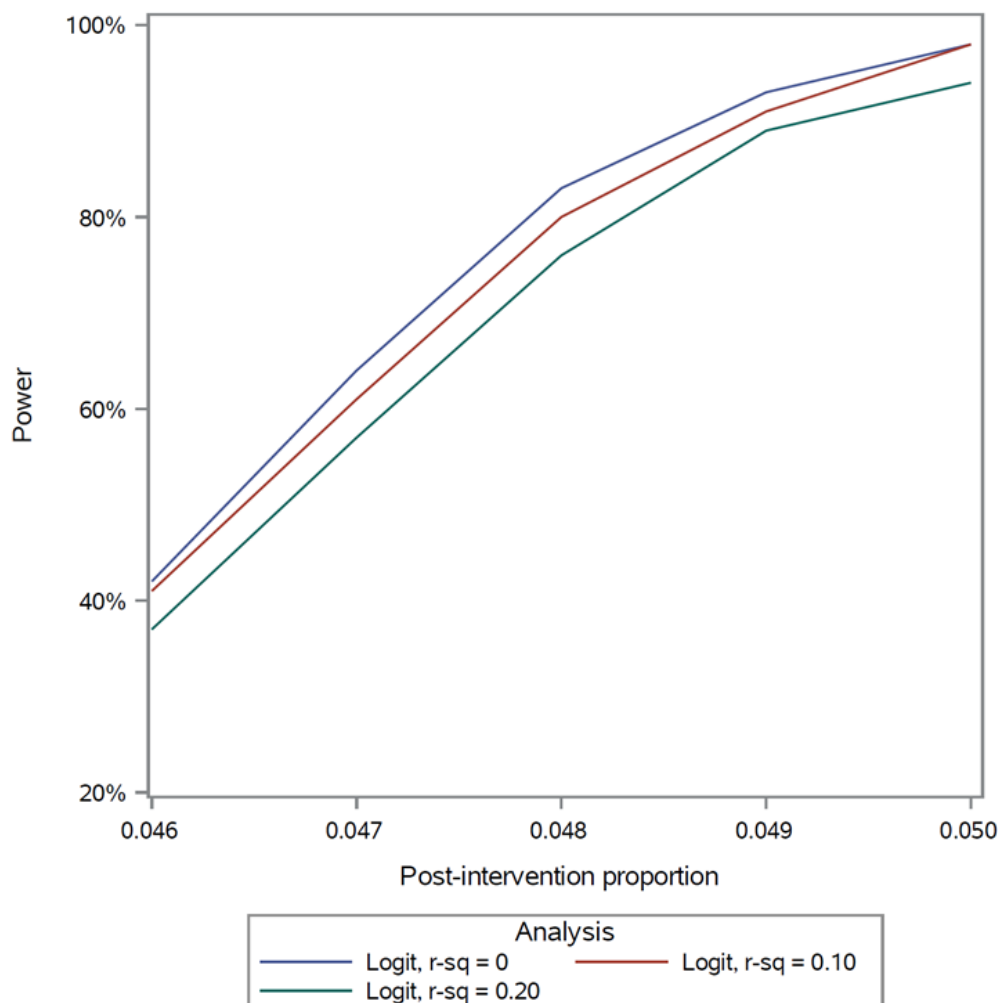
Ethical Considerations

The project was considered secondary research, for which a waiver of consent was approved by the RUMC IRB on May 10, 2022.

Results

The methods of screening and outcomes are summarized by time period in Figure 3. The preintervention study period will formally begin in September 2022 after a new round of education and in-servicing on screening to social workers and nurses for the manual screening phase. Monthly data monitoring and DSMB reporting are scheduled every 6 months throughout the study period. We anticipate reporting final results by June 2025.

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Figure 3. Study components and outcomes. AI: artificial intelligence. SMART-AI: Substance Misuse Algorithm for Referral to Treatment Using Artificial Intelligence.
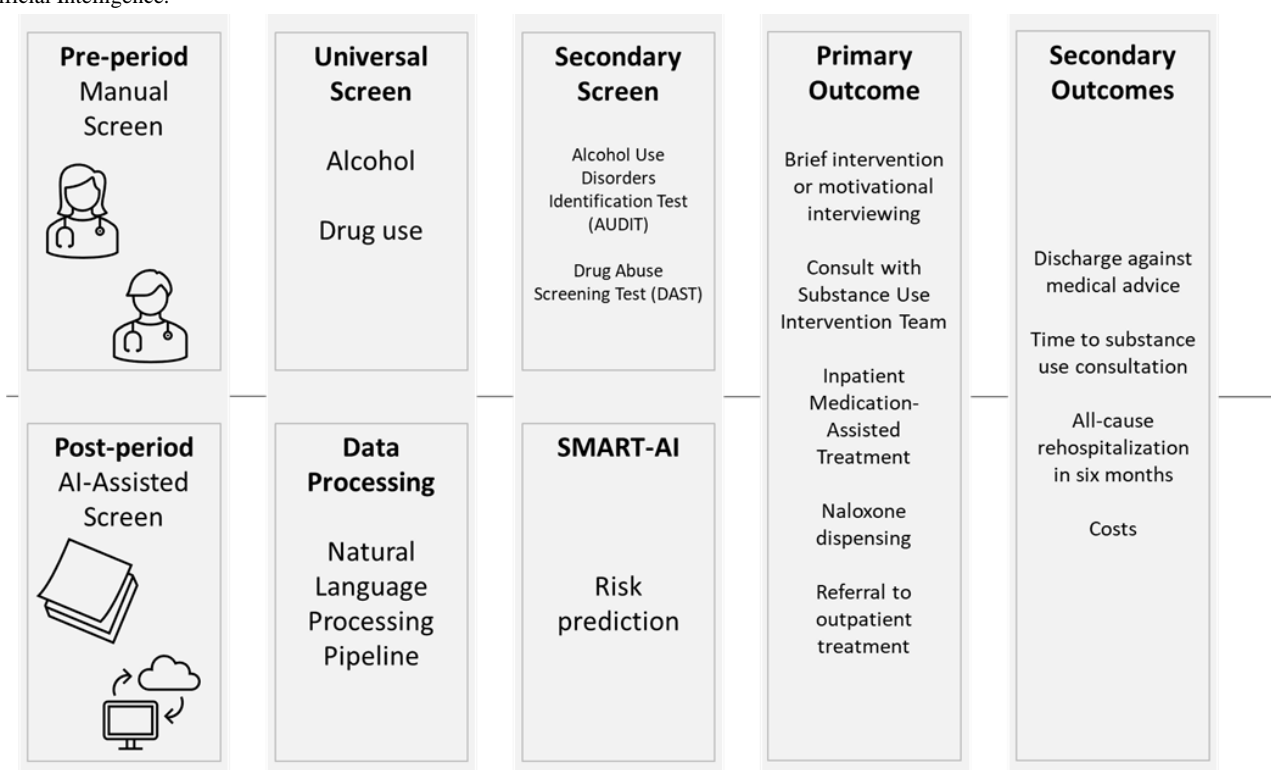
Discussion

There remains a paucity of protocols for evaluating AI systems in health care, because deploying such systems in large, complex health systems is relatively new [31]. Many AI models that are published and validated using retrospective data never reach the implementation phase for bedside evaluation [32]. Herein, we provide a protocol incorporating an automated substance use screening tool into an established screening program with the intent to improve throughput and efficiency over manual procedures. Our use case is an example of an AI system intended to improve efficiency and throughput within a reasonable time frame for hospital operations. In these cases, statistically superior performance on outcomes may not be expected or required for prospective implementation, and interventions may be desirable if they are both substantially equivalent (noninferior) on clinical outcomes and cost-effectiveness, given the high cost of building IT infrastructure and hiring vendors with high costs in licensing and software support. Our protocol provides one of the first use cases of NLP in CDS with AI-assisted screening for unhealthy substance use.

To our knowledge, no systems currently exist for AI-assisted screening of unhealthy substance use in health care settings. Screening rates for substance use disorders in health care systems remain low with many missed opportunities for care interventions, especially in emergency department settings where the prevalence of unhealthy substance use is high [33]. Further, comprehensive screening programs are needed to better understand the epidemiology and morbidity of substance use–related conditions. The total annual estimated attributable medical cost in patients with substance use–related admissions is US $13.2 billion, including US $7.6 billion from

alcohol-related disorders alone [34]. The cost-effectiveness of treatment for hospitalized patients with substance use disorders has been described [21,35], but the role of an AI-assisted screening approach to further improve screening efforts and how it translates to health outcomes and cost remains unknown.

Past work on AI health systems has surfaced the following obstacles in going from research and development environments into clinical settings: (1) culture/personnel, (2) clinical utility of AI tools, (3) financing, (4) technology support, and (5) adequate data [36]. We provide an in-house solution by working with our data science team to develop a novel screening tool to address the priority of hospital-wide screening. The clinical utility of the tool and return on investment will be examined in our primary outcomes. Additional challenges remain in information systems discovery and program management with clinical champions and executive sponsorship to help align with institutional business needs. Using open-source software for NLP processing and following best practices in the model evaluation should help keep costs low. However, costs in the cloud computing platform with Health Level Seven (HL7) standards and EHR vendor integration have limited our implementation to a fully integrated CDS that is embedded directly into the EHR. Less costly steps to leverage existing data warehouse capabilities are currently planned as an alternative to the integrated EHR workflow to provide daily screening reports to the care team. Ultimately, this may affect the process measures and, in turn, proposed outcomes.

More protocols are needed describing AI-assisted CDS tools for hospital implementation with an evaluation framework that is conducive to system-wide implementation. Although conventional parallel-group randomized controlled trials may be considered the gold standard for evaluation, they are costly

and require substantial external resources to be implemented. Alternatives such as the stepped wedge cluster randomized trial offer operational efficiency and some cost reductions [37] but can introduce new biases and require larger sample sizes to achieve similar power. When randomized trials are not feasible due to available resources, carefully selected quasi-experimental designs provide good alternatives for evaluation. Without randomization, these designs have limitations including the potential for bias due to secular trends and confounders, which may only partially be controlled for analytically. Additionally, with widespread implementation across a large hospital, any single condition or disease contributes to a low prevalence of cases monthly and may prove difficult to evaluate effectively. A low case rate may limit statistical power in analytic approaches such as the interrupted time-series design [38].

This protocol follows best practices in reporting our AI system and implementation approach, with an evaluation framework on large-scale effectiveness [39]. In addition, we have an established DSMB to also provide oversight into safety and ethics. We are meeting some of the core components of the Quadruple Aim to enhance health care efficiency [40]. Reducing costs and improving population health are the components we address, but our protocol is limited in examining other aims such as patient experience and provider well-being. Future work should include protocols incorporating the other components of the Quadruple Aims for optimizing health care delivery.

We attempt to minimize limitations in the pre-post design by using a well-powered but short time frame to minimize secular trends and by collecting extensive patient characteristics to control for potential changes to the demographics of our target population over time. Nevertheless, limitations of our pragmatic study include disruptions in hospital staffing to perform the consultations recommended by the AI system and that threaten the fidelity of the automated screening. In addition, unpredicted secular trends may occur and introduce additional confounding into the study or disruptions in health IT services to maintaining and updating the software dependencies for the AI infrastructure. Alternative strategies include incorporating implementation frameworks into the study protocol that are capable of achieving a rapid plan-do-study-act cycle to meet the operational needs of the health system and minimize disruptions, so that appropriate evaluation of the AI system's effectiveness may be achieved.

The successful implementation of the SMART-AI screening tool in hospitalized patients is a step toward an automated and comprehensive universal screening system for unhealthy substance use. We expect our results to demonstrate that the automated screener will increase the proportion of hospitalized patients with unhealthy substance use who screen positive and receive a brief intervention or referral to treatment. The dissemination of the expected results from this research would allow standardized and scalable "NLP-capable" measures for health care systems to identify patients with unhealthy substance use.

Acknowledgments

Data Availability

Data sharing is not applicable to this publication as this is a protocol paper and data collection has not begun.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Overview of data elements for the cost-benefit analysis.
[DOCX File , 16 KB - resprot_v11i12e42971_app1.docx]

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Abbreviations

ACF: autocorrelation function
AI: artificial intelligence
AIC: Akaike information criterion
AMA: against medical advice
ARIMA: autoregressive integrated moving average
AUDIT: Alcohol Use Disorders Identification Test
BIC: Bayesian information criterion
CDS: Clinical decision support
CNN: convolutional neural network
cTAKES: Clinical Text and Knowledge Extraction System
CUI: Concept Unique Identifier
DAST: Drug Abuse Screening Tool
DSMB: Data Safety Monitoring Board
EHR: electronic health record

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GLMM: generalized linear mixed effects model
HL7: Health Level Seven
MAT: medication-assisted treatment
NLP: natural language processing
NNE: number needed to evaluate
RUMC: Rush University Medical Center
SBIRT: Screening, Brief Intervention, and Referral to Treatment
SMART-AI: Substance Misuse Algorithm for Referral to Treatment using Artificial Intelligence
SUIT: Substance Use Intervention Team
UMLS: Universal Medical Language System

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Protocol

Home Automation for Adults With Disability Following an Injury: Protocol for a Social Return on Investment Study

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Abstract

Background: People with disability following a serious injury require long-term care. The most common injuries resulting in long-term disability are spinal cord and acquired brain injuries. While the long-term effects are difficult to predict and will vary between individuals, the costs of care and recovery span well beyond the initial treatment phase and include long-term care. Long-term care is changing with the availability and advances in cost and function of technologies, such as home automation. "Home automation" refers to technology that automates or remotely controls household functions. Home automation costs vastly differ, but home automation has the potential to positively impact the lives of people with disabilities. However, there is a dearth of evidence relating to the impact of home automation for people with a disability and few rigorous evaluations about the costs and return on investment.

Objective: The purpose of this study is to describe the impact of home automation for people with long-term disability following a serious injury (such as a motor vehicle accident) using case studies, and by conducting an evaluation of the costs and outcomes for individuals, families, and the wider community using a Social Return on Investment (SROI) approach.

Methods: SROI is a form of economic evaluation that develops a theory of change to examine the relationship among inputs, outputs, and outcomes and, in recent years, has gained popularity internationally, including in Australia. SROI has six phases: (1) identify scope and stakeholders, (2) map outcomes, (3) evidence outcomes and give them value, (4) establish impact, (5) calculate the SROI, and (6) report findings. Individuals with a disability who use home automation and key stakeholders will be interviewed. Stakeholders will be individuals involved in home automation for people with disabilities, such as allied health professionals, medical practitioners, equipment suppliers, engineers, and maintenance professionals. Users of home automation will be people who have a disability following a serious injury, have the capacity to provide consent, and have 1 or more elements of home automation. The impact of home automation will be established with financial proxies and appropriate discounts applied to avoid overestimating the social return. The SROI ratio will be calculated, and findings will be reported.

Results: The project was funded in November 2021 by the Lifetime Support Authority. Recruitment is underway, and data collection is expected to be completed by October 2022. The final results of the study will be published in March 2023.

Conclusions: To our knowledge, this study represents the first study in Australia and internationally to employ SROI to estimate the social, personal, and community outcomes of home automation for people with a disability following a serious injury. This research will provide valuable information for funders, consumers, researchers, and the public to guide and inform future decision-making.

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Introduction

People with a disability following a serious injury (such as a motor vehicle accident) require treatment, care, and support. The most common injuries resulting from an accident are spinal cord injuries and acquired brain injuries [1]. While the long-term effects are difficult to predict and vary between individuals, the costs of care and recovery span well beyond the initial treatment phase and include long-term care [2,3]. For many years after an injury, people with disabilities may require assistive equipment, home modifications, and attendant care, as well as informal care provided by family members or friends [4]. Long-term care for people with disabilities can be costly. For example, data from the United Kingdom suggest the most significant cost of long-term care for people with acquired brain injury is the cost of care attendants, which comprises approximately 80% of costs [3]. However, long-term care for people with disabilities following a serious injury is changing with the availability of new technologies.

"Home automation" refers to technology that automates or remotely controls household functions [5,6]. For example, controlling doors, blinds, heating and cooling, lighting, windows, doorbells, intercom systems, taps, and entertainment systems. The advances in both the cost and functionality of technology have made home automation more accessible. Acquiring home automation products requires several stages, such as assessment and selection, authorization and acquisition, implementation and training, and review and maintenance. It involves multiple people, such as the home automation user, family or support network, funder, allied health professional, medical practitioner, equipment supplier, and installer [7].

Home automation costs vastly differ, and the potential benefits of home automation can be wide ranging. These may include improved safety, improved comfort, greater independence and autonomy, improved social participation, improved quality of life, and the potential for the person with disability to be left alone for longer periods of time, leading to a reduced need for care attendants [6-13]. For example, in adopting a modeling approach to examine the trade-off between home automation and informal and formal care, Agree and colleagues [8] found that home automation use was associated with reduced hours of personal care for people with disabilities, particularly for those with high education levels, were unmarried, and had good cognition. In a study evaluating the impact of home automation for people with spinal cord injuries, functional abilities to perform daily tasks were improved, and home automation was identified as positively impacting individuals' psychosocial health, perceptions of quality of life, and independence [12]. Indeed, a recent literature review of the relationship between home automation and disability provided evidence to support a strong relationship between home automation and increased independence, leading to improved social inclusion of people

with disabilities [6]. However, despite the many benefits, there appear to be few users of home automation, and electronic assistive technologies remain underused in long-term care settings [6,7].

There have been an increasing number of studies evaluating smart homes and home automation in different populations. A recent scoping review examining the effectiveness of smart home technologies for older people with dementia identified 5 studies that provided evidence to support the use of smart home technologies in improving their health outcomes [14]. A qualitative study by Dermody and colleagues [15] explored the uptake and perceptions of home automation for older adults living in the community. The findings suggested that older people were receptive to using home automation to increase their independence, despite some minor concerns about their privacy and personal safety. However, increased information and support were required in order to adopt home automation successfully [15]. A recent scoping review on the impact of smart home and communication technology devices and systems for people with disabilities identified 21 studies. Notably, of the 21 studies, only 2 specifically focused on the impact of home automation technology for people with disabilities, and neither included a cost nor a return on investment component [16]. Overall, there is a gap in the current research literature on rigorous evaluations and information about the costs and return on investment [16,17].

In Australia, funding for home automation for people with disabilities is provided by the National Disability Insurance Agency (NDIA), an Australian government organization that funds costs associated with disability, with individual state organizations such as the Lifetime Support Authority (LSA) in South Australia funding home automation for people who sustain serious injuries following a motor vehicle accident. Internationally, funding for home automation is available in high-income countries. For example, local government councils provide grants for home automation in the United Kingdom, and support is also available through registered disability charities (National Health Service [18]). Similarly, in the United States, home automation is funded by individual state programs for assistive technology [19]. Home automation has great potential to positively impact the lives of people with disabilities.

The overarching aim of the study is to understand the impact of home automation on people with disabilities following a serious injury. The objectives of the study are as follows: (1) to describe the impact of home automation for people with long-term disability following a serious injury (eg, acquired through a motor vehicle accident) using case studies, and (2) to evaluate the Social Return on Investment (SROI) of home automation for this population. The findings from this study will provide valuable and significant information for funders,

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consumers, researchers, and the public to guide future decision making about home automation.

Methods

Design and Methodology

A steering group will be established at project commencement, involving the research project team, representatives from the funding body (LSA), a disability advocacy group, and an equipment supplier. The steering group will also include 2 consumer representatives who have experienced serious injury or care for someone with serious injury. The steering group will oversee the conduct of the study, provide accountability and transparency, inform the analysis, and support the dissemination of findings.

The study will employ a SROI approach. The SROI methodology was developed in the United States in 2000 by the Roberts Enterprise Fund [20] and subsequently refined and tested in the United Kingdom by the New Economics Foundation [21]. The approach is widely implemented in the United Kingdom due to the Department of Health encouraging health and social care research to adopt the SROI methodology and the creation of the Social Enterprise Investment Fund, which provides funding and support to organizations adopting this approach [20,22]. In recent years, SROI has gained popularity internationally, including in Australia [23-25].

SROI is a form of evaluation that commences with a theory of change to examine the relationship among inputs, outputs (activities), and outcomes. The approach is unique as it emphasizes the engagement of stakeholders to inform the analysis and for the valuation of personal, community, and societal outcomes that are not typically included in more traditional forms of economic evaluation (for example, cost-utility analysis, cost-benefit analysis, and cost-effectiveness analysis). The method captures the overall social impact of an intervention in a simple ratio such as 4:1 (indicating that Aus $4 [US $2.68] of social value has been created for every Aus $1 [US $0.67] invested). The SROI methodology has six distinct phases: (1) identify scope and stakeholders, (2) map outcomes, (3) evidence outcomes and give them value, (4) establish impact, (5) calculate the SROI, and (6) report findings [26].

Stage 1—Identify Scope and Stakeholders

Key stakeholders in home automation will be identified and invited to participate in interviews (n=10) to determine inputs (eg, assessment procedures, costs of home automation, installation and ongoing costs, time involved in the process), and intended outcomes for the home automation user. Stakeholders will be individuals involved in home automation (designer, prescriber, advisor, and installer) for people with serious disabilities, such as allied health professionals, medical practitioners, equipment suppliers, rehabilitation engineers, installers, and service and maintenance professionals.

Users of home automation will be interviewed (n=5) to determine the outcomes of home automation. The selected sample size considers the relatively small population size of people with disabilities following a serious injury requiring high levels of care and the small subgroup that uses home automation

[7]. Participants will be people who have a disability following a serious injury, have the capacity to provide consent to participate in the research, and have 1 or more elements of home automation. Where appropriate, interviews will be conducted with family members. This will be deemed appropriate when the person with disability provides consent for the family member to participate in the interview and when the family member has a good understanding of the person's home automation and daily activities.

Interviews will be semi-structured, and the interviewer will follow an interview schedule. The interviews will be conducted face to face, over the phone, or via videoconference (depending on the participant's location and preference) at a time convenient to the participant. All interviews will be audio recorded and professionally transcribed. The interview schedule will consist of 4 sections: socio-demographic questions, inputs of home automation, outputs (activities) of home automation, and the outcomes experienced (capturing negative as well as positive outcomes). The participant will also have the opportunity at the end of the interview to discuss any impacts and outcomes of home automation that have not already been discussed.

Purposive sampling will be adopted to recruit stakeholders and home automation users for the interviews. Recruitment for users of home automation will initially be done via LSA. In addition, local providers of home automation and disability organizations will be contacted to inform them about the research and to advertise the study to potential participants by sharing information, using the opt-in approach. Finally, social media (Facebook and Twitter advertisements for consumer groups) will be used to promote the research and recruit participants. Stakeholders will be recruited through the NDIA, professional networks, the LSA, organizations that provide home automation, and the steering group. An email will be sent to potential participants with information about the study, allowing them to opt in by replying to the research team. If necessary, social media (Facebook and Twitter) will be used to promote the research and advertise for potential stakeholder participants.

Stage 2—Map Outcomes

The inputs, outputs (activities), and outcomes involved in the home automation process will be mapped (this is referred to as the "theory of change"), guided by the interview data from stage 1, existing literature, and with input from the steering group. Given the wide variety of home automation options, 4 scenarios will be developed based on LSA's most common injury types relevant to requiring home automation (spinal cord injury and acquired brain injury) and the differing levels of severity of the injury and the type of home automation. The data from the existing literature and interviews will be used to develop the scenarios, and the inputs, outputs, and outcomes will be described in relation to these scenarios to provide context for the analysis and to support the interpretation of findings. Tables will be produced to illustrate the funder's inputs (costs to the funder and costs of professional services to support the use of home automation), the calculations for each scenario, and the payback period for each scenario. A scenario-based approach was recently used successfully in a SROI analysis calculating the social impact of modified vehicles for people with

disabilities, in which 5 scenarios were developed to illustrate the social return for low to high-cost modifications of vehicles [23]. A significant advantage of adopting a scenario-based approach in SROI analysis is that findings are more generalizable [23,26].

Stage 3—Evidence Outcomes and Give Them Value

Evidence of outcomes will be obtained from stage 1 interview data as well as relevant Australian and international data from published home automation studies. Values for outcomes will be obtained in two ways: (1) from extensive searches of existing SROI literature reporting the same or similar outcomes and how they were valued, and (2) from value games with participants and their families. Value games are a revealed preference approach in which participants rank an outcome without considering its market value among several items that can be purchased [27,28]. In this way, the unique value of outcomes for this population can be identified.

Stage 4—Establish Impact

The impact of home automation will be established with appropriate discounts applied to cumulated financial proxies to avoid possible overclaiming. Discounts are calculated based on what would have happened without the intervention (deadweight), what outcomes were displaced by the intervention (displacement), who else has contributed to the outcomes aside from the funder (attribution), and whether the experience of the outcomes declines over time (drop off). The "benefit period" (the period over which the social return will be calculated) will be determined. Benefit periods need to be long enough to capture the most valuable outcomes for participants, and in this context, consider the life span of home automation products.

Stage 5—Calculate the SROI

The SROI ratio is calculated with costs incurred and benefits realized at different time periods made comparable using discounting to calculate the net present value to ensure the values of the outcomes are in today's dollars. Sensitivity analysis will also be performed to determine how sensitive the SROI ratio is to changed assumptions in the calculation [27,29,30]. The payback period will also be established for each scenario to understand the period over which the costs of the intervention are "paid back" in accumulated social value.

Stage 6—Report Findings

The results will be widely disseminated in different formats for different audiences. Findings will be presented in project reports and in peer-reviewed articles. Findings will also be disseminated at relevant conferences. It is also anticipated that the Flinders University media team will share the findings internally and externally to promote the research.

Ethical Considerations

Ethical approval (human subject research) was obtained by the Flinders University Social Human Research Ethics Committee in South Australia (project number 5039) in March 2022. Participants will give informed consent and can opt out of the research. Participant's information will remain private and any identifying details will be omitted. It is acknowledged that this research is of a sensitive nature, and participants may become

upset or distressed during the interview. Participants who become upset will be comforted by the interviewer, offered details on counseling services, and may withdraw from the research if they wish. The study will include people with significant disabilities, and therefore, the interviews will be accommodating to ensure the comfort of the participant, for example, by monitoring fatigue and shorter interviews. It is also the intention that interviews will be conducted with family members on behalf of the person with the disability if this is a preferred option. Participants will also be given the option of requesting another person to be present at the interview if they wish. Potential participants will be given a participant information sheet and a consent form. All participants will be provided with the researcher's contact information and an opportunity to ask questions and discuss any aspect of the study. All study data will be stored confidentially, and any identifying data will be removed to ensure the data is deidentified. Any publications arising from the data will not identify any individual person. Informed written consent to participate in the interviews and for the use of this data for analysis will be sought from all participants. In recognition of the participant's time and contribution, they will receive an honorarium (Aus $50 [US $35] voucher) on completion of the interview.

Results

The project was funded in November 2021 by LSA (Grant No. R21005). Recruitment of participants for the interviews commenced in June 2022, and we expect data collection to be completed by October 2022. As of September 2022, we have recruited 10 stakeholders and 6 users of home automation. Data analysis will be conducted during November and December 2022, with the results expected to be published in March 2023.

Discussion

The aim of the study is to understand the impact of home automation for people with disabilities following a serious injury, and this will be achieved by describing the impact using case studies and evaluating the SROI of home automation for this population.

To our knowledge, this study represents the first study in Australia and internationally to employ a SROI methodology to estimate the social, personal, and community outcomes of home automation for people with a disability following a serious injury. SROI is advantageous because it involves both consumers and stakeholders in the analysis and valuation of personal, community, and societal outcomes, resulting in a simple ratio that demonstrates how much social value (in Aus $) is created for every Aus $1 [US $0.67] invested.

Home automation is tailored depending on an individual's needs and can range from inexpensive (Aus $200 [US $130]) to more costly (Aus $25,000 [US $20,000]) depending on the type of home automation [7]. Given the wide range of types of home automation and variations in costs, the SROI analysis will adopt a scenario approach that represents low-cost home automation through to high-cost home automation. A benefit of this approach is that the findings will be more generalizable as the

SROI analysis is not based on a single home automation scenario [23].

Home automation has the potential to offer significant benefits to people with disabilities. The World Health Organization (WHO) states home automation enables people with a disability to experience increased independence, improved health, and well-being and can also lead to a reduction in caregiver hours, impacting the broader community [13]. Recognizing the challenges encountered by individuals when accessing assistive technology in some countries, the WHO has introduced the Global Cooperation on Assistive Technology. This initiative aims to provide improved access to assistive technology for people with disabilities worldwide by reinforcing the WHO's existing strategies on people-centered and integrated health services and disability [13]. In Australia, agencies such as the NDIA advocate for access to assistive technology for people with disabilities to improve their economic and community participation, benefiting not only the individual but also their family and the wider community.

Upon completion of the study, the strengths and limitations will be summarized. The research builds on what is already known about home automation by considering the benefits of home automation reported by users in the research literature. Results will provide valuable information for funders, consumers, researchers, and the public to guide and inform future decision-making and practice about home automation. By providing a simple social return ratio, the payback period can be calculated, and comparisons between high-cost and low-cost home automation can be made to guide decisions. Furthermore, the study may be helpful to researchers who want to assess the social value of other types of interventions, and the model could be adapted for research in other fields.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

Authors' Contributions

The study was conceptualized by KL, CH, PW, and KM. JC drafted the manuscript and is leading the data collection. All authors reviewed the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

LSA: Lifetime Support Authority
NDIA: National Disability Insurance Agency
SROI: Social Return on Investment
WHO: World Health Organization

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Proposal

Clinical Source Data Production and Quality Control in Real-world Studies: Proposal for Development of the eSource Record System

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Abstract

Background: An eSource generally includes the direct capture, collection, and storage of electronic data to simplify clinical research. It can improve data quality and patient safety and reduce clinical trial costs. There has been some eSource-related research progress in relatively large projects. However, most of these studies focused on technical explorations to improve interoperability among systems to reuse retrospective data for research. Few studies have explored source data collection and quality control during prospective data collection from a methodological perspective.

Objective: This study aimed to design a clinical source data collection method that is suitable for real-world studies and meets the data quality standards for clinical research and to improve efficiency when writing electronic medical records (EMRs).

Methods: On the basis of our group's previous research experience, TransCelerate BioPharm Inc eSource logical architecture, and relevant regulations and guidelines, we designed a source data collection method and invited relevant stakeholders to optimize it. On the basis of this method, we proposed the eSource record (ESR) system as a solution and invited experts with different roles in the contract research organization company to discuss and design a flowchart for data connection between the ESR and electronic data capture (EDC).

Results: The ESR method included 5 steps: research project preparation, initial survey collection, in-hospital medical record writing, out-of-hospital follow-up, and electronic case report form (eCRF) traceability. The data connection between the ESR and EDC covered the clinical research process from creating the eCRF to collecting data for the analysis. The intelligent data acquisition function of the ESR will automatically complete the empty eCRF to create an eCRF with values. When the clinical research associate and data manager conduct data verification, they can query the certified copy database through interface traceability and send data queries. The data queries are transmitted to the ESR through the EDC interface. The EDC and EMR systems interoperate through the ESR. The EMR and EDC systems transmit data to the ESR system through the data standards of the Health Level Seven Clinical Document Architecture and the Clinical Data Interchange Standards Consortium operational data model, respectively. When the implemented data standards for a given system are not consistent, the ESR will approach the problem by first automating mappings between standards and then handling extensions or corrections to a given data format through human evaluation.

Conclusions: The source data collection method proposed in this study will help to realize eSource's new strategy. The ESR solution is standardized and sustainable. It aims to ensure that research data meet the attributable, legible, contemporaneous,

original, accurate, complete, consistent, enduring, and available standards for clinical research data quality and to provide a new model for prospective data collection in real-world studies.

Introduction

Background

Real-world data (RWD) are the data relating to patient health status and delivery of health care routinely collected from a variety of sources [1]. Real-world evidence (RWE) is clinical evidence regarding the use and potential benefits or risks of a medical product derived from analysis of RWD [1]. A real-world study (RWS) collects RWD in a real-world environment and obtains RWE of the use value and potential benefits or risks of medical products through analysis. There is considerable interest in the use of RWD to generate RWE to support regulatory decisions regarding the effectiveness of medicines. However, large data sets of uncertain quality and origin, lack of readily available analytical tools, and lack of sufficiently methodologically proficient researchers can lead to flawed study designs and analyses that yield incorrect or unreliable conclusions [1]. Although important advances are being made in the field of methodologies to access RWD, these factors are not sufficient to fully overcome the fundamental issues of confounding, data quality, and bias [1]. The US Food and Drug Administration (FDA) states that gaps in RWD sources need to be addressed first, as electronic health record (EHR) and medical claims data may not capture all the data elements needed to answer questions of interest [2]. Another important challenge is the difficulty in connecting or integrating the various data sources that provide information about individual patients [3]. The review by Grimberg et al [4] outlines the RWD challenge radar and summarizes the challenges and risks of using RWD from 3 perspectives (organizational, technological, and people-based), for example, inefficient data collection, lack of data quality control, diversification of data standards, and facing data compliance issues [4].

In clinical studies, source data refer to all the information in the original records or their certified copies, including clinical findings, observation results, and records of other relevant activity that are necessary for the reconstruction and evaluation of the trial [5]. eSources are data that are originally recorded in an electronic format. An eSource generally includes the direct capture, collection, and storage of electronic data (eg, electronic medical records [EMRs], EHRs, or wearable devices) to simplify clinical research [6]. It can improve data quality and patient safety and reduce clinical trial costs. However, owing to many challenges [7], such as limited interoperability of EMRs and electronic data capture (EDC) systems, unstructured data (eg, researcher notes or comments), and the need for some data (eg, research-specific data that are not included in the EMR) to be manually transcribed and treated, accessing and correcting the source data in real time during data collection can be slow.

Despite the existence of several FDA guidelines [6,8] and European Medicines Agency guidelines [9], the development, implementation, and evaluation of EMR-specific electronic resource solutions are limited. The ideal eSource technology will be able to completely bypass EDC data input, capture the source data directly from EMR, and transmit it to an electronic case report form (eCRF). In the past 10 years, a variety of eSource solutions have been developed, evaluated, and improved [10-12]. There has been some eSource-related research progress in relatively large projects, such as the OneSource project, Electronic Health Records for Clinical Research project, and Seventh Framework Program–Translational Research and Patient Safety in Europe project [13-15]. However, most of these studies focused on technical explorations to improve interoperability among systems to reuse retrospective data for research. Few studies have explored source data collection and quality control during prospective data collection from a methodological perspective.

The attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, and available (ALCOA+) standard has been adopted in the guidelines and industry norms of many regulatory agencies and has become a recognized quality standard for clinical research data [16]. The FDA and European Medicines Agency use ALCOA+ as a guide for protecting data integrity. The World Health Organization has also issued *Guidance on Good Data and Record Management Practices* based on this principle [17]. Good documentation practices and data integrity are integral elements of data management and the foundation of any quality system. The ALCOA+ principles are the cornerstone of good documentation practices and apply to both electronic and paper data. At the good clinical practice (GCP) seminar held in 2020 [18], the FDA and the UK Medicines and Healthcare Products Regulatory Agency proposed new global challenges to data integrity, such as the use of eSource, EHR, and other patient data repositories as RWD sources. Although regulators in different countries have recently issued guidance and strategies to enhance data integrity [17,19-22], challenges remain in how to apply this principle in practice to safeguard data integrity in RWD.

Source data verification (SDV) means to check the consistency of data recorded in the database with the source data, and it is a key link in maintaining data accuracy in quality control and evaluating data integrity in on-site verification by regulatory authorities. In China, external access and data sharing are not possible owing to the sensitivity of medical data. Therefore, SDV is usually performed using a printed and signed copy of EMRs. Owing to the inability to reconcile hospitals' concerns about the privacy of patient medical data and researchers' needs for data transparency, the transformation and upgrade of EMR

systems by existing medical system providers still cannot meet the requirements of clinical research [23].

Data integrity in clinical research is a critical issue for both the health care system and research community, and the consequences of not maintaining data integrity can be severe, including regulatory violations, need for additional research, reputational damage, and paper retraction. A retraction analysis of clinical studies has shown that it is important to develop processes that enhance the detection of defective products in their respective likely environments [24]. After the China National Medical Products Administration issued the most stringent data verification requirements in 2015, a total of 80% of studies on new drug applications were withdrawn [25]. In 2016, a foreign researcher published an article in the *British Medical Journal* claiming that 80% of China's clinical trial data were fraudulent, which brought great reputational damage to China's clinical research field [26]. In 2018, our team presented an opinion in the *British Medical Journal's* international community on how to protect the accuracy of clinical trials in China [23]. We propose a solution to improve the integrity of clinical research data in China by using the hospital clinical research source data management platform and source data management process architecture. A clinical source data management platform for electronically synchronizing and storing all study-related source data not only protects the integrity and accuracy of study data but also facilitates SDV by internal or external supervisors, auditors, and researchers themselves.

Currently, there are many medical standard–setting organizations and institutions dedicated to the interoperability of EMRs to support RWD collection and analysis [27]: (1) diverse common data models, such as Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model, Observational Medical Outcomes Partnership [28], FDA Sentinel [29], and National Patient-Centered Clinical Research Network [30], and (2) data exchange standards, such as the Health Level Seven Fast Health Interoperability Resources [31], CDISC operational data model (ODM) [32], and openEHR. However, these standards are not yet able to address all of China's needs, and much work is still needed before they can be implemented. Improving medical data interoperability cannot fundamentally solve the problem of data integrity. In addition, except for some large state-funded projects, most of the research is limited to case studies, thus failing to propose a general theoretical method, and very few studies can achieve the transformation from theory to results, real implementation, and promotion.

In the previous study by our research group, a hospital clinical research source data management platform and source data management process architecture were proposed [33]. The core factor for improving the quality of research data is the promotion of the electronification of clinical research source data; in particular, there is a need to break through the barriers between the clinical diagnosis and treatment data and the clinical research system. Subsequently, the research group explored an RWD collection mode based on hospital informatization and verified it using an RWS of medical devices [34]. The study found that when natural language processing (NLP) was used, the

completion time was reduced by 90% compared with methods that relied on manual input [34].

This Study

This study is an in-depth exploration based on previous results. Using the eSource concept, we designed a source data collection method for clinical medicine that is suitable for RWSs, meets the data integrity standards for clinical research, and realizes electronic transmission from source data to clinical research data. We developed a piece of software using the proposed method and applied it to an RWS to verify its feasibility [35].

Methods

Design and Optimization of the Source Data Collection Method

On the basis of the task decomposition steps proposed by the ALCOA+ principles, we designed the method by referring to the eSource logical architecture diagram proposed by TransCelerate BioPharm Inc [7], RWD, eSource-related regulatory guidelines [2,3,6,8,9,36-38], and the research group's previous experience. In the process of designing and optimizing the method, the members of the research team and experts in related fields extensively solicited, communicated, and discussed suggestions through focus groups and expert consultations. Experts in related fields included the big data company's technical staff (product managers, front-end and back-end developers, etc), clinical trial personnel in different roles (principal investigators, clinicians, project managers, clinical research associates [CRAs], clinical research coordinators [CRCs], data managers [DMs], etc), hospital information personnel, experts from the drug regulation department, and so on. Using this method, we cooperated with a big data company to develop the eSource record (ESR) system. The ESR system is a piece of software that is implemented in a hospital in addition to an EMR system and a trial management system (such as an EDC system). It can be considered as a connecting bridge between an EMR system and EDC system. To create a complete set of clinical research source data solutions, we invited experienced experts from EDC companies in different clinical trial roles to provide their input. Guided by GCP principles, we addressed the issue of data connection between an ESR and EDC system.

Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki. Ethics approval was obtained from the Peking University's institutional review board (IRB00001052–21081).

Task Decomposition of ALCOA+ Principles in Source Data Collection Methods

A—Attributable

It can be very simply summarized as that the person who performs the data-related task must be the person who performs the task. For any operation, an ESR system should reliably track only the user who created, modified, or deleted the data. The entire process from the source data to the final analysis data set should be clearly recorded. The producer of each source datum, date and time it was produced, relationship between the source

datum and its attributor (such as the patient), reason for the modification of the source data and related evidence, and so on should be clearly reflected in the quality of the source data in the chain of custody.

L—Legible

The data should be readable and understandable and clearly show the sequence of steps or events the data have gone through. It should cover the terminology mapping function and use CDISC standard terminology as much as possible. The ESR solution has designed but has not yet implemented a standard terminology input mode that can correct mistakes in terminology use for documentation.

C—Contemporaneous

Data activities should be time-stamped, and the time of occurrence should be recorded. ESR can use recording and other functions to retain the voice recording of the physician during the consultation of the patient and to realize the real-time collection of source data.

O—Original

All the initially captured data must be retained; they should not be replaced or deleted. ESR should preserve the source data to ensure the originality of the original record. It should only back up the data in the hospital and the data outside the hospital, without any data cleaning operations, to ensure the originality of the certified copy. The certified copy of the original record shall be verified as having all the same attributes and information as the original record and shall be certified according to the dated signature. All recording files and various source files, such as pictures uploaded during optical character recognition (OCR), will be retained.

A—Accurate

Data input, storage, and maintenance should be accurate and effective. ESR conducts quality control on data through multiple links, such as electronic system verification; clinician medical record writing; data encryption; transmission; management process; and CRC, CRA, and DM verification, to ensure the accuracy of data.

C—Complete

The data should have a traceable audit trail to prove that nothing has been deleted or lost. ESR can highlight the uncollected indicators in the medical record writing promptly to remind the clinician to record the research indicators completely. It can also check the integrity of the data through the data quality control link and return it to the clinician. The CDISC ODM data standard format for eCRF is not widely or professionally implemented in China because it is not a requirement for drug submissions. However, EDC companies have started to implement CDISC ODM as a method of data exchange. Currently, the ESR solution uses the CDISC ODM as a method of data exchange with EDC companies. However, certain features, such as the audit trail feature, are not implemented consistently by different EDC companies; therefore, the CDISC ODM format used by the ESR will vary based on the partnered company.

C—Consistent

Regardless of where the data are accessed from, they should be displayed consistently. The ESR can verify the consistency of source data and research data through CRC verification, and the CRA and DM can perform traceability verification, raise data questions, and further check consistency.

E—Enduring

Records and information should be accessible and readable for the entire period that they may be needed, possibly decades after they are recorded. The ESR can prevent data loss in the event of interruption through system backup. Verified electronic record backup should be provided to ensure disaster recovery.

A—Availability (Available)

All applicable personnel responsible for reviewing or operating procedures should access files and records in a readable format. The ESR can output source data in an appropriate format for reference through processes such as data processing, data structuring, and data standardization.

Results

Description of the Source Data Collection Method

Overview

The method includes 5 steps: research project preparation, initial survey collection, in-hospital medical record writing, out-of-hospital follow-up, and eCRF traceability. A flowchart of this method is shown in Figure 1.

Figure 1. Flowchart of the source data collection method. CRC: clinical research coordinator; eCRF: electronic case report form; HIS: hospital information system; NLP: natural language processing; OCR: optical character recognition.
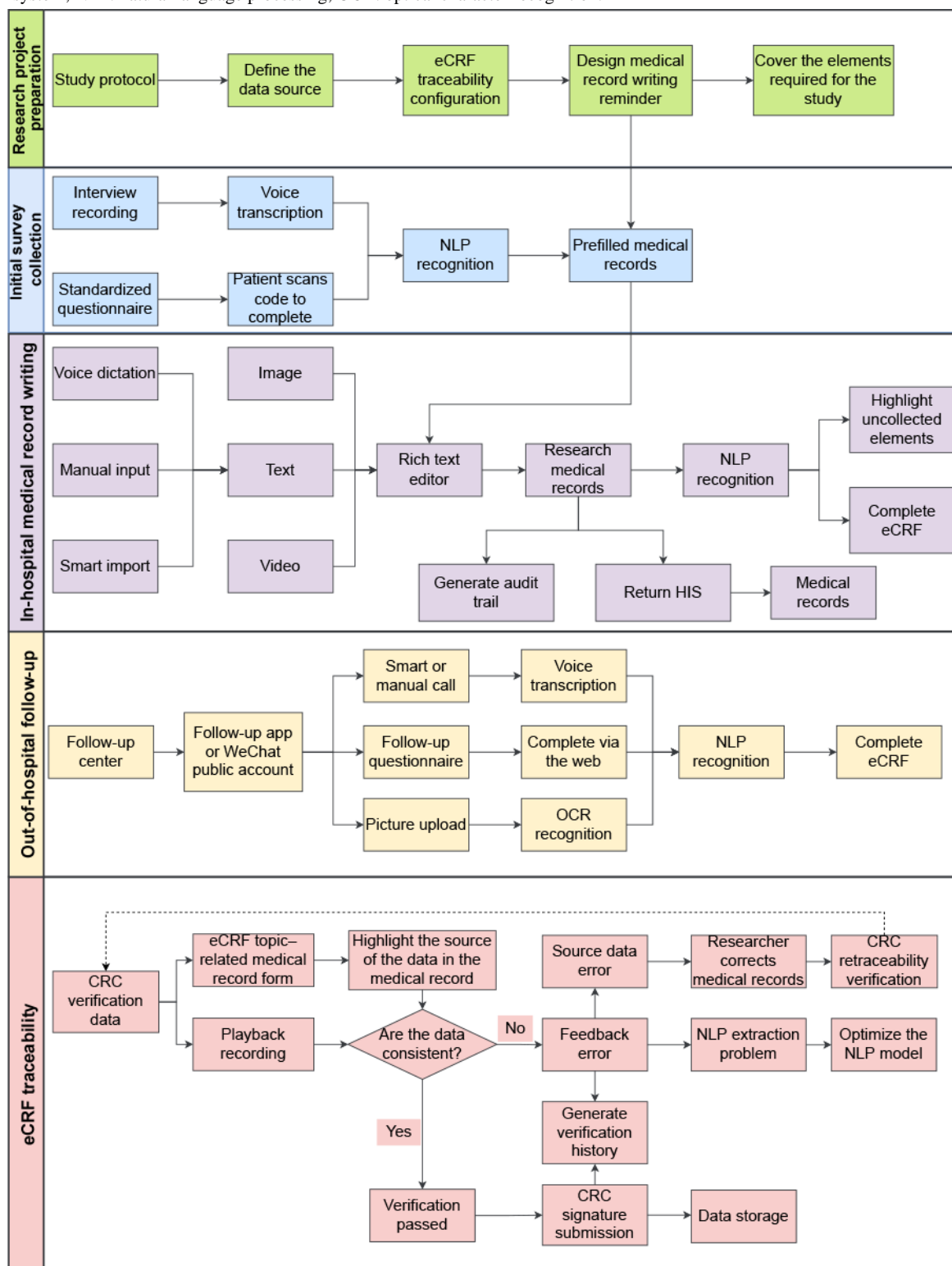
Research Project Preparation

In the preparation stage of a research project, such as a randomized controlled trial, the researcher needs to determine the research plan. The plan should clearly define the data elements that need to be collected; determine the data source and data type; and define the source data collection method, time of data collection, and personnel who will collect the data.

According to the data sources, research data can be divided into data collected by the hospital electronic system, additional data collected during research, and data collected outside the hospital. The data collected by the hospital EMR system are medical data generated by the patient during the hospital visit or hospitalization; these may include EMR data, medication data, and medical insurance data. Research-specific data are additional data collected in the hospital according to the needs of the

research project; these may include the recording of certain additional index data during surgical operations. Data collected outside the hospital are research-related data that are generated after the patient is discharged and may include follow-up data such as adverse events. Research data are divided into 2 data types: structured data and unstructured data. An eCRF can be designed based on the research plan. eCRF topics can be associated with the EMR form to configure the traceability path of different eCRF topics. For example, demographic data in eCRF can be traced back to the admission record form in the EMR. However, routine medical records do not contain certain necessary research-specific data, such as scale scores. Therefore, after completing the eCRF traceability configuration, clinicians can design medical record writing prompts and rules for the eCRF that conform to clinical habits and meet their data collection requirements, to cover the elements required for research and standardize the EMR recording process among different clinicians.

Initial Survey Collection

The collection of research data can be divided into initial survey collection and in-hospital medical record writing. During the collection of initial survey data, the clinicians' workload when writing EMRs can be reduced with the use of voice transcription and NLP technology and by allowing patients to fill in some of the information. For example, as the hospital admission medical record (basic information and past history) involves few complicated medical terms, a standardized questionnaire can be created, and the patient can scan a QR code to access it and complete it. The data for the main complaint and current medical history sections can be collected by clinicians through a traditional medical history interview; then, the dialogue between the clinician and patient is transcribed into text in real time using voice transcription technology, and information such as symptoms, medicines, time, disease diagnosis, and so on are analyzed and extracted using NLP technology. Finally, this information is prefilled into the medical records.

In-Hospital Medical Record Writing

In-hospital medical record writing is the process by which clinicians write medical records according to the research medical record template. The rich text editor allows clinicians to record information such as text, pictures, and videos. Data input methods for text-type information are divided into voice dictation, manual input, and intelligent import. Intelligent import technology refers to the automatic or semiautomatic transmission of clinical data from one data field or system to another data field or system (eg, via copy and paste, autofill, barcode scanning, or image OCR). Clinicians further process and sort machine-prefilled medical records and record the source data from the medical encounter in a timely and complete manner to create research medical records. NLP technology can highlight elements that are not collected by clinicians in real time as they write medical records. For medical records that have been completed and submitted with signatures, NLP can extract research data from the background and automatically complete the eCRF. The system can track all the revisions that clinicians have made in the research medical records for verification. As the research medical records were recorded by

the software we designed, to connect them to the hospital's EMR system, we transferred all the research medical records back to the EMR in the form of documents to create a medical record. This avoids the need for clinicians to complete the medical records twice in the 2 systems, because records completed in accordance with research requirements include more information and can meet the requirements for medical records.

Out-of-Hospital Follow-up

Through the follow-up center, clinicians can use follow-up apps or official WeChat accounts to collect out-of-hospital data needed for research. After setting the trigger conditions for the follow-up start time, frequency, and format, the system can automatically send the follow-up questionnaire to the patient, who can complete the questionnaire via the web. It is also possible to use smart or manual calls for follow-up questions; this allows patients to participate in question-and-answer dialogues, which the system can then transcribe into text. For laboratory examinations and imaging performed outside the hospital, the system offers file upload functions and OCR of pictures and text. After summarizing these different forms of follow-up data, NLP extracts these contents and enters them into the eCRF.

eCRF Traceability

In the steps mentioned previously, NLP automatically extracts research data from EMRs and out-of-hospital follow-up records and uses them to complete the eCRF. This can greatly reduce the workload of the CRC, who will no longer need to manually complete the eCRF and can focus on data verification. As the researcher completed the configuration of the eCRF topic and medical record form during the preparation phase of the research project, when the CRC opens the eCRF traceability function, the EMR written by the physician and the eCRF form will be displayed on the screen at the same time. When the CRC clicks on the eCRF topic, the system can automatically scroll to locate and highlight the position of answers in the source file. The CRC can also be led to the sources of data by playing the recordings maintained in the system (eg, recordings of consultations or medical records created by physicians using voice input). Then, the CRC can check whether the data recorded in the source file are consistent with the data extracted by NLP. If all the data pass this check, the CRC will sign and submit the certification to complete the data storage. If the CRC finds inconsistent data, they can provide feedback indicating the presence of an error. For problems related to NLP extraction, the CRC can make manual corrections and provide feedback to the technicians to optimize the NLP model. If there is an error in the source data, such as an error introduced by the physician during the writing of the medical record, feedback is provided to the clinician, who will correct the content of the EMR and resubmit it. The NLP will extract it again, and the CRC will recheck the issue. The system will record the history of all the CRC verifications.

Data Docking Between the ESR and EDC

Although the ESR that we designed can theoretically integrate EDC functions, as the implementation of this method requires

a transition phase and integration of the CDISC Clinical Data Acquisition Standards Harmonization data standard used by EDC, we will discuss the process of creating a data connection between the ESR and EDC (Figure 2). First, clinicians and data administrators enter the EDC to create an empty mirror eCRF based on the CDISC data standard and pass it to the ESR system. The eCRF is decomposed using the abovementioned source data collection method, and the research medical record writing requirements and configuration traceability paths corresponding to different data collection points are designed. The ESR integrates out-of-hospital data and process supervision source data. Clinicians need to write their medical records only on the ESR, and the ESR can automatically synchronize data with the in-hospital EMR system. The intelligent data acquisition function of the ESR will automatically complete the empty eCRF to create an eCRF with value. Then, the in-hospital, out-of-hospital, and process supervision data can be backed up to form a certified copy database. The certified copy database needs to undergo data management to create a clinical research database. Then, the CRC can use ESR functions such as audio replay, picture review, and highlight traceability desensitization data to track the clinical research database in real time to verify the valued eCRF data and submit it to create a confirmed eCRF. By transmitting data that mirror the eCRF values, the EDC

receives and submits the eCRF. When the CRA and DM conduct data verification work, they can query the certified copy database through interface traceability and send data queries. The data queries are transmitted to the ESR through the EDC interface. If the source data are incorrect, they will be generated in the ESR system, and the corresponding researchers will be notified to correct the medical records. For the ESR system to send data queries to the EMR system, the EMR company adds a module to visualize the ESR interface; therefore, all notifications or queries can be directly handled within the EMR. Researchers can choose to correct the source data via the web or offline in the EMR system. If some supplementary research data are recorded through the ESR system, the correction of source data can be completed via the web in the ESR system. After completing the source data correction, ESR automatically synchronizes the source data to the certified copy database again, re-extracts the research data, completes the eCRF, and finally passes the eCRF values to the EDC system through the interface. The data verification process described previously is performed until the verification is completed. When all data verification is completed, the principal investigator can sign and lock the database to secure the research and analysis data that can be used by statisticians.

Figure 2. Data docking between the eSource record (ESR) and electronic data capture (EDC) systems. CRO: contract research organization; eCRF: electronic case report form; EMR: electronic medical record; NLP: natural language processing.
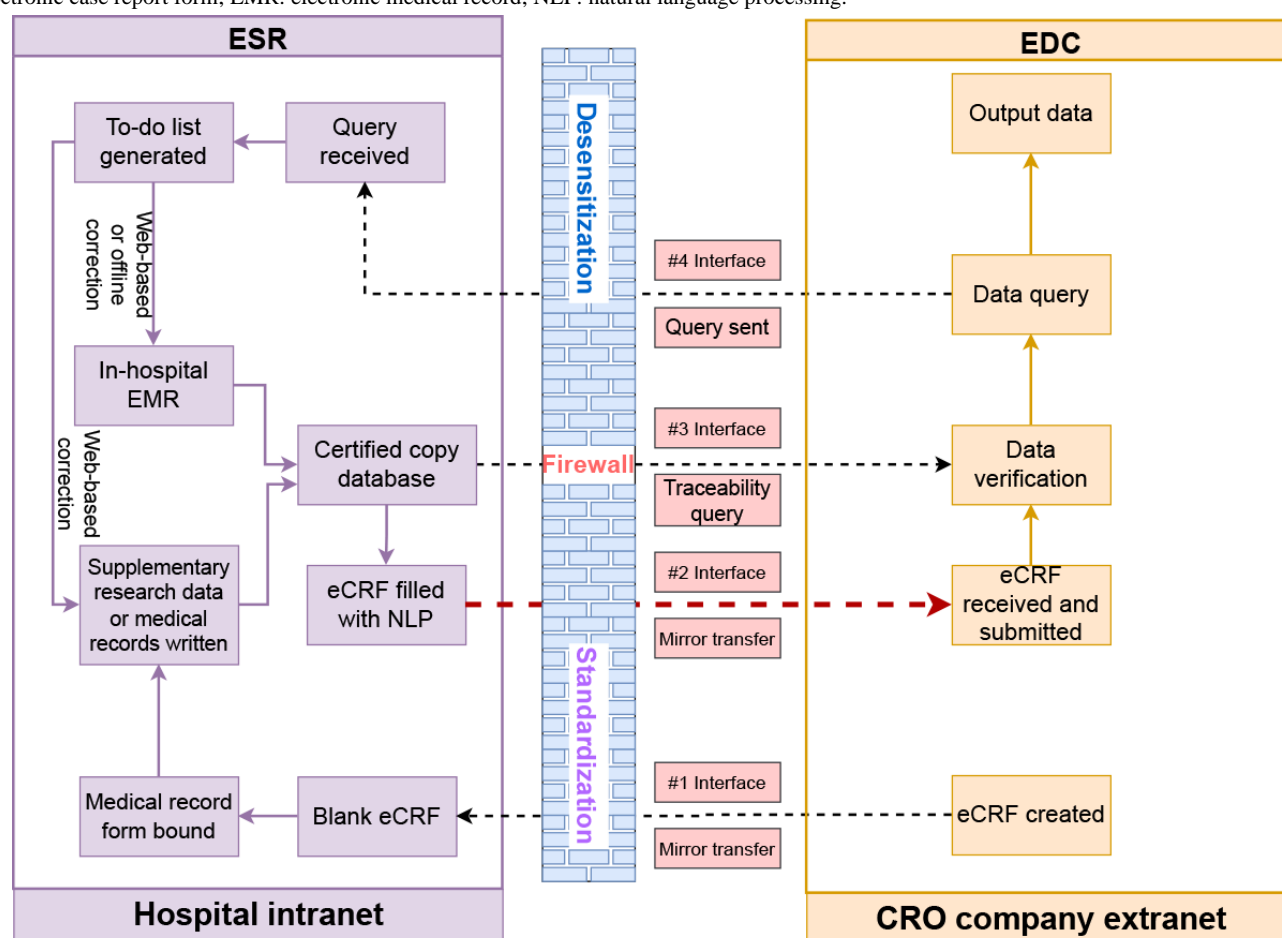
Data Standard Transformation From RWD to Research Data

Research data need to communicate with source data systems if data integrity is to be met. There are 2 approaches mentioned in the relevant FDA report [8], including interoperable systems and fully integrated systems. Data integrity can be fully guaranteed only if clinical researchers are allowed to enter study data directly into the EHR (fully integrated system). In contrast, interoperable systems usually only pass a portion of the data that are mature and standardized. EDC and EMR systems will interoperate through the ESR. The EMR and EDC systems transmit data to the ESR system through the data standards of Health Level Seven Clinical Document Architecture and CDISC ODM, respectively. When the implemented data standards for a given system are not consistent, ESR will approach the problem by first automating mappings between standards and then handling extensions or corrections to a given data format through human evaluation. The ESR can receive the familiar document format in the EMR and eCRF fields through EDC, provide writing suggestions in the EMR document, and send the suggestions back to the EMR system. The ESR process includes 5 steps, as shown in Textbox 1 [39,40].

Textbox 1. Steps in the eSource record (ESR) method.

Step 1

- Electronic data capture sends the eCRF and electronic medical record sends the patient clinical form to the ESR system. The source data collection module of the ESR system will be responsible for the annotation of electronic medical records, whereas the data transcription module of the ESR system will be responsible for locking the electronic case report form (eCRF) field to capture text segments of source data, complete the eCRF, and generate a traceability interface for clinical research coordinator review.

Step 2

- The second step involves modeling the research data set and generating labels. Structured data are directly mapped to the Clinical Data Interchange Standards Consortium (CDISC) model. Unstructured data do not have a widely used intermediate layer and do not consider the Observational Medical Outcomes Partnership model but directly converts to the CDISC model. The process of converting unstructured data to research data requires annotating the text and extracting the relevant content using natural language processing models.

Step 3

- The third step involves model training and extraction of entities and relationships between entities. Regarding entity extraction, the Chinese-named entity recognition model of bidirectional encoder representation from transformers, bidirectional long short-term memory neural networks, and conditional random fields are used.

Step 4

- The fourth step involves the generation of research-specific term database. The research-specific term database refers to the mapping library between the actually extracted terms in the tags and the standard terms. The establishment of a research-specific term database requires the extracted tags, CDISC operational data model code lists, and international standard terms (such as International Classification of Diseases 10th Revision).

Step 5

- The final step is related to normalization rules after entity extraction and before completing the eCRF. The output of the natural language processing model mainly has 2 tables, including the list of all the extracted label values (entity table) and the list of relationships between entities (entity relationship table). The first task was to assign each entity label with a standard value and standard label type using a research-specific term database. The second task was to convert the entity relationship table to a single record based on the domain.

Case Verification

In 2021, we selected an RWS to evaluate the effectiveness and safety of cosmetic medical equipment (cross-linked glucan) for chin augmentation in the Boao Lecheng pilot zone. The interface that allows the CRC to use the ESR for data traceability verification is shown in Figure 3. This figure shows the interface under the eCRF traceability verification label. The contents of the outpatient medical records are shown on the left. The eCRF topic is shown on the right. When the mouse stays in the answer box for "body temperature" on the right, the answer "36 °C" is retrieved from the text related to the physical examination and is highlighted on the left. The operation interface for CRC or DM traceability in EDC is shown in Figure 4. This figure shows the interface under the eCRF traceability verification label. The contents of the outpatient medical records are shown on the right. The eCRF topic is shown on the left. When the mouse stays in the answer box for "body temperature" on the right, the answer "36 °C" is retrieved from the text related to physical examination and highlighted on the left. When you click the *retrospect* function in the drop-down menu, the original record will pop up and the text will be highlighted. This figure shows the body weight from the physical examination part of the outpatient medical record. Details about case verification are available in our previously published study [41]. The preliminary evaluation shows that in the clinical medical environment, the ESR-based eSource method can improve the efficiency of source data collection and reduce the workload required to complete data transcription [41]. Since the initial verification in this RWS, we have collaborated with many other projects for more extensive verification. These pilot projects have begun the process of deploying the tool in hospitals and will start soon. A project currently using the ESR is the RWS on the safety and efficacy of injectable cartilage-regenerating collagen fillers for

the treatment of cartilage damage. At the same time, we have initiated collaboration with medical system providers to develop a way to integrate this tool with EMRs. These rich cases will provide a large amount of data for evaluating the value of the tool and promoting the development of clinical research in China.

Figure 3. The clinical research coordinator interface for data traceability verification in the eSource record.

Figure 4. Interface for traceability operation in electronic data capture.

Discussion

Principal Findings

Although previous studies have applied Fast Health Interoperability Resources or openEHR standards to interoperability cases to serve as experiential references [42,43], clinical research data include research-specific data that are not routinely recorded in the EMR. In addition, the free-text data recorded by the physician in medical records are not adequate to meet these data standards, and additional data must be extracted using NLP technology. Wehrle et al [44] created a data control framework to support high-quality RWSs using the NeuroTransData system to collect data from registry databases in multiple disease areas. Although this study covers the data

cycle from input to analysis, the limitation is that SDV cannot be performed on all data. The method randomly sampled data from only 10 patients per year and investigated the consistency of source data documentation in EHRs, practice management software systems, and NeuroTransData registry. The study by Chatzidimitriou et al [45] illustrated the challenges and solutions for collecting and analyzing RWD using the chronic lymphocytic leukemia database as an example. The researchers proposed a unified data management framework to allow the collection of homogeneous high-quality data sets and the connection of multiple forms of biological and medical information. The main limitation of this framework is that it does not include quality control measures for SDV. Abdolkhani et al [46] discussed wearable health data solutions for RWD quality control in a workshop format. However, this study only proposed 5 general solutions for the attributes of health data and has not yet formed a complete theoretical framework.

Our study explores ways to implement eSources when conducting clinical research in the current medical environment. Our ESR solution provides novel options for addressing these challenges. It is simple and can be easily implemented, without requiring changes in the medical system. By managing data from different sources, the ESR can meet the requirements of data standards and provide traceability for verification. It can address the scientific research pain points of clinicians in the following ways: (1) clinicians can formulate medical record writing rules consistent with their clinical habits that comply with the research plan; (2) NLP tools can be integrated into web-based operations, allowing clinicians to extract text information without any experience in programming; (3) on the basis of the initial model and the corpus marked by clinicians, the model can undergo dynamic learning and optimization; (4)

after the model meets the expected requirements, it can automatically label and extract information, which solves the problems related to traditional manual data collection; and (5) a feedback loop is established for clinicians' case writing to improve subsequent medical record writing specifications and ultimately ensure high quality of research data.

Limitations

Just as the data standards and use communities of different data models are different, the ESR will inevitably face some challenges in its follow-up, such as how to integrate with the EMR as a lightweight plug-in to improve clinicians' acceptance when connecting to EDC and health information systems produced by different manufacturers. The biggest hurdle is that China's hospital medical record system vendors built their systems long before industry standards were implemented, resulting in lack of standards that could be used for data exchange. Finally, all the challenges of implementing ESR presented by different stakeholders are not fully addressed in this study.

Conclusions

The main contribution of this study is the creation of a source data collection method that realizes a new eSource strategy. The ESR solution aims to meet the ALCOA+ standards for clinical research data integrity and provide a new model for prospective data collection in RWSs. Unlike other attempts to solve data interoperability, which are not always applicable, the ESR that we proposed was designed in accordance with the GCP principle, which is standardized and sustainable. The integration of NLP technology into the ESR improves its flexibility, thus increasing the ease with which clinicians can extract research data.

Data Availability

Data sharing is not applicable to this paper, as no data sets were generated or analyzed during this study.

Authors' Contributions

All the authors contributed to the study. BW wrote the first draft of the manuscript. CY conceived the idea for this study. BW, XL, JL, and FJ participated mainly in the preliminary design of the method. HZ is the product manager of the eSource record system. CY provided critical comments and revised the manuscript. All the authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ALCOA+: attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, and available

CDISC: Clinical Data Interchange Standards Consortium
CRA: clinical research associate
CRC: clinical research coordinator
DM: data manager
eCRF: electronic case report form
EDC: electronic data capture
EHR: electronic health record
EMR: electronic medical record
ESR: eSource record
FDA: Food and Drug Administration
GCP: good clinical practice
NLP: natural language processing
OCR: optical character recognition
ODM: operational data model
RWD: real-world data
RWE: real-world evidence
RWS: real-world study
SDV: source data verification

Protocol

Experiences of Health Care Access Challenges for Back Pain Care Across the Rural-Urban Continuum in Canada: Protocol for Cross-sectional Research

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Abstract

Background: Back pain is common and costly, with negative impacts on both individuals and the health care system. Rural, remote, and Indigenous populations are at greater risk of experiencing back pain compared to urban and non-Indigenous populations. Potential barriers to health care access among Canadians with chronic back pain (CBP) have been identified; however, no study has used lived experiences of people with CBP to drive the selection, analysis, and interpretation of variables most meaningful to patients.

Objective: The aims of this study are to (1) engage with rural, remote, and urban Indigenous and non-Indigenous patients, health care providers, and health system decision makers to explore lived experiences among people with CBP in Saskatchewan, Canada; (2) cocreate meaningful indicators of CBP care access and effectiveness; and (3) identify program and policy recommendations to overcome access barriers to CBP care.

Methods: In phase 1, one-on-one interviews with 30 people with current or past CBP and 10 health care providers residing or practicing in rural, remote, or urban Saskatchewan communities will be conducted. We will recruit Indigenous (n=10) and non-Indigenous (n=20) rural, remote, and urban people. In phase 2, findings from the interviews will inform development of a population-based telephone survey focused on access to health care barriers and facilitators among rural, remote, and urban people; this survey will be administered to 383 residents with CBP across Saskatchewan. In phase 3, phase 1 and 2 findings will be presented to provincial and national policy makers; health system decision makers; health care providers; rural, remote, and urban people with CBP and their communities; and other knowledge users at an interactive end-of-project knowledge translation event. A World Café method will facilitate interactive dialogue designed to catalyze future patient-oriented research and pathways to improve access to CBP care. Patient engagement will be conducted, wherein people with lived experience of CBP, including Indigenous and non-Indigenous people from rural, remote, and urban communities (ie, patient partners), are equal members of the research team. Patient partners are engaged throughout the research process, providing unique knowledge to ensure more comprehensive collection of data while shaping culturally appropriate messages and methods of sharing findings to knowledge users.

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Results: Participant recruitment began in January 2021. Phase 1 interviews occurred between January 2021 and September 2022. Phase 2 phone survey was administered in May 2022. Final results are anticipated in late 2022.

Conclusions: This study will privilege patient experiences to better understand current health care use and potential access challenges and facilitators among rural, remote, and urban people with CBP in Saskatchewan. We aim to inform the development of comprehensive measures that will be sensitive to geographical location and relevant to culturally diverse people with CBP, ultimately leading to enhanced access to more patient-centered care for CBP.

International Registered Report Identifier (IRRID):   DERR1-10.2196/42484

Introduction

Back pain is a common and costly health problem, as well as the leading cause of disability worldwide [1]. In Canada, 1 in 5 adults experience chronic back pain (CBP) [2], with associated health care costs estimated at US $6 billion to US $12 billion annually [3]. Canadians living in rural/remote areas are 30% more likely to experience CBP compared to urban dwellers, with Indigenous people reporting disproportionately higher rates [4]. CBP negatively impacts an individual's quality of life and the health care system due to high rates of primary physician care visits [5], specialist consultations, diagnostic procedures [6], and opioid use [7]. Early access to physiotherapy care among people with back pain can result in up to 89% less likelihood of opioid prescription [8]. Therefore, improving access to nonpharmaceutical back pain treatment options such as physiotherapy is an especially important public health issue in Canada.

People living with CBP in Saskatchewan and Canada face diverse barriers to accessing physiotherapy services, which include the geographical location of the services, costs, and wait times [9-13]. In large geographic spaces like Saskatchewan, approximately 36% of the population live in rural settings; however, only 10% of the physiotherapists practice in these communities [12,14]. Approximately one-third of the Canadians do not have additional health insurance that would help to cover costs of care for treatments such as physiotherapy services [5], which are typically not covered through the provincial public health system. In conjunction with reduced access and limited resources to support publicly funded physiotherapy services, the lack of interprofessional team support in rural settings are key challenges identified by Canadian physicians [15]. In Saskatchewan, a prior evaluation of an urban-based spinal triage service (a collaborative practice model between orthopedic surgeons and physiotherapists developed to reduce wait times and address the problem of excessive referrals that were largely nonsurgical candidates) found that more than 70% of the patients referred to the service were from rural and remote communities [16]. Patients and providers of this service highlighted specific gaps in primary and rehabilitation care in rural and remote contexts, including reduced access to appropriate and timely care [11]. This is emerging as a critical challenge in Canada for individuals living with CBP.

In addition to non-Indigenous populations in rural and remote locations facing disparities in access, Indigenous populations experience unique inequities in their access to CBP care and are 30% more likely to experience CBP [4]. There is a paucity of data on the experiences of Indigenous peoples living with CBP in Canada. Within the scope of this paper, Indigenous refers to unique and distinctively different population groups, including First Nations (specifically Cree) and Métis peoples. Research examining CBP among Aboriginal people in Australia found that this condition can be profoundly disabling and that issues of sex and gender, cultural obligations, and emotional consequences are important considerations for health care [17]. Similarly, in Canada, a complex constellation of historical, psychosocial, cultural, and environmental factors influences general health and well-being among Indigenous people [4,18]. Racism and discrimination, rooted in Canada's history of colonization and intergenerational trauma, play a significant role impacting disparities in access to health care and health outcomes, including CBP [19-22]. To redress these disparities and inequities, improve CBP outcomes, and inform culture- and strength-based strategies/interventions, we must work in partnership with and among Indigenous community members to obtain a greater understanding of the unique characteristics, strengths, needs, and challenges that are negotiated daily. Actively engaging Indigenous community members throughout the research process can ensure that Indigenous worldviews, language, culture, community practices, and protocols are followed and will inform how we can enhance and measure health care access and delivery in culture-based and meaningful ways.

Although the potential barriers to health care access among Canadians with CBP have been identified through population-based secondary data analyses [9] and through qualitative exploration of focused population groups (eg, farmers [23], patients receiving spinal triage service [24]), no known study in Canada has used the lived experiences of people with CBP to drive the selection, analysis, and interpretation of variables that are most meaningful to patients. Furthermore, no published studies have integrated Indigenous perspectives into identifying measures that will be relevant to informing future interventions, policies, and service provision to Indigenous peoples living with CBP. By integrating patients' lived experiences of CBP and practitioners' experiences providing care for people with CBP, this project will facilitate the identification and development of potential programs and

policies to overcome access barriers. This work will focus on patient-identified measures that should be used to evaluate and inform the scale and spread of ongoing [25-27] and future community-based intervention studies to be more meaningful for patients and improve patient-reported outcomes.

The objective of this study is to engage with rural, remote, and urban Indigenous and non-Indigenous people with CBP, health care providers, and health system decision makers to (1) explore the lived experiences of access to health care among people with CBP in Saskatchewan as well as identify components unique to each group; (2) cocreate indicators of access to and effectiveness of back pain care that are most meaningful to people with CBP to inform evaluation of health care access interventions; and (3) identify programs or policy changes that could be implemented and evaluated in future, more comprehensive, and patient-oriented funding applications and projects.

Methods

Defining CBP

Low back disorders include a large group of clinical and etiological entities and there is no "gold standard" clinical classification or validated diagnostic criteria for many of these conditions [28]. Furthermore, the International Classification of Diseases-10 system does not have an adequate and distinct diagnostic code(s) for chronic pain or CBP [29]. Therefore, for this study, CBP includes self-reported pain and disability that lasted for a minimum of 3 months [30] that is related to low back injury (ie, sprain/strain) or low back pain with or without associated hip or leg symptoms due to pain referral.

Defining Rural, Remote, and Urban

The metropolitan influenced zone (MIZ) classification developed by Statistics Canada was chosen for defining rural, remote, and urban residence because it is readily comparable to other Canadian research and considers not simply the geographic proximity but the degree of connectivity with urban areas [31,32]. Urban residence is classified as living in a town or city with ≥10,000 residents as determined on the basis of having a number other than 0 in the second position of the postal code. Rural status is defined as those communities outside of a census metropolitan area or a census agglomeration and include all MIZ categories: strong, moderate, or weak, as per Statistics Canada definitions [31]. Remote status comprises areas with no MIZ, which includes all census subdivisions that have a small, employed labor force (less than 40 people) as well as any census subdivision where no individuals commute to a census metropolitan area or a census agglomeration urban core [31]. Indigenous people living on reserve land will be further classified, since reserves are commonly situated in nonurban settings and may experience obstacles related to lack of access to health resources and community infrastructure that may be different from MIZ alone [18]. Due to the multifactorial nature of rural, remote, and urban status in terms of health care access, we will also ask participants how they perceive the meaning and definition of these geographic terms and other ways they define their home communities to further understand how these terms could be defined to be meaningful regarding access to health care.

Patient-Oriented Approach

Patient-oriented research is the cornerstone to evidence-informed health care, referring to research processes informed by full and active involvement of patient partners in all aspects of the research [33]. The goal of engaging patients on the research team is to improve the translation of innovative approaches to ultimately ensure that the right patient receives the right clinical intervention at the right time [33]. The theoretical result of patient-oriented research is improved health outcomes. The Patient-Centered Outcomes Research Institute states that "The evidence base for stakeholder engagement in clinical research is growing; it shows that engagement is associated with increased recruitment and retention of study populations; more patient-centered and culturally appropriate methods; and greater relevance of research questions and outcome measures" [34].

In staying true to patient-oriented research processes, patient involvement in this project started with the identification of the research topic. Building on our existing work and community partnerships, the research topic of the outlined protocol was identified as a priority by patients through prior Saskatchewan-based research with non-Indigenous populations [10,11,23,27]. In addition, in a prior year-long community-based needs assessment of a remote Northern Saskatchewan Cree community, in partnership with Indigenous and non-Indigenous scholars, including people with CBP, Indigenous Elders, health care providers, and decision makers [25], participants described that CBP impacts a large proportion of the population and profoundly affects the physical, mental, and social quality of life of remote Indigenous patients.

Patient team members have already been recruited to this study. Team members were recruited through research team members' networks and contacts. We currently have 2 non-Indigenous patient team members (1 rural and 1 urban) and 1 Cree team member (remote), all of whom have lived experiences with CBP. The role of our patient team members will involve close collaboration at every stage of the research, including identifying research priorities, objectives and questions, design, data collection, analysis, and dissemination. This will be accomplished through having dedicated time for open dialogue during team meetings that will privilege patient perspectives and voices. Further to this, research team leaders will follow up with patient team members individually after each meeting by using adaptive approaches of communication and engagement to best support their comfort levels and preferred methods of communication.

Layered strategies for respectful Indigenous engagement ensure that the research follows culturally appropriate and respectful processes and is directed by Indigenous perspectives. Researchers will follow the recommendations of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans Chapter 9: Research Involving the First Nations, Inuit, and Métis Peoples of Canada [19] and principles of Ownership, Control, Access, and Possession [35]. The Indigenous patient team member has long-standing relationships with the research team and has been instrumental in guiding and grounding all

aspects of this research in Cree knowledge, practice, and protocol. A Métis Elder also advised on community-wide education and participant recruitment.

Patient team members will be actively engaged to identify and refine the research outcomes specific to this project. Furthermore, patient participants recruited specifically for this project will be actively engaged to identify meaningful outcome measures and indicators pertaining to future CBP care intervention research.

Recruitment for people with CBP will occur primarily online through funding partner websites, university websites, and social media. We will use posters at health care provider clinics as well as team networks. Recruitment for health care providers will occur through research team and collaborator networks via posters, social media, as well as an email invitation for health care providers through targeted recruitment. For research team members who have pre-existing relationships with Indigenous community members, we will be looking to their guidance on other recruitment methods that will be unique to each community. For phase 1, potential participants will contact our research team to be screened for eligibility. They will be provided with the consent form and have the opportunity to review and ask questions prior to the interview. At the conclusion of the interview, informed consent will be confirmed. For phase 2, verbal consent will be obtained at the time of the phone survey.

Interdisciplinary Team

Our diverse multidisciplinary research team includes Indigenous and non-Indigenous scholars, health care providers, and decision makers who have expertise and experience in health services research, collaborative models of care, musculoskeletal health, health economics, mixed methods, rural and remote health service delivery, integrated knowledge translation, Indigenous health, community-based participatory action health research approaches, health promotion intervention research, intergenerational and life course approaches to care and research, primary health care service delivery, and management. We also have team members that have already successfully led patient-oriented research projects and teams in rural, remote, and Indigenous communities. Inclusion of patient team members (2 non-Indigenous and 1 Indigenous from urban, rural, and remote communities) with unique knowledge, lived experience of CBP, language, and culture will be actively engaged in all stages of the research project. To complement and complete our team, we have connected with individuals and organizations as collaborators to help ensure the feasibility and relevance of our research and increase likelihood that findings will inform clinical practice, health care policies, and ultimately patient care/quality of care in a community-relevant and culturally respectful manner.
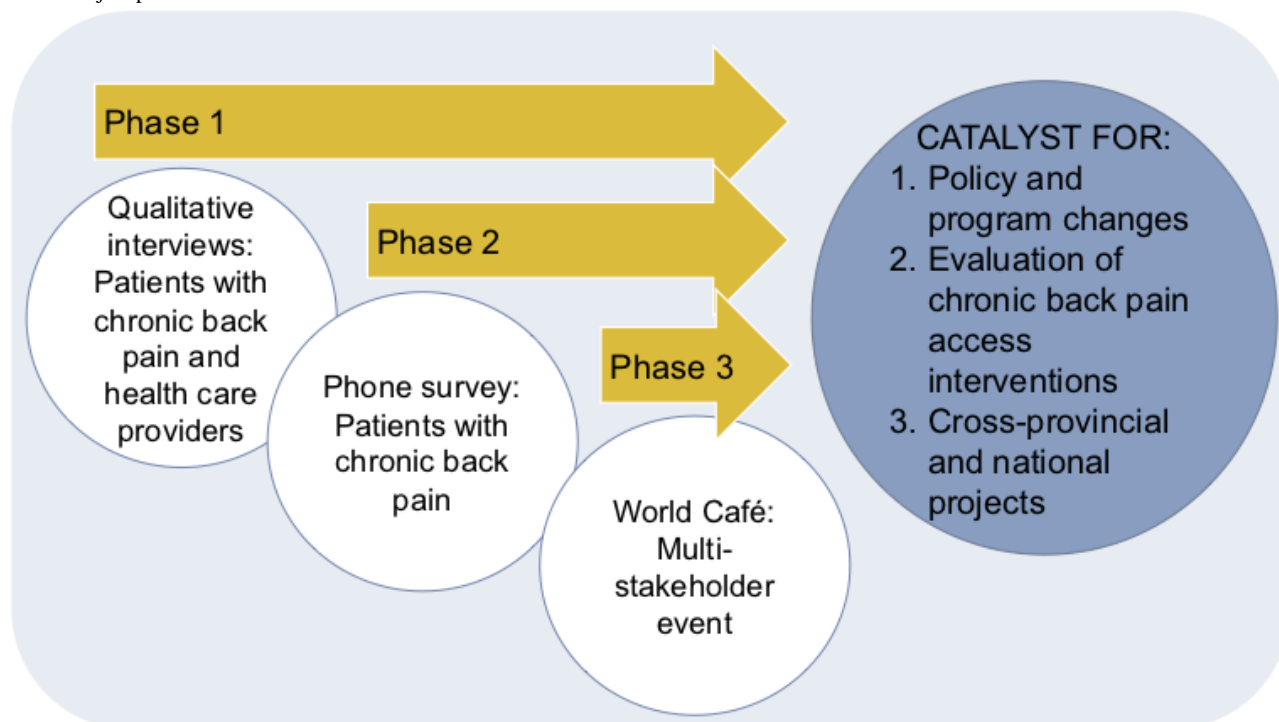
Ethics Approval

The Behavioral Research Ethics Board at the University of Saskatchewan provided ethics approval (Beh 1973) for this project and the methods described.

Procedures

This research will occur in 3 phases, with each phase informing the next (Figure 1).

Figure 1. Project phases and outcomes.

Phase 1: Interviews and Web-Based Survey

In this phase, we will use a qualitative interpretive research paradigm, which aims to understand a phenomenon based on personal experiences, interpretations, and perceptions [36,37]. We will use purposive sampling to select a variety of people with CBP and health care providers. Participants will complete a closed web-based survey with a unique link provided for each participant. A completion check will be performed prior to the interview. We will conduct one-on-one interviews with approximately 30 people living with CBP (age>18 years with a minimum 3 months history of current or past low back pain) (Multimedia Appendix 1) and 10-12 health care providers who provide CBP care (including physicians, nurse practitioners, physiotherapists, occupational therapists, chiropractors, massage therapists, pharmacists, psychologists, and traditional healers) (Multimedia Appendix 2); all participants will reside or practice in rural, remote, or urban Saskatchewan communities and may or may not serve Indigenous communities. We will recruit both Indigenous (n=10) and non-Indigenous (n=20) people with CBP, with a goal of recruiting 10 people from each of the rural, remote, and urban communities. Data collection will be stopped at the point of saturation when no new information relevant to our research questions is generated [38]. Although the number of interviews will depend on the emerging analysis, it is anticipated that the proposed sample size for this phase is reasonable based on our prior qualitative research in this area [23,27,39]. We will perform interviews in-person (whenever feasible and preferred by participants and as allowed by public health guidelines surrounding the COVID-19 pandemic) or over telephone or videoconference. We will pay particular attention to the unique experiences shared by Indigenous participants living with CBP in rural, remote, and urban communities as guided by our Indigenous team members and collaborator partners. Interviews will be recorded, transcribed, and analyzed thematically using qualitative coding software (NVivo, QSR International) after obtaining consent from participants. Participants will have the opportunity to review transcripts prior to data analysis and synthesis. The information gained through these interviews will be examined together with the patient advisor team members at the analysis phase to guide the next stage of the project.

Phase 2: Population-Based Phone Survey

Findings from the interviews will be used to inform development of a population-based phone survey focused on exploring perceived health care access barriers and facilitators among 383 rural, remote, and urban residents with CBP. The same inclusion criteria as above will be used. Survey research specialists at the Canadian Hub for Applied and Social Research (CHASR) will co-design the survey with the research team (Multimedia Appendix 3). The survey will be deployed by CHASR. The estimated sample of 383 is based on the estimate that 20% of the adult population has CBP [2], the adult population of Saskatchewan (N=843,975) according to most recent census data [40], and a margin of error of +5.00%. Oversampling of rural and remote areas will be performed to reflect the higher prevalence of CBP [2,4]. The CHASR sampling methodology for telephone surveys includes obtaining samples from a third-party vendor (ASDE Survey Sampler), which obtains its

panel through random digit dialing. To facilitate a more representative sample, both landline and mobile telephone numbers will be purchased. In accordance with the 2016 Communications Monitoring Report [41], 25.8% of the Saskatchewan households are mobile-only households and this will be reflected in the sample. Once the sample has been purchased, telephone numbers will be dialed randomly using the Voxco Computer Assisted Telephone Interviewing telephone survey software (Voxco, v.4.5). Telephone numbers are scheduled to be called up to 5 times without a response before the number is discarded. The survey items will be predominantly quantitative with some open-ended questions for qualitative analysis. Preliminary descriptive quantitative and qualitative analysis and reporting will be performed by analysts at the University of Saskatchewan's CHASR with further analysis and interpretation undertaken by the research team (including patient team members). Stratification of survey findings by residence (ie, rural, remote, urban) and Indigenous self-identification will be undertaken to uncover patterns of perceived barriers and facilitators to access care identified by geographically and culturally diverse groups of people with CBP. In addition to examining patterns across geography and culture, survey analysis will include disaggregation by sex and gender-related variables (specific variables to be determined in conjunction with patient team members and informed by qualitative interviews).

Phase 3: Knowledge Translation and Community Engagement

An integrated knowledge translation approach will be utilized by engaging patients, health care providers, and decision maker team members throughout the research process and all phases of the project; however, phase 3 specifically focuses on end-of-project knowledge translation activities. Findings from phases 1 and 2 will be presented to provincial and national policy makers, health system decision makers, health care providers, urban rural and remote people with CBP, and other knowledge users at an interactive end-of-project knowledge translation event. This 1-day event will take place either in-person, virtually, or a combination of both, as public health guidelines surrounding the COVID-19 pandemic allow. Approximately 50 participants in addition to the research team will be invited to take part in this knowledge translation World Cafe´, and will include rural, remote, urban, and Indigenous people with CBP, Indigenous Elders, health care managers, health care providers, and provincial and national decision makers. The morning of the event will include sharing the findings from the first 2 phases of the project. The afternoon will employ a World Cafe´ method [42] of facilitated dialogue that will serve to catalyze future patient-oriented research projects as well as actionable recommendations for policy and practice to improve pathways to accessing care for CBP. World Cafe´ is a collaborative and conversational process known to support knowledge exchange and creation, often through successive small group discussions [42]. Participants with different geographical, cultural, sex/gender, and role (ie, patient, health care provider, policy maker) backgrounds will be put into groups and will go through evolving rounds/cafe´ tables and discuss a range of topics. Each table will have a facilitator

with experience in the given topic and will be responsible for taking notes as a form of data collection as well as to summarize and inform the next group discussion. As groups move through the rounds, discussions will elaborate on and enhance previous groups' dialogues. This type of information exchange will allow participants to provide their unique perspectives and expertise on specific topic areas as well as to learn from the other participants. Through this method, relationships and connections will be made between participants with CBP, Indigenous and non-Indigenous community members, decision makers, and other stakeholders to create momentum and support for ongoing research, policy change recommendations, and promotion of the knowledge generated. Ideas and recommendations garnered from the World Cafe´ will be collected and synthesized by the project team members and culminate in a report to be shared with event participants and other relevant knowledge users who were not able to take part in the event. This event will allow for a participatory 2-way dialogue between the research team and knowledge users to help interpret the meaning and plan for the next steps of health service delivery planning, advocacy, and future research directions.

Patients as Partners

Patient team members will contribute to conducting the research in the development of interview guides (phase 1), survey questions (phase 2), and recruitment strategies (phase 1 and 2); input in the analysis and interpretation of interview and survey findings (phase 1 and 2); and participation in the development of knowledge translation and exchange activities, including planning and participating in the end of project knowledge translation event (phase 3). Their involvement will also include supporting recruitment at community levels and determination of appropriate messages as well as identification of target audiences and methods of sharing the findings to knowledge users (people with CBP, decision makers, health care providers, the public at large).

COVID-19–Related Methodological Considerations

Our team has had to make adaptations to our research plan and approach considering the current and evolving local COVID-19 public health measures and guidelines. Our team meetings to date, including communication with patient team members, have been held virtually. Further, we have adapted all data collections in phase 1 and 2 to be conducted virtually (ie, videoconference, online, or phone) at this time. It is unclear at this point if phase 3 will be required to be done entirely virtually, in-person, or some combination of both approaches. Further alterations to our research have included consideration of how the COVID-19 pandemic has impacted perceived access to CBP care through the addition of specific questions regarding this issue in phase 1 and 2 of the project.

Results

This study was funded on February 2020. Research ethics board approval was received on September 4, 2020, following reopening of closures caused by the COVID-19 pandemic and research restart processes. Rolling participant recruitment started in January 2021. Interviews began in January 2021 and were completed in September 2022. Surveys and interviews of 33

patients and 16 health care providers were conducted. The population-based phone survey (phase 2) was administered between May 5 and 25, 2022 and preliminary descriptive quantitative and qualitative analyses and reporting data analyses were received from CHASR on July 21, 2022. Final analysis will be completed by November 2022. The anticipated barriers and facilitators for access to care for people with CBP are expected to be identified, with overlapping as well as distinct themes across rural, remote, urban and Indigenous populations, with some unique to each population as well.

Discussion

Anticipated Outcomes and Considerations

This research project is timely amid persisting health equity gaps in rural, remote, urban, and Indigenous populations, the current opioid crisis, and the potential impact of the COVID-19 pandemic on health and access to care [7,8,18,43,44]. We anticipate the outcomes of this project will have immediate and long-term impacts on patient-oriented research and patient-centered care. Engaging patients and other stakeholders as partners in research is recognized as a promising approach to generate evidence that is trusted, meaningful, and useful to clinicians, patients, and their families when making health care decisions [34]. The design of this project and engagement with patients and other stakeholders will build our capacity to engage in future meaningful patient-oriented research endeavors respectfully and effectively. Patient team members will benefit by engaging in a respectful dialogue about their CBP health needs and by actively guiding how they would like to see care delivered and evaluated. It will advance knowledge of the access barriers and facilitators to CBP care as identified by rural, remote, and urban residents. Findings will reveal factors that uniquely impact CBP care among Indigenous communities and peoples, further highlighting important culture-based considerations that will impact policy, resource, and implementation practices required to meet the health needs of diverse Indigenous populations living in Saskatchewan. This research will be shared with provincial and federal decision makers to help inform policies and strategies to enhance health service accessibility for CBP in rural, remote, urban, and Indigenous communities. The findings from this research will be shared through community and stakeholder presentations, academic conferences and networks, and peer-reviewed publications.

Patient and provider partnerships in this research will allow for the examination of priorities and concerns of those working within and relying on the health system services for CBP care. Working with Indigenous and non-Indigenous people with CBP from rural, remote, and urban locations will provide patient and community perspectives on CBP care gaps and needs. This is particularly important for Indigenous peoples who are required to navigate 2 worldviews in their access to health care (the Western worldview upon which most health systems in Canada are based and their unique Indigenous worldview). Our project integrates Cree knowledge and perspectives throughout the research process, thereby ensuring that the Cree culture, language, practices, and protocols essential to Cree wellness

guide this work. Researchers and practitioners must work in partnership with Indigenous people and take responsibility to create space to uplift Indigenous worldviews above those of Western [45,46]. This, in turn, may be relevant to other First Nations, Métis, and Inuit populations and has the potential to optimize care for and with Indigenous people and foster a health system that works to dismantle racism and discrimination. It is anticipated that this study will lead to the creation of more effective, accessible, and appropriate CBP care that is responsive to the unique needs of individuals living in rural and remote areas and Indigenous peoples living in Saskatchewan. The involvement of key decision-maker stakeholders in the project (ie, provincial and federal managers/directors and policy makers) will help to ensure that the learning from this project can be translated into the development of policies and services to enhance equitable access to care for CBP across the province and beyond.

Strengths and Limitations

This project is designed to engage with multiple groups and knowledge users in the circle of patient care, including patients, providers, and policy and decision makers, thereby having the potential to contribute to health care systems and practices. The examination of patient and provider perspectives from rural, remote, and urban areas and Indigenous communities will create greater contextualization and allow for patient, geographic, and Indigenous wellness-specific factors to be addressed when it comes to examining how current services and models are addressing the needs of people living in Saskatchewan with CBP. Engaging Cree patient perspectives will support the integration of Cree epistemology and ensure that the principles of self-determination and self-governance are recognized and upheld. This research approach aims to address the issue of barriers and facilitators more holistically to access CBP care and highlight future areas to address and inform the health care system, clinical care guidelines, and other resources that are patient-oriented and community-directed.

The limitations of this research include potentially small subsample sizes that may not allow for specific comparisons between groups. In addition, the research findings may not be broadly generalizable, given that it has a Saskatchewan-specific focus.

Future Direction

The information gained in this project will ultimately provide patient-driven perspectives and outcomes that will serve as a catalyst for future research in a health care environment where new and innovative approaches are needed to address challenges to accessing more effective and appropriate CBP care.

Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide for patients with chronic back pain.
[DOCX File , 19 KB - resprot_v11i12e42484_app1.docx]

Multimedia Appendix 2
Interview guide for health care providers.
[DOCX File , 17 KB - resprot_v11i12e42484_app2.docx]

Multimedia Appendix 3
Telephone survey template.
[DOCX File , 28 KB - resprot_v11i12e42484_app3.docx]

Multimedia Appendix 4
Peer review report by Canadian Institutes of Health Research / Instituts de recherche en santé du Canada (CIHR/IRSC) - Catalyst Grant: Patient-Oriented Research/Subvention catalyseur : Recherche axée sur le patient (Canada).
[PDF File (Adobe PDF File), 575 KB - resprot_v11i12e42484_app4.pdf]

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Abbreviations

CBP: chronic back pain
CHASR: Canadian Hub for Applied and Social Research
MIZ: metropolitan influenced zone

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Protocol

Recasting Jung Through an Indigenist Approach to Deepen Shared Knowledges of Well-being and Healing on Australian Soils: Protocol for a Qualitative Landscape Research Study

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Abstract

Background: The colonization of Australia is responsible for complex layers of trauma for the First Nations peoples of the continent. First Nations Australians' well-being is irrevocably tied to the well-being of the land. The application of a landscape-based approach to collaborative research shows promise in enabling genuine relationships that yield rich and informative data. However, there is a lack of practical evidence in the field of landscape research—research tied to First Nations Australians' worldviews of landscape.

Objective: This study aims to deepen shared knowledges of well-being and healing on Australian soils. We aim to examine ritual co-design as a novel method for deepening these shared knowledges.

Methods: This research comprises a qualitative and participatory action research design operationalized through an Indigenist approach. It is a 2-phase project that is co-designed with First Nations Australians. Phase 1 of this project is a relational study that endeavors to deepen the theory underpinning the project, alongside the development of meaningful and reciprocal community connections. Phase 2 is a series of 3 participatory action research cycles to co-design a new communal ritual. This process seeks to privilege First Nations Australians' voices and ways of knowing, which are themselves communal, ritual, and symbolic. The framework developed by psychiatrist Carl Jung informs the psychological nature of the enquiry. An Indigenist approach to landscape research recasts the Jungian frame to enable a culturally safe, context-specific, and landscape-based method of qualitative research.

Results: The research is in the preliminary stages of participant recruitment. It is expected that data collection will commence in late 2022.

Conclusions: It is expected that this qualitative and co-designed project will strengthen the cross-cultural co-designer relationships and that the data gathered from these relationships, and the accompanying practical outcomes, will provide new insight into the interaction between human and landscape well-being. The field of landscape research is in an embryonic phase. This new field is embedded in the understanding that First Nations Australians' well-being is irrevocably tied to the well-being of the land, and this study seeks to build on this evidence base. A strength of this research is the relational methodology, in which First Nations Peoples' needs and desires will inform future research directions. It is limited by its context specific nature; however, it is expected that findings will be usable in guiding future research directions in the multidisciplinary field of landscape research.

International Registered Report Identifier (IRRID):   PRR1-10.2196/36328

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Introduction

Resisting Colonial Australia

We acknowledge the Elders, families and forebears of the Aboriginal and Torres Strait Islander peoples of the Australian continent, islands and adjacent seas, who remain the spiritual and cultural custodians of their lands and waters and who continue to practice their values, languages, beliefs and customs. [1]

This research acknowledges colonization as the genesis for complex layers of trauma in Australia, and it resists the colonial value system through the development of a culturally safe, empowering, and reflective mode of enquiry. It acknowledges that Australia's history of colonization has seen the dispossession and dislocation of the continent's "First People" from their lands and cultures though physical violence and political policies such as assimilation. This has resulted in complex layers of trauma for First Nations Australians [2].

Numerous reports with statistics of disadvantage in health and well-being [3]—known as deficit discourse [4]—indicate the gaps between First Nations (we respectfully use First Nations Australians to signify Aboriginal and Torres Strait Islander Peoples) and non–First Nations Australians. Underpinning the gaps is a history of dispossession, dislocation, and removal of First Nations children from their lands and families, resulting in the "Stolen Generation" [5]. Similar to other colonized parts of the world, this pattern reveals a long-lasting impact on the health and well-being of First Nations peoples and that colonization is an ongoing traumatic experience rather than a one-off historical event [6].

Centering the Landscape in Research

For First Nation Australians, landscape or Country is a physical setting for performance and ritual but also the essential factor from which all other understandings of the universe stem, as Yolngu academic Dr Elaine Maypilama explains, "Country is land, air, water and stories of Dreaming" [7]. This landscape-based understanding of the world is dynamic and multilayered. It forms the "rules, norms and beliefs of existence between species and humans through connecting Aboriginal peoples' back to ancestral beings from the time of creation" [8]. Mary Graham [9], a Kombumerri person, says, "The land is law. Land is a sacred identity and how we treat it determines our humanness...all meaning comes from land," suggesting that the health of the land determines the health of First Nations people and culture, and the denial of these connections causes "unspeakable loss...and deep injury and trauma" [10]. For example, the recent Juukan Gorge destruction leaves both a physical wound to the land and a psychological wound on the souls of First Nations Australians, especially for Puutu Kunti Kurrama and Pinikura peoples [11].

Healing Trauma Through Arts-Based Approaches

According to Bard and Yjindjarbandi researcher Dr Dawn Bessarab [12], First Nations communities use storytelling, performance, and visual arts to express culture—the cosmology and the interconnectedness of people, places, and histories [12]. Stories and myths are then enacted, shared, and presented in performances and rituals that provide a setting through which community members experience the most complete metaphorical expression of their cosmology [13]. Using arts-based approaches, which involve opportunities for storytelling and counter-storytelling, provides a valuable basis for developing meaningful healing and transformative research with First Nations peoples [14-16].

Recasting Jung Through an Indigenist Approach

An Indigenist approach to the research takes Western theories and recasts them through methodological reform—where theories are challenged rather than imposed as given truth [17]. The research team comprising First Nations (MJL and DD) and non–First Nations (SZ, GJ, and CM) peoples proposes the Jungian framework as a novel approach to deepening the growing body of relational research in Australia. The Jungian framework is used for developing connections and research concepts between First Nations and non–First Nations Australians [18] through Jung's understanding of the importance of meaning-making, spirituality, storytelling, and symbolism to human psychological well-being [19].

Jung's search for understanding the essential connection between human and nature naturally resonates with First Nations cultures [20], who experience a kinship with Earth, grounded in systems of relationships and reciprocities that form the basis of all life [21]. Jung's extensive study of comparative mythology and anthropology extended to First Nations Australians [22]. Petchkovsky [23] asserts that Jung's concept of Active Imagination is a valid mode to understanding First Nations Australians' land-based creation stories, performed rituals, and rites of passage that constitute human life and express cosmology.

Aim

The aim of this study is to deepen shared knowledges of well-being and healing on Australian soils. The relational study endeavors to deepen the theory underpinning the project alongside the development of meaningful and reciprocal connections with First Nations Australians. From within these new connections, community needs and desires for research directions will be developed collaboratively. The objective of the research is to co-design a new communal ritual. Ritual co-design serves as both a research method and as a physical metaphor expressing the shared knowledges gained. The ritual co-design process explores First Nations Australians' ways of knowing [24], which are themselves communal, ritual, and

symbolic. Furthermore, feminist theory, women, Jung's archetypal female principal, women's practices, and ways of knowing have an essential and central role in this process.

Methods

The methodology is a qualitative and participatory action research (PAR) design operationalized through an arts-based Indigenist approach. It seeks to develop a culturally safe, reflexive, and practical method for cross-cultural research for the benefit of First Nations Australians.

Cultural Validation

The above aims and objectives have yet to be culturally validated [25] by the future First Nations co-designers of the study. Therefore, the following details of the study design are also suitably flexible and open to reevaluation [26]. This cultural validation will itself only yield context-specific knowledges that are not necessarily applicable to other First Nations individuals or communities in Australia [27]. This approach and elucidation represents culturally safe research practice that places the locus of power with First Nations peoples to determine whether the specific aims and research processes diminish their cultural identity [28]. Validation will be achieved by triangulating perspectives from culturally appropriate yarning [12] with First Nations community members, non–First Nations researcher ethnographic reflection [29], and through literature review.

Phase 1: Relational Study

In an endeavor to uphold the Indigenist strategies outlined (data collection), a process of combined autobiography (understanding one's own life experiences retrospectively and in light of current learning) and ethnography (a process of becoming a participant observer in a culture for the purposes of learning more about others) will be adopted [30]. In this context, this process will be used to produce a rich and accessible body of personal and interpersonal information that can form new directions for further research [31] and is consistent with non–First Nations peoples' need to reflexively examine themselves and their orientation toward culturally safe practices [32].

Phase 2: Ritual Co-design

The Jungian nature of the enquiry will guide the co-design of the ritual through Jung's psychological understanding of spirituality, storytelling, and symbolism. Symbol and metaphor will be used in communication [33,34] using Indigenous methods of yarning [35], dadirri [36], sand talk [13], and photovoice [37].

There is a substantial body of research on First Nations and non–First Nations rituals and ceremonies written from majority Western perspectives [22,38,39]. This research is almost always authored by either international (non-Indigenous) researchers or non–First Nations Australians [40,41]. The academic discussion of ritual (including ritual responsibilities) and ceremony by First Nations Australian voices is in an embryonic but growing phase [42,43]. Female First Nations voices are similarly underrepresented despite the fact that "women played an important role spiritually within Aboriginal society...with

their own special ceremonies and stories," as recounted by Eualeyai and Kamillaroi woman and academic Larissa Behrendt [44]. Evidence for ritual co-design as a method for cross-cultural knowledge creation is absent in landscape research [42,43].

Ethics Approval

Ethical approval for the phase 1 relational study has been received by the University of New England (UNE) Human Research Ethics Committee (HREC; HE21-142). A separate Human Research Ethics Application [45] for phase 2 of the research project will be submitted to the Aboriginal Health and Medical Research Council (AHMRC)–HREC and the UNE-HREC. Additional ethical protocols will be addressed with the community contacts developed in the phase 1 relational study and will be approached according to the guidelines of the AHMRC-HREC and Australian Institute of Aboriginal and Torres Strait Islander Studies (AIATSIS).

Consent to Participate

Before any research is undertaken, free, prior, and informed consent will be obtained from the relevant First Nations peoples. The researcher acknowledges that collective consent does not remove the requirement to respect individual rights to participate in Aboriginal and Torres Strait Islander research and that individuals require additional consent [46].

Participant Recruitment

The development of meaningful relationships is key to genuine and trusting research relationships between First Nations and non–First Nations peoples [47]. The participant recruitment process begins with directly contacting First Nations community members involved at the intersection of landscape research, Country, well-being, and healing. This includes First Nations–controlled community organizations and services and individual community members and leaders [48]. The research team will identify relevant contacts through peer-reviewed literature, personal networks, and searching the internet for similar projects.

The ritual co-design aims to invite 5-10 female collaborators, self-identifying as First Nations Australians, to be a part of this research as cocreators of the design. Female First Nations Australians will be contacted through culturally safe protocols [49], which means developing relationships with community members and leaders and recruiting future co-designers through passive snowball sampling [50].

Permission for participants' identity to be kept anonymous will be respected, as well as the identity of any family or community members, present or passed, mentioned in the recounting of stories and histories.

Inclusion and Exclusion Criteria

This research is a gendered enquiry, as informed by successes in similar studies [51-53]. Individuals under 18 years of age will not be included in the study. Due to the inclusive and flexible research philosophy, no individuals are specifically excluded because that will be for First Nations community members to advise according to their local protocols; however, this is a gender-specific Indigenist approach and the lead researcher is a female non–First Nations Australian [54,55].

Data Collection

For phase 1, the autoethnography and regular critical reflexive practice of the relational study will be conducted simultaneously to, and informed by, social yarning with First Nations community members [50] and in addition to searches of academic journals and grey literature. The researcher (SZ) will undertake weekly reflexive practice through critical reflection [29], which will be converted into Jungian-style mandalas (symbolic diagrams) on a bimonthly basis. No quantitative or qualitative data will be collected from individuals that are consulted during phase 1.

For phase 2, the ritual co-design, data collection methods are underpinned by a value system that prioritizes reciprocal and involved transparent knowledge sharing [35]. Four methods of data collection honoring First Nations Australian methodological praxis will be used: yarning and dadirri [56], storytelling and counter-storytelling [12], sand talk [13], and photovoice [37]. These 4 methods will be used simultaneously to develop a rich, layered, and diverse body of data that will be subject to evaluation within the 3 cycles of the PAR design [57].

Culturally safe landscape research reframes relationships to make research co-designed with First Nations peoples, so their worldviews drive the research to meet their needs [58-60]. This predicts a nonlinear process of data collection more akin to a spider's web or bricolage of information [61]. Briefly:

1. Yarning is defined by an open dialogue that flows between community members and researchers that lends itself to the development of trust and active participation and accountability on all sides [35]. According to Dr Miriam Rose Ungunmerr-Baumann, a Ngangikurungkurr woman, dadirri (pronounced "da-did-ee") or "deep listening" refers not only to active listening but also speaks to a willingness to "listen" past the words that are being spoken [56].
2. In psychological research, storytelling and counter-storytelling [33,34] seek to acknowledge power relations and White privilege in research practice. It draws focus to First Nations–led strategies that affords research participants avenues to express personal and collective cosmology, lived experience, and a version of history that challenges that of the dominant society [62].
3. Sand talk is a practical and relational communication method developed by academic Tyson Yunkaporta [13] of the Apalech Clan, of Far North Queensland. This communication technique comprises yarning, dadirri, and storytelling when drawing symbols on sand that articulate complex patterns and concepts.
4. Photovoice is a method of data collection often used in research with women, First Nations, and marginalized communities [63]. Similar studies found that Aboriginal Australian women saw alignment between photovoice methods and cultural customs for sharing knowledge [37]. This research will use photovoice methods to capture and record the symbols of the sand talk yarns.

The interviews, communications pertaining to research cycle planning, yarns, and photovoice discussions will be audio-recorded and transcribed verbatim to assist with data evaluation [64]. Parallels can be drawn between the First Nations methods of data collection—described above—and similar methods used by Jungian and post-Jungian practitioners. For example, sand talk [13] is methodologically similar to sandplay methods developed by post-Jungian academics and practitioners [65,66]. Both sand talk and sandplay use symbol, story, and metaphor to communicate complex emotions and concepts using the medium of sand. Such similarities will be subjected to cultural validation with the future First Nations co-designers of the study before influencing the study design.

Data Evaluation

The data collected during the ritual co-design will be evaluated based on a three-fold process:

1. The qualitative data generated will be rich, layered, and diverse. As such, the evaluation must be structured to present a cohesive interpretation of the findings [57]. This study will be evaluated through a feminist paradigm, found to be successful with female First Nations community members [51]. However, care will be taken in differentiating feminist theory from First Nations women's practices, experiences, and ways of knowing [44].
2. This data evaluation will be conducted within the cycles of the PAR design with First Nations co-designers and the wider First Nations community. A key feature of previous successful healing programs [67] has been the First Nations participation in leadership and evaluation of the study design.
3. The qualitative data generated will be coded and evaluated using qualitative text analytics software. Leximancer will be used to identify the most prominent words and themes to produce a map of the key concepts, guiding the researcher to construct a coherent and rigorous evaluation of the rich body of data gathered [68].

Assessment

Previous researchers cite the importance of practicing critical reflexivity in ensuring cultural safety [69] for First Nations Australians [70,71]. The reflexive data collected during the relational study (autoethnography and reflexivity) will be assessed by First Nations co-designers [26]. The researcher (SZ) will undertake weekly reflexive practice, which will be converted into Jungian-style mandalas. These reflexive writings and mandalas will be yarned about with the First Nations co-designers during the course of the proceeding research cycles. The co-designers themselves will assess whether the reflexive material is evidence of an emerging awareness of cultural safety and respects their cultural identity [28].

The transformation in knowledges of landscape, well-being, and healing will be assessed through combined application of the Environmental Identity scale [26] and the Negative Life Events Scale, which is a measure of emotional and social well-being [72]. The application of such emotional and social well-being scales in First Nations communities in Australia is a sensitive but growing area of research requiring cultural validation [73]. Through an assessment process [25], these scales will be reevaluated, in an effort toward ensuring the cultural safety of the First Nations co-designers [10]. These

processes seek to further advance practical evidence in the field of landscape research [60,74].

Data Management and Sovereignty

In this research, issues of access to data, control of data, data recording, and record keeping are guided by the ethical principles of the AHMRC-HREC [75] and AIATSIS [46]. Ownership, management, and communication of research data and results will be negotiated between First Nations Australians and the researcher at an early stage in the research. This process will also address the lack of evidence of data sovereignty agreements by co-designing an agreement with the future co-designers. The contribution of First Nations Australians' knowledge, resources, and access to data will also be acknowledged by ensuring open access, enabling First Nations peoples to research results.

Research Timeline

Taking time to develop trust is an essential first step in developing research with First Nations Australians [76]. In the phase 2: ritual co-design, the 3 research cycles will take approximately 6 months. This timeframe is based on similar collaborative studies that prioritize Indigenist ways of knowing and being [51,77]. This means prioritizing respect regarding commitments and reasonable timeframes, demonstrated by requesting times for meetings that are convenient to community members and holding meetings at community organizations or places nominated by the community members [78]. Therefore, meetings may take longer to schedule and conduct, and hence, the timelines and milestones are suitably flexible.

Results

The research is in the preliminary stages of participant recruitment for phase 2: ritual co-design. The phase 1 relational study has already been completed. It is expected that data collection for phase 2 will commence in late 2022.

Discussion

Expected Findings

It is expected that this qualitative and co-designed project will strengthen cross-cultural co-designer relationships and that the data gathered from these relationships and the accompanying practical outcomes will provide new insight into the interaction between human and landscape well-being. Previous studies have found success when privileging landscape (or Country) when co-designing research with First Nations individuals and communities. This study builds on this evidence base by proposing a novel ritual co-design methodology as a practical method of deepening shared knowledges.

The strength of this study lies in the relational methodology stemming from the Indigenist approach. This approach sees the study prioritizes strong and trusting cross-cultural relationships that form the basis of all research directions and practical outcomes. As a result of these strong relationships, the study is able to respond to community needs, ensuring that outcomes and findings are both meaningful and genuine. A limitation of the study is that the findings will yield context-specific knowledges that are not necessarily applicable to other First Nations or non–First Nations individuals or communities in Australia. However, It is expected that this qualitative data will be able to be used by future researchers to guide directions in qualitative and quantitative research methodology.

Dissemination Plan

The findings of the research will be continually disseminated throughout the research cycles within the co-designer group and the wider community. This dissemination plan includes attendance at First Nations community meetings as requested; through conducting project information sessions with local community groups; and through peer-reviewed articles, local reports and documents, and conference presentations [50]. This continual dissemination and regular critical reflection is expected to increase rigor in the research through collaborative discussion and subsequent planning of the next step.

Data Availability

Ownership, management, and communication of research data and results will be negotiated between First Nations and non–First Nations co-designers and the researcher at an early stage in the research, which will be formalized through a Research Agreement. This process will also address the lack of evidence of data sovereignty agreements by co-designing an agreement. The contribution of First Nations peoples' knowledge, resources, and access to data will also be acknowledged by ensuring open access, enabling First Nations peoples to access research results.

The data sovereignty agreement will address:

1. Who has ongoing custody of the data
2. Where this data will be stored

3. Who owns the cultural and intellectual property, in particular the data that relates to First Nations Australian knowledges, histories, and traditions
4. How consent for future uses be negotiated
5. How privacy will be maintained if data are used in the future

The raw data of the study will be comprehensively collated into a Microsoft Excel spreadsheet and offered to the future First Nations community to accompany the published reports and documents. Further, upon research completion or closure of the project, the data will be centrally archived and labelled with a persistent identifier to enable future retrieval. The metadata (describing the research data) of the research data and/or materials will be recorded in the Metadata Store of the Library Services of the University of New English (UNE). Once the metadata record has been completed, the record will be issued with a digital object identifier and made publicly accessible in Research UNE (RUNE) and Research Data Australia. This procedure reflects the UNE's open access policies and procedures, which encourage researchers to share and publish data and metadata records.

Authors' Contributions

SZ was responsible for coordinating the contribution of all authors to this paper. All authors made significant contributions to the development and conceptualization of the protocol. SZ was responsible for drafting this paper. GJ, MJL, and CVM contributed to the idea of the project and the research design, critical editing, and guidance on the paper. DD advises on the cultural oversight of the project and was involved in yarning through this paper. All authors were responsible for critically revising the paper. All authors approved the final version of this paper for submission.

Conflicts of Interest

None declared.

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Abbreviations

AHMRC: Aboriginal Health and Medical Research Council
AIATSIS: Australian Institute of Aboriginal and Torres Strait Islander Studies
HREC: Human Research Ethics Committee
PAR: Participatory Action Research
UNE: University of New England

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Corrigenda and Addenda

Correction: Development and Effectiveness of a Mobile Health Intervention in Improving Health Literacy and Self-management of Patients With Multimorbidity and Heart Failure: Protocol for a Randomized Controlled Trial

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Related Article:

Correction of: https://www.researchprotocols.org/2022/4/e35945

In "Development and Effectiveness of a Mobile Health Intervention in Improving Health Literacy and Self-management of Patients With Multimorbidity and Heart Failure: Protocol for a Randomized Controlled Trial" (JMIR Res Protoc 2022;11(4): e35945), the authors noted one error.

In the originally published article, one of the members of the ASYAG_PPIC Team's name incorrectly appeared under the Acknowledgments section as:

José Crespo-Piñero

It has now been replaced by:

José Castro-Piñero

The final Acknowledgments section will appear as follows:

This study has received financial support from The Institute of Research and Innovation in Biomedical Sciences of the Province of Cadiz. The initial protocol has undergone peer review by the funding body. The funding body supervises the conduct of the overall project but is not involved in any operations. The authors are responsible for the execution, content, and results of the materials. The ASyAG_PPIC Team (Institute of Research and Innovation in Biomedical

Sciences of the Province of Cádiz [INiBICA], University of Cádiz, Cádiz, Spain) consist of: José María Cano-Guerrero; Inés Carmona-Barrientos; María Ángeles Carrasco-Bernal; Mónica Casado-Daza; José Castro-Piñero; Cristina Castro-Yuste; Magdalena Cuenca-García; Ignacio DelARco-Herrera; Pedro Díaz-deSouza; Mercedes Díaz-Rodríguez; María Falcón-Romero; Jorge del Rosario Fernández-Santos; Laura Gallardo-Amaro; María Paz Gómez-Jiménez; Gloria González-Medina; Eulalia Hernández-Encuentra; Luis Javier Moreno-Corral; Petronila Oliva-Ruiz; Francisco Javier Ordoñez-Muñoz; Ceferino Prieto-García; Inmaculada Ramón-Macías; Manuel Rosety-Rodríguez; Víctor Segura-Jiménez; María Jesús Viñolo-Gil; Juan Carlos Paramio-Cuevas; Mercedes Ruiz-Carreira; Eduardo Sánchez-Sánchez; Alexandra Torres-Castaño; Javier María Yagüe-Sánchez.

The correction will appear in the online version of the paper on the JMIR Publications website on December 7, 2022, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other

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full-text repositories, the corrected article has also been   resubmitted to those repositories.

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Protocol

Conceptions of Legacy Among People Making Treatment Choices for Serious Illness: Protocol for a Scoping Review

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Abstract

Background: Legacy—what one leaves behind and how one hopes to be remembered after death—is an unexplored and important dimension of decision-making for people facing serious illnesses. A preliminary literature review suggests that patients facing serious illness consider legacy when making medical decisions, for example, forgoing expensive treatment with limited or unknown clinical benefit to preserve one's inheritance for their children. To date, very little is known about the conceptual foundations of legacy. No conceptual frameworks exist that provide a comprehensive understanding of how legacy considerations relate to patient choices about their medical care.

Objective: The objective of this scoping review is to understand the extent and type of research addressing the concept of legacy by people facing serious illness to inform a conceptual framework of legacy and patient treatment choices.

Methods: This protocol follows the guidelines put forth by Levac et al, which expands the framework introduced by Arksey and O'Malley, as well as the Joanna Briggs Institute Reviewer's manual. This scoping review will explore several electronic databases including PubMed, Medline, CINAHL, Cochrane Library, PsycINFO, and others and will include legacy-specific gray literature, including dissertation research available via ProQuest. An initial search will be conducted in English-language literature from 1990 to the present with selected keywords to identify relevant articles and refine the search strategy. After the search strategy has been finalized, 2 independent reviewers will undertake a 2-part study selection process. In the first step, reviewers will screen article titles and abstracts to identify the eligibility of each article based on predetermined exclusion or inclusion criteria. A third senior reviewer will arbitrate discrepancies regarding inclusions or exclusions. During the second step, the full texts will be screened by 2 reviewers, and only relevant articles will be kept. Relevant study data will be extracted, collated, and charted to summarize the key findings related to the construct of legacy.

Results: This study will identify how people facing serious illness define legacy, and how their thinking about legacy impacts the choices they make about their medical treatments. We will note gaps in the literature base. The findings of this study will inform a conceptual model that outlines how ideas about legacy impact the patient's treatment choices. The results of this study will be submitted to an indexed journal.

Conclusions: Very little is known about the role of legacy in the treatment decisions of patients across the continuum of serious illness. In particular, no comprehensive conceptual model exists that would provide an understanding of how legacy is considered by people making decisions about their care during serious illness. This study will be among the first to construct a conceptual model detailing how considerations of legacy impact medical decision-making for people facing or living with serious illnesses.

International Registered Report Identifier (IRRID): DERR1-10.2196/40791

Introduction

Overview

Legacy—what one leaves behind and how one hopes to be remembered after death—is an unexplored and important dimension of decision-making for people with serious illness. Reflecting on one's values and legacy when living with a serious illness can provide a heightened sense of dignity, purpose, and meaning, as well as improvement in depressive symptoms and quality of life [1-3]. Such reflection may also provide clarity regarding medical decisions and reduce decisional regret [1,2,4]. Although actions concerning legacy may be taken at any timepoint along an illness experience, legacy work, when undertaken, is often incorporated into end-of-life care or palliative care, and such interventions have been shown to promote emotional and spiritual care of advanced cancer patients [1,5-8].

Based on a preliminary literature review and previous research [9], we are exploring the conceptual foundations of legacy. We conceptualize 3 types of legacy: primary, secondary, and tertiary. Primary legacy includes a living person's considerations of how they would like to be remembered after death, as well as what artifacts they intentionally leave behind. This may include various types of material and social artifacts, such as financial and legal documents, professional products, and items created for the purpose of memory and social continuity for loved ones [3,10,11]. Planning one's legacy can be an adaptive process or rite of passage [12] for people living with serious illness [13-15] and may include decisions about medical care. We define secondary legacy as the manner in which others remember a loved one or family member, including bereavement [16] and memorialization [17-19] activities initiated after a person's death. We term the recognition of the legacy of international or national [20], political [21], or professional impact [22] of a public person not necessarily personally known to those memorializing them to be tertiary legacy.

To date, little research has been conducted on the concept of primary legacy, despite a wealth of scholarship on bereavement and other secondary and tertiary legacy activities. The extant literature on primary legacy typically examines interventions that might include the creation of a legacy document, such as dignity therapy or life review, or how various material artifacts, such as Physician Orders for Life-Sustaining Treatment (POLST), can be created and used, and their impact on patients' understanding of their illness and preparation for death. We note, in particular, the foundational contribution Boles and Jones [23] offer in their systematic review of legacy interventions for children and adults receiving palliative care [24].

However, how patients define legacy, what it means to them, and how that meaning informs medical decisions are not well understood. A preliminary literature review suggests that people facing serious illness such as cancer consider legacy when making medical decisions, for example, forgoing expensive treatment with limited or unknown clinical benefit to preserve one's inheritance for their children [25,26]. Yet, very little is known about the role of legacy in the treatment decisions of patients across the continuum of serious illness, from receiving genetic test results that indicate a predisposition to serious illness to receiving a life-limiting diagnosis to choosing treatment options for end-of-life care [27,28]. In particular, no comprehensive conceptual model exists that would provide an understanding of how legacy is considered by people facing serious illness.

Objective of Conducting the Scoping Review

The objective of this scoping review is to inform a conceptual framework of primary legacy and patient treatment choices by understanding the extent and type of academic discourse, addressing the concept of legacy by people facing serious illness. This scoping review will examine the conceptions of primary legacy as it relates to medical decision-making, excluding literature discussing secondary legacy.

We conducted a preliminary search of MEDLINE, the Cochrane Database of Systematic Reviews, and JBI Evidence Synthesis, and identified no current or in-process systematic reviews or scoping reviews on the topic of legacy and treatment choices of patients. This scoping review will describe the current literature base and identify research gaps. The results will inform a conceptual model of legacy and medical decision-making that will guide future research.

Methods

Protocol Design

This protocol follows the guidelines put forth by Levac et al [29], which expands the framework introduced by Arksey and O'Malley [30], as well as the Joanna Briggs Institute Reviewer's manual [31]. This protocol and the future scoping review are reported in accordance with the PRIMSA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Review) guidelines [32]. We describe the protocol for this scoping review according to these 6 stages: (1) identification of the research question; (2) identification of relevant studies; (3) selection of eligible studies; (4) charting the data; (5) collating, summarizing, and reporting of the results; and (6) consultation with stakeholders in order to identify additional references about potential studies to include and to collect feedback about the findings uncovered by the review.

Stage 1: Identifying the Research Question

Through preliminary literature reviews, the research questions this scoping review seeks to answer are (1) how is legacy

conceptualized by people facing serious illness? and (2) how is legacy conceptualized during medical care decisions by people facing serious illness?

Stage 2: Identifying Relevant Studies (Inclusion Criteria)

This review will follow the population, concept, and context framework put forth by the Joanna Briggs Institute [33,34]. The population we will investigate are people facing serious illness. The concept of interest for this scoping review is articles that discuss, directly or indirectly, how people want to be remembered after their own death. This review will not discuss articles not related to illness or medical care, or articles discussing the legacy of another person after death (ie, secondary legacy). As we are primarily concerned with the concept of legacy, this study will exclude intervention, effectiveness, and feasibility studies unless they include a rich qualitative component that speaks to the concept of legacy. The context for this review is open, and sources of evidence relating to any contextual setting are eligible for inclusion [34].

Our preliminary literature review confirms that the concept of legacy is discussed across various disciplines. Given the multidisciplinary sources of evidence, we want to ensure comprehensiveness in literature sources and will include a variety of relevant literature databases. We will explore several electronic databases, including PubMed, MEDLINE, CINAHL, Cochrane Library, PsycINFO, and others, to be informed by the subject matter expert (SME) librarian. We will also hand search the gray literature to identify highly relevant sources, such as reports, and evidence-based legacy programs. Gray literature sources include dissertations (to be accessed via ProQuest) and letters to the editor. We will include empirical articles written in English from 1990 to the present. This time period was chosen in consultation with an SME expert to reflect significant shifts in the provision of hospice and palliative care that provided multiple treatment options for people facing serious illness [35]. Our inclusion and exclusion criteria are represented in Textbox 1.

Textbox 1. Inclusion and exclusion criteria for the scoping review.

Inclusion criteria

- Population

  - People with or facing serious illness, such as people with a known family history of disease or people who have experienced a health scare, with a priority focus on historically underserved or vulnerable populations

- Concept/study focus

  - Articles that discuss, directly or indirectly, how people want to be remembered after their own death (primary legacy)

  - Articles that discuss how people consider legacy when making treatment choices

- Study designs

  - Empiric studies, conceptual scholarship, and opinion pieces. Priority focus on studies with relevant qualitative components

- Literature sources

  - Priority sources include peer-reviewed books and journal articles

  - Legacy-specific gray literature—reports, white papers, etc

  - Evidence-based legacy programs are included

- Timing of search

  - 1990 to the present

- Language

  - English

Exclusion criteria

- Population

  - Clinicians and care team members

  - Caregivers only (studies that include both patient and caregiver perspectives will be included)

Note: Population limitations may not be relevant for conceptual or humanities pieces

- Concept/study focus

  - Articles discussing the legacy of another person after their death (secondary or tertiary legacy).

  - Articles focusing on legacy as a component of bereavement

- Study designs

  - None. Lower priority focus on intervention effectiveness and feasibility studies

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Stage 3: Search Strategy and Study Selection

After conducting a preliminary exploration of the academic literature, noting search terms associated with highly relevant articles, and consulting a university SME librarian, we have designed a preliminary search strategy. An initial search will be conducted in English-language literature from 1990 to the present with selected keywords to identify relevant articles and refine the search strategy using MEDLINE/PubMed, CINAHL, PsycInfo, SocialWork, AnthropologyPlus, Web of Science, ProQuest, and Embase databases. We have limited this time window on the guidance of an SME librarian to reflect substantial cultural changes in the United States in end-of-life care. After the search strategy has been finalized, piloted, and conducted, we will undertake a 2-part study selection process.

In the first step, 2 independent reviewers will use an electronic abstract screening tool for abstract and full-text review to assess the eligibility of each article based on predetermined exclusion or inclusion criteria. Discrepancies regarding eligibility will be resolved by consensus or consultation with a third team member.

After completing the abstract review, 2 team members will review the full text of articles identified as potentially relevant using the same dual approach, noting reasons for exclusion. Relevant study data will be extracted, collated, and charted to summarize the key findings related to the construct of legacy. To further seek completeness, we will examine the reference lists of highly relevant papers and hand search the gray literature for potentially relevant articles. We will describe the literature flow using the PRISMA (Preferred Reporting Item for

Systematic Reviews and Meta-Analyses) literature flow diagram [36,37].

Stage 4: Preliminary Charting Elements and Associated Questions

Based on the preliminary table of charting elements adapted from Gilfoyle et al [38], we will develop a data abstraction tool (Textbox 2). The team will pilot the tool using a small sample of up to 5 included studies, iteratively refining as needed before proceeding with full abstraction.

For each study included in the review, we will conduct a dual nonindependent review, in which one reviewer will abstract data, and a second reviewer will check for accuracy and completeness. We will use the data abstraction tool developed by the reviewers. A preliminary list of the data to be abstracted is shown in Textbox 2. Abstracted data will include participants, concept, context, study methods, and key findings relevant to the review questions. Any questions that arise from a reviewer will be resolved through additional reviews by one or more team members to check for accuracy and completeness. We may contact the authors of papers to request missing or additional data. We will include the final data abstraction form with the completed review.

Textbox 2. Preliminary table of charting elements and associated questions for data abstraction.

Publication details

- Author
- Years of data collection
- Year of publication
- Country of origin
- Publication type
- Whether publication is open access

Study characteristics

- Funder
- Research question
- Discipline
- Aims/purpose
- Methodological design
- Study population and demographics (eg, age)
- Disease state
- Disease progression
- Sample size and response rate
- Recruitment approach
- Study context (eg, oncology or hospice)
- Methods (eg, interview, focus group, or intervention)

Intervention type (if applicable)

- Perspective
  - From what perspective is research presented? (eg, Patient voices directly or commentary from the author?)

Findings

- Definition of legacy
  - What terms and keywords do the authors use to define legacy?

- Legacy concepts/constructs
  - What concepts or constructs are included?

- Theoretical frameworks
  - What theoretical/epistemological frameworks inform this study?

- Care context
  - What care context does the study examine?

- Treatment choices
  - How is legacy considered in treatment decision-making?

- Material and social artifacts
  - What items, values, or types of artifacts do people leave behind for the purposes of legacy?

- Social milieu
  - What aspects of a person's social milieu are discussed?

- Practical steps in creating a legacy

- How is legacy discussed in terms of people's labor?

- Legacy tension

  - What types of tension regarding legacy are discussed?

- How death relates to legacy

  - Was type and manner of death discussed as impacting or contributing to legacy?

- Social personhood

  - How is social personhood discussed in the context of legacy? (eg, how do people think about continuing as a social presence in people's lives after they die?)

Author conclusions

- What recommendations are made by the author?

Study limitations/applicability

- What are the limitations in study design, population, or approach that limit interpretation applicability for the scoping review?

Stage 5: Collating, Summarizing, and Reporting the Results

After abstracting data, the team will review the data and identify themes related to the research questions. We will report findings using a combination of tables and diagrammatic representations. Narrative summaries will accompany each result, describing how the results relate to the research questions, including any unexpected or particularly notable findings. We will comment on any gaps observed in the literature base, research needs, and implications for practice. We will synthesize the findings into the final conceptual model.

Stage 6: Consultation with Knowledge Users

As put forth by Levac et al [29], consultation with stakeholders is an important element of methodological rigor in scoping reviews. We will share preliminary findings from stage 5 with stakeholders and incorporate their expertise and perspective [29]. We will map findings from these conversations to conceptual domains through the active collaboration of stakeholders from the community, health services, and academic sectors.

Ethical Considerations

This scoping review consists of reviewing and collecting data from publicly available materials and as such does not require ethics approval.

Results

This study will identify how people facing serious illness conceptualize legacy, and how their thinking about legacy impacts the choices they make about their medical treatments. We will describe our literature flow using the PRISMA flow diagram [36]. We will present data extracted via charts and tables and narratively describe the results, noting gaps in the literature base. We will provide a discussion of their significance and present a conceptual model outlining how legacy motivations impact health-related treatment choices.

Discussion

Summary

This paper describes the protocol for a planned scoping literature review. Very little is known about the role of legacy in the treatment decisions of patients across the continuum of serious illness. In particular, no comprehensive conceptual model exists that would provide an understanding of how legacy is considered by people making decisions about their care during serious illness. This study will include a scoping review of major research databases to develop a conceptual model that can inform future studies and interventions that investigate the role of legacy in medical decision-making. This scoping review protocol adheres to Levac et al's [29] guidelines, building on Arksey and O'Malley's [30] framework, and to the methods manual from the Joanna Briggs Institute.

This scoping review contains important strengths. It is embedded in an established health research partnership and will include the involvement of coresearchers from multiple sites with diverse expertise in the analysis and interpretation stages. This scoping review includes multiple reviewers for all phases of identification and selection. This scoping review has a priority focus on historically underserved or vulnerable populations. This scoping review is limited to English-language articles published from 1990 to the present; translation of non-English language articles is not feasible for this review. This represents a potential limitation and may result in some missed articles. However, although the formal literature search is a limited time period, we intend to include seminal or highly relevant articles identified through hand searching. We also intend to prioritize the inclusion of research with participants who are non-English speakers.

Conclusion

This study will be among the first to construct a conceptual model detailing how considerations of legacy impact medical decision-making for people facing or living with serious illness.

Data Availability

A list of included articles used in the scoping review this protocol outlines will be published in future work detailing the results of the scoping review.

Authors' Contributions

All authors have made substantive intellectual contributions to the development of this scoping review protocol. MFG conceptualized the framing of the legacy construct, the review approach, and drafted the protocol. NBH provided mentorship on the review approach, inclusion, and exclusion criteria and provided a careful review of each draft of the protocol. MPB contributed to the conceptualization and editing of the protocol.

Conflicts of Interest

None declared.

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Abbreviations

POLST: physician orders for life-sustaining treatment
PRISMA: Preferred Reporting Item for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
SME: subject matter expert

<u>Protocol</u>

Human Decision-making in an Artificial Intelligence–Driven Future in Health: Protocol for Comparative Analysis and Simulation

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Abstract

Background: Health care can broadly be divided into two domains: clinical health services and complex health services (ie, nonclinical health services, eg, health policy and health regulation). Artificial intelligence (AI) is transforming both of these areas. Currently, humans are leaders, managers, and decision makers in complex health services. However, with the rise of AI, the time has come to ask whether humans will continue to have meaningful decision-making roles in this domain. Further, rationality has long dominated this space. What role will intuition play?

Objective: The aim is to establish a protocol of protocols to be used in the proposed research, which aims to explore whether humans will continue in meaningful decision-making roles in complex health services in an AI-driven future.

Methods: This paper describes a set of protocols for the proposed research, which is designed as a 4-step project across two phases. This paper describes the protocols for each step. The first step is a scoping review to identify and map human attributes that influence decision-making in complex health services. The research question focuses on the attributes that influence human decision-making in this context as reported in the literature. The second step is a scoping review to identify and map AI attributes that influence decision-making in complex health services. The research question focuses on attributes that influence AI decision-making in this context as reported in the literature. The third step is a comparative analysis: a narrative comparison followed by a mathematical comparison of the two sets of attributes—human and AI. This analysis will investigate whether humans have one or more unique attributes that could influence decision-making for the better. The fourth step is a simulation of a nonclinical environment in health regulation and policy into which virtual human and AI decision makers (agents) are introduced. The virtual human and AI will be based on the human and AI attributes identified in the scoping reviews. The simulation will explore, observe, and document how humans interact with AI, and whether humans are likely to compete, cooperate, or converge with AI.

Results: The results will be presented in tabular form, visually intuitive formats, and—in the case of the simulation—multimedia formats.

Conclusions: This paper provides a road map for the proposed research. It also provides an example of a protocol of protocols for methods used in complex health research. While there are established guidelines for a priori protocols for scoping reviews, there is a paucity of guidance on establishing a protocol of protocols. This paper takes the first step toward building a scaffolding for future guidelines in this regard.

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Introduction

Background

Nonclinical health services such as health regulation and health policy are more extensive and complex than clinical health services in their scope and scale. They can be viewed regionally, nationally, or globally. Furthermore, health regulation and health policy often intersect and overlap. For example, during the COVID-19 pandemic, health regulation and health policy provide a continuum of rules, laws, and public health measures that may vary from one region to another and from country to country. An array of organizations at different levels of government may be involved in the oversight and control of health regulation and health policy, with input and influence from numerous private entities and commercial concerns. Therefore, there are often differences in perspective and tensions between opposing interests. For all these reasons, health regulation and health policy can be viewed as "complex health services." Health care, then, can be broadly divided into clinical health services and complex health services.

Artificial intelligence (AI) is beginning to transform complex health services. It can recognize patterns and compute correlations far beyond human capacity [1]. For instance, machine learning can be applied to big data at the population level from electronic health records, medical imaging, and genomic data [2] to predict the incidence of disease in a population. AI is used to analyze data from numerous digital resources and monitor social media to assist with critical public health initiatives such as the timely supply of vaccines [3]. AI analysis of social media has shed light on important issues such as cigarette smoking [4], unlawful sales of opioids online [5], and the thinking that underlies vaccine hesitancy [3].

However, AI-driven health policy and health regulation may not be as accountable, unbiased, or transparent as required in health care and may be prone to incorrect or unfair decisions [6]. AI can entrench existing biases or introduce other forms of bias in decision-making [7]. AI is an "anormative black box" [8]—it is possible to know its inputs and outputs but not its internal reasoning or logic. Furthermore, its algorithms are often exceedingly long, complex, and essentially disconnected from sense-making, making it a challenge to criticize or audit AI systems [8]. Importantly, there are legislative and regulatory gaps in the policies and ethics that should govern AI such as bias, lack of transparency in AI algorithms, privacy and data governance concerns, and cybersecurity issues [9]. Appropriate safety policies and precautions, risk management matrices, and areas of responsibility still need to be developed to address these concerns [10].

Regardless, AI is taking a prominent role in decision-making and is being used to solve increasingly complex tasks [11]. Early forms of AI such as machine learning and decision support systems are becoming increasingly important in decision-making in complex health services. These forms of AI collate, filter, search, and find patterns in big data, enabling human decision makers to make evidence-based decisions at speed [12]. In most nations and jurisdictions, AI is not currently allowed to make the final decisions in health policy and health regulation [13].

However, its footprint in decision-making is growing steadily. While humans are leaders, managers, and decision makers in complex health services today, it is unclear whether they will continue to have meaningful decision-making roles in an AI-driven future.

Complex health services are beginning to incorporate several advanced AI techniques, such as deep learning and natural language processing [14], into sophisticated AI-based decision support systems [2]. It is only a matter of time before AI begins to drive or dominate complex health services. Therefore, this research is timely and essential.

Research Design

The proposed research is designed as a four-step project, divided into two phases. Phase 1 aims to address the question of whether humans will continue to have meaningful decision-making roles in complex health services in an AI-driven future, based on any unique human attributes that may influence decision-making for the better. This phase consists of three distinct steps. The first step is a scoping review of literature to identify and map attributes that influence human decision-making in complex health services. The second step is a scoping review of literature to identify and map the attributes that drive AI decision-making in complex health services. The third step aims to provide a comparative analysis of the decision-making attributes of humans and AI, and make clear recommendations for future research in this area. It may include a narrative comparison, followed by a mathematical comparison, of these two sets of attributes.

Phase 2 aims to explore the question of whether humans will compete, cooperate, or converge with AI to continue in decision-making roles. This phase consists of a simulation, which is the fourth and final step of the proposed research. The simulation is based on mathematical modeling, where human and AI attributes are used to create virtual *agents* in an environment that closely replicate complex health services.

Significance and Expected Outcomes of This Research

There is an urgent need to determine whether humans are likely to continue in meaningful decision-making roles in complex health services in an AI-driven future. There is a dearth of literature on the role that AI may play in decision-making in this context. More broadly, this research is expected to contribute to addressing the question of whether humans will continue to play a meaningful role in a future likely to be dominated by AI [15]. The increasing sophistication of algorithms, matched by advances in data acquisition and data storage, is integrating AI into many facets of life [16]. This presents both opportunities and challenges. Therefore, while harnessing AI's potential, it is important to develop strategic frameworks that identify and balance benefits and risks early.

Methods

Protocol for the Scoping Reviews of the Literature

This is the protocol for the first two steps of phase 1:

1. A scoping review of the literature to identify and map attributes that influence human decision-making in complex health services

2. A scoping review of the literature to identify and map the attributes that influence AI decision-making in complex health services

Method

Both scoping reviews are based on the framework recommended by Peters et al [17]. The framework is based on PCC (Population, Concept, and Context), which has been adapted for each scoping review. In keeping with the framework, the scoping reviews focus on the headings set out below.

Titles and Review Questions

The title of the first scoping review is "Attributes That Influence Human Decision-making in Complex Health Services: A Scoping Review." The research question is what attributes have been reported in the literature that influence human decision-making in complex health services?

The title of the second scoping review is "Attributes that Influence AI Decision-Making in Complex Health Services: A Scoping Review." The research question is what attributes have been reported in the literature that influence AI decision-making in complex health services?

Inclusion and Exclusion Criteria

The reviews will consider all articles relating to human decision-making and AI decision-making in complex health services. The populations of interest are human decision makers and AI decision makers. The concept is decision-making in the context of complex health services.

Articles that focus on decision-making in areas not relevant to the research questions will be excluded. For example, articles

focusing on the following topics will be excluded: clinical health; maternal health, abortion, and discrimination against women; decision space for health recruitment; legal matters; environmental health, contamination, and toxicity; computers, human-computer interaction, and automated decision rules; mathematical modeling; and assessment of organizational performance.

Types of Evidence Sources

The reviews will consider a wide range of evidence sources, including empirical research (eg, qualitative and quantitative studies), case studies, expert opinions, critiques, commentaries, editorials, textual data, and narrative data. However, to ensure that these sources are of a reasonable quality, the reviews will include peer-reviewed journal articles only, and exclude book chapters, conference papers, and gray literature.

Search Strategy

An initial informal exploration will be undertaken to determine optimal search system and database combinations. Suitable search systems thus identified will be searched for peer-reviewed literature. The search will include all available databases in these search systems. The search terms used will be as logical, relevant, and comprehensive as possible.

Evidence Screening and Selection

The search will be limited to peer-reviewed journal articles in English only because of constraints on budget and time. However, no limits will be placed on the year of publication to try and capture articles through time that may reference seminal works on decision-making in the context of complex health services. Article screening and selection will be based on PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [18] (Figure 1).

Figure 1. Flow diagram based on the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [18].
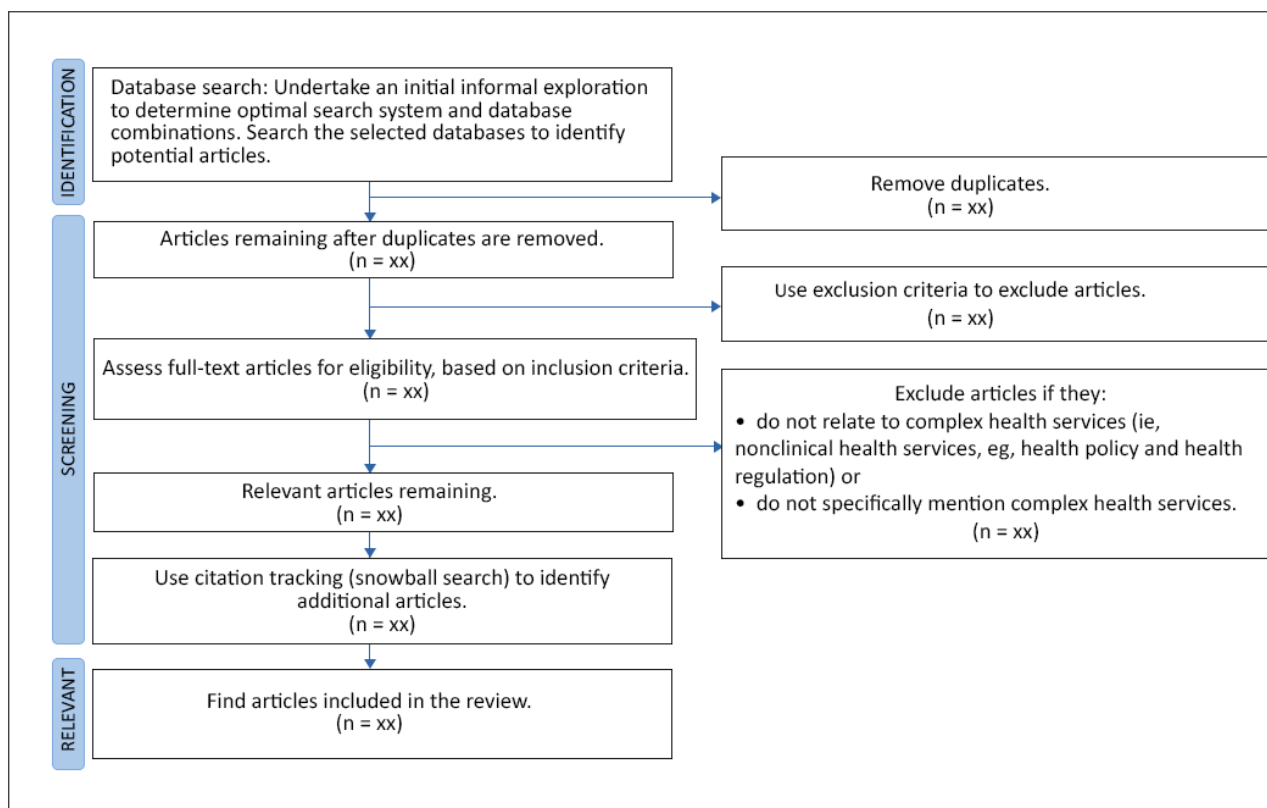
Data Extraction

A framework was developed for the selection, data extraction, and categorization of articles based on the work of Sav et al [19] and used as a standardized process to extract data. The process includes extracting the first author, year of publication, title, country of the first author, language of publication, source (search system), article type, and summary of the topic of the article.

Data Analysis

Data analysis will be undertaken to identify attributes mentioned in the literature reviewed, conduct a frequency count of attributes (analyze how many articles mention a given attribute), and identify broad qualitative themes.

Presentation of Results

Based on the framework for data analysis, the results will be presented in tabular form and in visual diagrammatic formats such as tree maps.

Discussion: Scoping Reviews

Each scoping review will conclude with a discussion of the salient findings.

Protocol for the Comparative Analysis

The third step of phase 1 is a comparative analysis of human and AI attributes. It is a narrative comparison, followed by a mathematical comparison, of two sets of attributes—human and AI. This analysis will investigate whether humans have one or more unique attributes that could influence decision-making

for the better and ensure that humans continue in meaningful decision-making roles in complex health services.

There is a growing awareness that appropriate methods are required to address the increasing complexity of health research. Therefore, the narrative comparison may not only include frames of reference, logical arguments, and links to each point in the argument but also incorporate the hermeneutic spiral. This is the iterative process of comparative analysis that "moves back and forth between individual elements of the text and the whole text in many cycles" [20].

For the mathematical comparison, qualitative comparative analysis (QCA) may be appropriate, as it is an established method used in social science research [21,22] and public health research [23]. It can be applied to the complexity of the proposed research, provide the in-depth analysis required, and produce broad enough contexts for generalizations to be made. Furthermore, as it is based on set theory [24], it can be used to frame human and AI attributes as sets and examine any relationships between these sets. The data sets generated in the proposed research are likely to be of an appropriate size for QCA to be applied. However, if the size is not suitable for QCA, related methods of analysis may be used. For example, cross-case analysis [21] could be used for small data sets and linear regression analysis [22] for large data sets.

Method

A comparative analysis will be performed on the human and AI attributes identified and mapped in the first and second scoping reviews of phase 1. The mathematical comparison will proceed as follows:

- Each set of attributes (human and AI) will be viewed as a mathematical set.
- Each set could be divided into subsets such as unique and nonunique attributes.
- A comparative analysis of these sets and subsets will then be undertaken to determine whether humans may have one or more unique attributes that influence decision-making.

Tools

Software suited for QCA will be used to complete this step. For instance, software such as NVivo (QSR International), ATLAS.ti (ATLAS.ti Scientific Software Development GmbH), Quirkos (Quirkos Software), or Tosmana (University of Trier) may be suitable.

Discussion: Comparative Analysis

The comparative analysis will conclude with a discussion of the salient findings.

Protocol for the Simulation

The fourth and final step in phase 2 of the proposed research is a simulation based on mathematical modeling. Its purpose is to explore whether humans are likely to compete, cooperate, or converge with AI to continue in meaningful decision-making roles in complex health services. This will be achieved by creating a virtual system, using mathematical modeling, that closely resembles the nonclinical health care environment. Human attributes identified in the first scoping review in phase 1 will be used to simulate a human decision maker within the simulated environment. Similarly, AI attributes identified in the second scoping review will be used to simulate an AI decision maker. Simulations will then be conducted to explore, observe, and document whether humans are likely to compete, cooperate, or converge with AI.

Simulations based on mathematical modeling inform decisions in many health care settings [23]. In the last 5 to 6 years, three contemporary models have been successfully used in simulations in health care design and prediction: the system dynamics model (SDM), the agent-based model (ABM), and the hybrid SDM-ABM model. One or more of these models could be deployed in the simulation in phase 2 of the proposed research.

These models use the concept of players, known as agents, who interact in a system or environment.

SDM can be used to simulate changes to a system over a period of time [25]. It provides an effective view of the system, or environment, at the macro level. ABM is effective in simulating environments and interactions between one or more decision-making agents [26]. These agents can make decisions based on their own attributes, interactions with other agents, interactions with the modeled environment, or a combination of these [27]. ABM provides effective views of agents and environments at the micro level. The hybrid SDM-ABM model provides both macro and micro views of environments and agents [28,29].

Method

The simulation may use the SDM, ABM, or hybrid model, or the most appropriate combination of the three.

Tools

Software tools will be required to complete the simulation. Maple 2021 (Maplesoft) software is currently the most suitable, as it has the depth and breadth needed for academic research that involves the simulation of complex, dynamic systems. This software has been used for complex simulations in fields as diverse as finance [30] and robotics [31,32].

Discussion: Simulation

The simulation will conclude with a discussion of the salient findings.

Ethical Considerations

Ethics approval is not required because this research project involves scoping reviews of literature, mathematical models, and simulation. It does not include studies that involve humans or other living beings.

Results

The results will be presented in tabular form and visually intuitive formats. For the comparative analysis and simulation, results will be presented in digital storytelling and multimedia formats as well. Table 1 shows the protocol for the presentation of results.

Table 1. Protocol for the presentation of results.

Step (phase)	Study	Tabular formats?	Heat maps?	Digital storytelling?	Multimedia?
Step 1 (phase 1)	Scoping review to identify and map human attributes that influence decision-making in complex health services	✓	✓		
Step 2 (phase 1)	Scoping review to identify and map AI[a] attributes that influence decision-making in complex health services	✓	✓		
Step 3 (phase 1)	Comparative analysis of the two sets of attributes: human and AI	✓	✓	✓	✓
Step 4 (phase 2)	Simulation of a health regulation and policy environment with human and AI agents	✓	✓	✓	✓

[a]AI: artificial intelligence.

Discussion

There are established guidelines for a priori protocols [33] that are developed before undertaking scoping reviews in health research. Numerous examples of such protocols are found in the literature. However, there is a dearth of guidance on establishing a protocol of protocols for methods used in complex health research. This paper takes the first step toward building a scaffolding for future guidance in this regard. It provides not only a roadmap for the proposed research but also an example of a protocol of protocols. This may be relevant and useful in spheres of complex research such as human-AI interaction and health informatics. This may also be an opportunity to further investigate the issue of bias, the dominance of rationality, and the likely influence of intuition.

Conflicts of Interest

None declared.

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Abbreviations

ABM: agent-based model
AI: artificial intelligence
PCC: Population, Concept, and Context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
QCA: qualitative comparative analysis
SDM: system dynamics model

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Protocol

Virtual Reality–Augmented Physiotherapy for Chronic Pain in Youth: Protocol for a Randomized Controlled Trial Enhanced With a Single-Case Experimental Design

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Abstract

Background: Chronic musculoskeletal (MSK) pain is a prominent health concern, resulting in pain-related disability, loss of functioning, and high health care costs. Physiotherapy rehabilitation is a gold-standard treatment for improving functioning in youth with chronic MSK pain. However, increasing physical activity can feel unattainable for many adolescents because of pain-related fear and movement avoidance. Virtual reality (VR) offers an immersive experience that can interrupt the fear-avoidance cycle and improve engagement in physiotherapy. Despite promising initial findings, data are limited and often lack the rigor required to establish VR as an evidence-based treatment for MSK pain.

Objective: This trial evaluates physiorehabilitation with VR in adolescents with MSK pain. This protocol outlines the rationale, design, and implementation of a randomized controlled trial enhanced with a single-case experimental design.

Methods: This study is a 2-group randomized controlled trial assessing the use of physiorehabilitation with VR in adolescents with MSK pain. The authors will collaborate with physical therapists to integrate VR into their standard clinical care. For participants enrolled in standard physiotherapy, there will be no VR integrated into their physical therapy program. Primary outcomes include physical function and engagement in VR. Secondary outcomes include pain-related fear and treatment adherence. Moreover, we will obtain clinician perspectives regarding the feasibility of integrating the intervention into the flow of clinical practice.

Results: The pilot study implementing physiorehabilitation with VR demonstrated that high engagement and use of physiorehabilitation with VR were associated with improvements in pain, fear, avoidance, and function. Coupled with qualitative feedback from patients, families, and clinicians, the pilot study results provide support for this trial to evaluate physiorehabilitation with VR for youth with chronic MSK pain. Analysis of results from the main clinical trial will begin as recruitment progresses, and results are expected in early 2024.

Conclusions: Significant breakthroughs for treating MSK pain require mechanistically informed innovative approaches. Physiorehabilitation with VR provides exposure to progressive challenges, real-time feedback, and reinforcement for movement and can include activities that are difficult to achieve in the real world. It has the added benefit of sustaining patient motivation and adherence while enabling clinicians to use objective benchmarks to influence progression. These findings will inform the

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decision of whether to proceed with a hybrid effectiveness-dissemination trial of physiorehabilitation with VR, serving as the basis for potential large-scale implementation of physiorehabilitation with VR.

Introduction

Background

Chronic musculoskeletal (MSK) pain in adolescence is a significant public health concern with median prevalence rates of 11% to 38% and 3% to 5% in adolescents experiencing significant pain-related disability [1,2], costing US $19.5 billion annually in the United States alone [3]. Notwithstanding the personal burden and persistent physical and economic consequences for families, chronic pain in adolescence can also predispose the development of adult chronic pain [2,4]. For adolescents and adults, functional restoration requires the progressive increase in physical activity [5-12] despite the presence of pain, with physiotherapy (PT) [13] being a critical element in guiding progression. Despite the well-documented importance of PT, daring to increase movement while in pain can be physically and emotionally unattainable. Fear of pain has been identified as a particularly salient influence on pain outcomes [14-17], at times hindering clinical improvement [18].

Virtual reality (VR) has the potential to facilitate breaking the cycle of fear of movement and avoidance during PT. VR enables the user to interact with a computer-generated environment that harnesses visual, audio, and tactile sensory inputs to provide an immersive experience to facilitate reaching therapeutic goals. Within the context of PT, access to a multisensory 3D experience can support patients in overcoming obstacles [19,20] that can seem insurmountable in the *natural* world, such as physical movement using the affected limb. Owing to increased market availability and declining costs, VR use in health care has rapidly increased in recent years.

Although most commonly applied in the context of acute pain relief [20,21], research conducted by our group has highlighted the potential for application in the realm of chronic pain rehabilitation [22-24]. We conducted a pilot feasibility study, which included the development and testing of several unique VR experiences for youth undergoing chronic pain treatment and rehabilitation [24]. Included in the pilot study were 17 youths with chronic pain who reported high levels of immersion, an important indicator of the level of engagement participants felt in their VR world. For adolescents with multi-session data (n=8), improvements in pain, fear, avoidance, and functional limitations were observed. These findings, coupled with qualitative feedback from patients, psychologists, physiotherapists, and occupational therapists, provide initial support for physiorehabilitation with VR as an acceptable, feasible, and potentially useful intervention for patients with chronic pain [24].

These findings are consistent with the extant literature, where VR has been suggested as an alternative to opioids with the therapeutic mechanisms centered on distraction [25,26]; neuromodulation of body perception [27]; and exposure to feared and, thus, avoided movements [22,23,28,29]. Moreover, VR can potentially enhance motivation and engagement during physical rehabilitation, facilitate repetitive motions, and incorporate real-time and longitudinal feedback for the patient and clinician [30-33]. Perhaps most exciting is the prospect of VR to engage several cortical and subcortical neuronal circuits that potentiate learning and recovery [34,35], with the potential for enhanced cortical reorganization [21,36]. Although most studies reflect proof-of-concept, feasibility, and pilot randomized controlled trial (RCT) studies, a recently published RCT of VR combined with exercise for adults with fibromyalgia demonstrated greater improvements in pain, fear of movement, fatigue, level of physical activity, and quality of life when compared with exercise alone [28].

Current VR studies lack the rigor and measurements over time that are critical for establishing VR as an evidence-based treatment for chronic pain rehabilitation. Moreover, the successful implementation of VR in practice requires further assessment. Initial findings suggest that clinicians find that VR supports individually tailored treatment, increases engagement in treatment, and improves the provider-client relationship, but clinicians also report persistent technology-related issues, adverse patient experiences of dizziness or headache with VR, and barriers associated with initial onboarding of the VR technology—namely, initial cost, lack of intuitive technology, need for training and technological support, and lack of staff to support implementation [37]. Altogether, the successful deployment of VR in chronic pain rehabilitation will require evidence coupled with a clear understanding of its feasibility and implementation challenges.

Objectives

This study is a randomized controlled feasibility trial enhanced with a single-case experimental design (SCED) to compare physiorehabilitation with VR with standard PT implemented within routine clinical care. We will evaluate the functional outcomes of physiorehabilitation with VR and standard PT and characterize the feasibility of a future hybrid effectiveness-dissemination trial of PT rehabilitation treatment with VR in routine PT practice. The primary effectiveness outcome is physical function for the adolescent, and the secondary outcomes are pain-related fear and fear of movement. For feasibility, the primary outcomes are treatment acceptability, engagement, and implementation in routine clinical care, and

secondary outcomes are adverse events with VR and treatment feedback from patients and clinicians.

Methods

Ethics Approval

This study was approved by Advarra, an external Institutional Review Board (IRB) for multisite studies, as well as by the IRB at Stanford University (eProtocol 63582). Procedures will follow the ethical standards of the IRB and the Helsinki Declaration of 1975 as revised in 2000. Informed consent and assent will be obtained from all participants. This study is registered at ClinicalTrials.gov (NCT04636177).

Participants and Setting

Adolescent participants will be recruited from one of the collaborating outpatient rehabilitation sites: an outpatient PT center within an academic medical center (eg, Stanford Children's Health) or a private outpatient PT center (eg, California Rehabilitation and Sports Therapy and Agile Physical Therapy). Adolescents are eligible to participate if they (1) have localized or diffuse MSK pain [38,39], (2) are aged between 10 and 17 years, and (3) are proficient in the English language. Adolescents are ineligible to participate if they have (1) pain because of acute trauma (eg, active sprain, fracture, or surgery); (2) significant cognitive impairment; (3) significant psychiatric diagnoses that would interfere with treatment or VR use, such as active psychosis or suicidality; or (4) a condition that interferes with VR use, including history of seizure, facial injury precluding safe placement of headset, visual impairment, and significant hearing impairment affecting the ability to follow audio instructions, as extracted from the medical record and confirmed by the referring clinician.

Recruitment

Adolescents who meet the eligibility criteria and their caregivers are informed of the study by their clinicians when they present to one of the clinical recruitment sites for their initial PT evaluation. In addition, a study flyer is posted on a bulletin board of all active clinical studies in the patient waiting room at each recruitment site. Clinicians and the flyer direct interested adolescents and caregivers to fill out an eligibility web-based screening form, which allows the research team to contact the family directly. If the eligibility criteria are met, a research coordinator contacts the family for additional screening and to complete the assent and consent process.

Study Design

This is a 2-group RCT enhanced with SCED using multiple measures. In single-case experiments, a participant is observed repeatedly at different levels of at least one independent variable, for example, assessing engagement with PT exercises throughout pretreatment baseline and across treatment. To accomplish this, adolescents will complete daily diaries during a pretreatment phase (estimated to range from 7 to 14 days in duration) and daily diaries from day 0, when VR headsets are distributed, to end of treatment (day 0+N) and for 7 days at the 3-month follow-up. Upon arrival at the first treatment session after the baseline assessment, adolescents are informed if they are assigned to physiorehabilitation with VR or standard PT. The treatment phase consists of an estimated 6 to 8 PT sessions of 1 hour, with the number and frequency of treatment sessions determined at the discretion of the clinician. In total, the study is expected to be completed over the course of 32 months. A total of 24 months are dedicated to study enrollment, randomization, and completion of the intervention. An additional 8 months are dedicated to completing 3-month follow-up assessments and data analysis (Figure 1).

Figure 1. Study flow depicting eligibility, consent, baseline, discharge, and 3-month follow time points. DD: daily diary; PT: physiotherapy; VR: virtual reality.
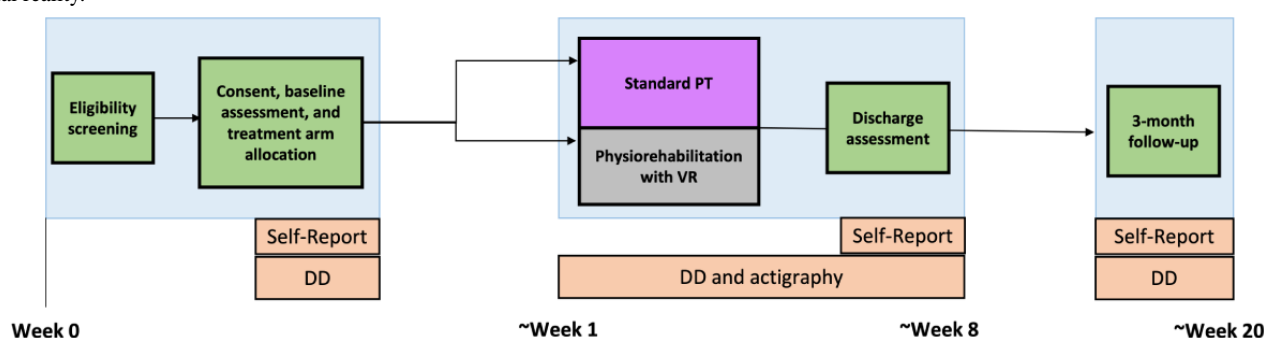
Rationale for Study Design

RCTs provide robust estimates of the between-subject treatment response (the average difference between the 2 groups) but do not provide sufficient data on how a specific individual responds to a given treatment because of heterogeneity in treatment effects. That is, an individual patient in an RCT could show no improvement, have an adverse reaction to treatment, or benefit from the active comparator even if the active comparator is shown to be statistically inferior. Although subgroup analyses are now encouraged to better elucidate differences in treatment responses between individuals, they require large cohorts of patients for sufficiently powered analyses. For specialized patient groups such as youth experiencing chronic pain, obtaining sufficiently large cohorts for mediation and moderation analyses within the confines of RCTs is often not feasible. SCED allows for the collection of statistically rigorous data at the level of the individual patient. Moreover, such data can be used in meta-analyses of individual effect sizes and multilevel modeling to provide group-level results from small and distinctive cohorts.

Randomization

Randomization schemes are developed and maintained by the study statistician, DB. Once enrolled, participants are randomized to either physiorehabilitation with VR or standard PT and 2×3 stratified on fear or disability—high fear or high disability (empirically validated clinical cutoff scores of 26-40 on the Fear of Pain Questionnaire-Short Form [FOPQ-SF] [40] *or* 30-60 on the Functional Disability Inventory [FDI] [41], respectively) *or* low or moderate fear *and* low or moderate disability (FOPQ-SF ≤25 *and* FDI ≤29)—and pain site (upper and trunk *or* lower *or* diffuse). A block randomization strategy is used with randomly generated blocks of 2 and 4 to ensure near-equal distributions across arms and minimize the probability of predicting the next assignment. The study biostatistician creates separate randomization lists for each of the 6 strata before the start of patient recruitment, with each list long enough to include the total planned study size. A series of block sizes (either 2 or 4, with probability weights of two-thirds and one-third, respectively) is randomly created and, within each block, half is randomly assigned to physiorehabilitation with VR and the other half to standard PT. Copies of the randomization lists are kept by the biostatistician and research coordinator and not shared with other members of the team.

Intervention Procedures

PT Procedure

All participants engage in a full course of PT for MSK pain that is delivered by a trained and licensed physiotherapist. PT sessions are individually tailored based on the Guide to Physical Therapist Practice 3.0, consisting of (1) therapeutic exercise (strengthening and endurance exercises), (2) neuromuscular re-education (balance and proprioception exercises), (3) therapeutic activities (functional performance and activities of daily living), and (4) use of modalities (heat or cold packs). All adolescents receive a home exercise program (HEP) as part of the standard PT treatment. The full course of PT includes approximately 6 to 8 PT sessions delivered over 6 to 12 weeks. An adequate dose of treatment is considered to be 75% completion of the prescribed sessions. The number of treatment sessions varies based on patient presentation and individualized treatment goals as determined by the clinician and research team. Patients can continue any treatments they are currently involved in. If they choose to initiate a new treatment after PT treatment begins, they are asked to notify the research team immediately as it may affect their involvement in the study.

VR Procedure

All participants receive a VR headset to use for the duration of treatment. The research team provides participants with an Oculus Quest 2 (Oculus) VR headset and orients the adolescents to its functionality.

Standard PT

For standard PT participants, the VR headset is preloaded with distraction-based games for recreational use at home until treatment is completed (Table 1). Clinicians do not discuss VR headset use with the standard PT participants. The research team provides an orientation session regarding the VR headset functions and preloaded games.

Table 1. Standard physiotherapy rehabilitation virtual reality (VR) game content.

Game	Description	Distraction type
Color Space[a]	Color in pieces of beautiful art and environments in virtual reality.	Creative design
Cubism[a]	Challenge the mind by solving deceptively simple puzzles and assembling increasingly complex shapes out of colorful blocks.	Puzzle game
Vacation Simulator[a]	Find optimal relaxation and efficient memory making while being at home.	Simulation
NatureTrek VR[a]	Explore tropical beaches, underwater oceans, and >20 different animals. Command the weather, take control of the night, or shape your own world.	Exploration
Star Chart[a]	Explore the Solar System, view constellations, and watch meteor showers. Stand on the moon; explore Mars with the Curiosity rover; and hold planets, moons, and stars.	Exploration
Wander[a]	Teleport to almost anywhere in the world, from the London Bridge to the Great Pyramids of Egypt.	Exploration

[a]Denotes game accessible through a public app store.

Physiorehabilitation With VR

Physiorehabilitation with VR participants bring their VR headset to each PT appointment, and a portion of the session can be delivered in VR. Participating clinicians are told that the goal for VR use in a session is at least 8 minutes, but they are also given clinical decision-making power to use VR more or less as they determine clinically feasible. Physiorehabilitation with VR engages participants in a series of immersive games customized and chosen to allow for a progressive increase in standing endurance and support individual PT goals (Table 2). Importantly, this trial does not test a specific VR game or program but the broad implementation of VR in clinical practice.

Games implemented for this purpose may include Fruity Feet (Stanford Chariot Program), Alien Defense (Stanford Chariot Program), Beat Saber (Beat Games), and Tilt Brush (Google), among others. Physiotherapists discuss VR headset use with physiorehabilitation with VR participants and actively incorporate VR activities into the HEP. The pediatric pain rehabilitation team at Stanford Children's Health worked collaboratively with the Stanford Chariot Program to develop physiorehabilitation with VR content [24]. Fruity Feet was developed using a user-centered approach with patient and clinician end-user feedback across four phases: (1) needs assessment, (2) prototyping, (3) iteration and refinement, and (4) feasibility and acceptability. It was designed to be

developmentally appropriate for youth by focusing on fun while leaning on stylized graphics and encouraging in-game feedback. Gameplay mechanics were built around PT movement goals, for example, multiplanar stepping (ie, forward, side, and back), stomping, marching, kicking, raising legs to different heights, and active ankle range-of-motion tasks for lower extremities. Importantly, it was also built to scale to a patient's mobility, ensuring that patients of all abilities could play the game and benefit from the VR intervention. Consistent with the recommendations for VR clinical trial methodology, this user-centered iterative design process yielded a program that, in addition to gamification, provides back-end mechanics, giving PT clinicians the capability to control intensity, affected side or extremity emphasis, mirroring, and movement exaggeration to leverage the potential neuromodulatory effects of VR coupled with targeted pain PT.

Table 2. Physiorehabilitation with virtual reality (VR) game content.

Game	Description	Rehabilitation engagement
Alien Defense Foot Cannon[a]	Squashing descending aliens before time runs out	Leg and hip strengthening with light cardiovascular exercise
Fruity Feet[a]	Stomping and kicking falling fruits and vegetables before time runs out	Leg and hip strengthening with light cardiovascular exercise
Alien Defense Slingshot[a]	Destroying aliens using the arms as a slingshot	Arm and shoulder strengthening
Bait![b]	Fishing and passing time in front of water	Arm and shoulder strengthening
Fruit Ninja[b]	Slicing fruit that is thrown the player's way	Arm and shoulder strengthening
Beat Saber[b]	Slicing blocks and dodging obstacles to the beat of the music	Arm, shoulder, leg, glute, and hip strengthening with cardiovascular exercise
BOX VR[b]	Punching and dodging obstacles to the beat of the music	Arm, shoulder, leg, glute, and hip strengthening with cardiovascular exercise
Dance Central[b]	Dance battling computerized opponents in various locations to popular songs	Cardiovascular exercise and full-body strengthening through dancing
OhShape[b]	Holding fun poses and dodging obstacles to the beat of the music	Arm, shoulder, leg, glute, and hip strengthening with light cardiovascular exercise and static holds
Pro Putt[b]	Playing VR golf	Arm swings and hip rotations
Racket Fury: Table Tennis[b]	Playing VR table tennis	Arm, shoulder, leg, glute, and hip strengthening with light cardiovascular exercise
Racket NX[b]	Hitting a ball against a 360 dome with a racket	Arm, shoulder, leg, glute, and hip strengthening with cardiovascular exercise
Space Burgers 2[a]	Racing through exciting, food-filled galaxies with optional stationary bicycle	Cardiovascular exercise through stationary biking or running arm motion
Synth Riders[b]	Following the targets as they lead the player through dance moves to popular songs	Cardiovascular exercise and full-body strengthening through dancing
Tilt Brush[b]	Drawing and painting in a 3D space	Arm and shoulder strengthening

[a]Denotes games accessible through Invincikids.

[b]Denotes games accessible through a public app store.

Assessment of Outcomes

Overview

Adolescents and caregivers complete baseline, discharge, and 3-month follow-up assessments. The adolescent completes daily diaries, and the caregiver completes weekly health cost diaries from the date of consent until the end of treatment at discharge. An additional 7 daily diaries by the adolescent and 1 additional health cost diary by the caregiver are completed at the start of the 3-month follow-up. All adolescent and caregiver surveys are completed on the web through the secure web-based app REDCap (Research Electronic Data Capture; Vanderbilt University), and the diaries are completed through the mobile phone–based app LifeData (LifeData, LLC) [42]. Baseline and discharge assessments are completed in person or on the internet, with the 3-month follow-up completed on the internet. Table 3 details the outcomes, measure names, respondents, and time of assessment.

Table 3. Outcomes (primary, secondary, additional, single-case experimental design, exploratory, and implementation) and covariates.

Category, subcategory, and measure	Respondent	Time point administered[a]			
		0	1	2	3
Effectiveness					
Primary outcomes: physical function					
Lower Extremity Functional Scale	Adolescent	✓		✓	✓
Upper Extremity Functional Index	Adolescent	✓		✓	✓
Secondary outcomes: pain-related fear and avoidance					
Fear of Pain Questionnaire-Short Form	Adolescent	✓		✓	✓
Photographs of Daily Activities for Youth	Adolescent	✓		✓	✓
Tampa Scale for Kinesiophobia-17	Adolescent	✓		✓	✓
Feasibility					
Primary outcomes: treatment acceptability and engagement					
Treatment satisfaction questionnaire	Adolescent			✓	✓
Virtual Reality acceptability questionnaire	Adolescent[b]			✓	
Virtual Reality acceptability questionnaire	Clinician[b]			✓	
Pittsburgh Rehabilitation Participation Scale	Clinician		✓		
ManageXR Usage data	Researcher		✓		
Secondary outcomes: treatment expectations, feedback, and adherence					
Treatment Expectancy and Credibility: Youth	Adolescent	✓			
Semistructured interview	All			✓	
Home exercise program	Clinician		✓		
VR[c] adverse events survey	Clinician		✓		
ManageXR usage data	Researcher		✓		
Percentage of dropouts	Researcher		✓		
Tracked adherence to treatment and surveys	Researcher		✓		
Additional					
Outcomes: multiple					
Functional Disability Inventory	Adolescent	✓		✓	✓
PROMIS[d] Pediatric Mobility scale	Adolescent	✓		✓	✓
PROMIS Pain Interference	Adolescent	✓		✓	✓
Pain Catastrophizing Scale: Youth	Adolescent	✓		✓	✓
Pain Intensity Numeric Rating Scale	Adolescent	✓		✓	✓
Pain Self-Efficacy Scale: Youth	Adolescent	✓		✓	✓
Patient Global Impression of Change	Adolescent			✓	✓
Presence Measure: Youth	Adolescent			✓	
Single case experimental data					
Outcomes: engagement self-efficacy, distraction, function, and pain					
Daily diary	Adolescent	✓	✓		✓
Exploratory					
Outcomes: physical activity and health-related costs					
Modified Borg Dyspnea Scale	Clinician		✓		
Physical assessment	Adolescent	✓		✓	

Category, subcategory, and measure	Respondent	Time point administered[a]			
		0	1	2	3
ActiGraph tracked physical activity levels	Researcher	✓		✓	
Health cost diary	Caregiver	✓	✓	✓	✓
Covariates					
Outcomes: demographics and pain history					
Demographic survey	Caregiver	✓			
Medical history survey	Caregiver	✓			

[a]0=baseline, 1=discharge, 2=assessed throughout treatment, either daily (adolescents), weekly (caregivers) or after each physiotherapy session (clinicians), and 3=3-month follow-up.

[b]Only completed by those in physiorehabilitation with virtual reality (VR) arm.

[c]VR: virtual reality.

[d]Measures that are assessed throughout treatment, either daily or after each physiotherapy session.

[e]HEP: home exercise program.

[d]PROMIS: Patient-Reported Outcomes Measurement Information System.

Baseline Assessment

Once eligibility is confirmed, the baseline assessment is completed in 2 parts. First, adolescents and caregivers complete consent and baseline self-report questionnaires. Adolescents and caregivers are oriented to the mobile diaries, which adolescents complete daily and caregivers complete weekly while enrolled in treatment. Following the baseline study visit, adolescents and caregivers undergo a pretreatment data collection period for the number of days between consent and their subsequent PT appointment. During this time, adolescents complete daily diaries, and caregivers complete weekly health cost diaries. The second part of the baseline assessment takes place at the adolescent's next PT session, during which a research coordinator completes a baseline physical assessment via ViFive (ViFive, Inc) [43], a motion capture app, consisting of the 6-minute Walk Test, Single Leg Balance Test, and Closed Kinetic Chain Upper Extremity test, and the adolescent receives an ActiGraph watch (ActiGraph, LLC) that monitors sleep and activity level throughout the trial.

Discharge Assessment

The discharge assessment occurs after all PT treatment sessions are completed. The discharge assessment consists of a physical assessment at the final session as well as self-report questionnaires. The diaries conclude, and the adolescents return the ActiGraph watch as well as the VR headset. Following completion of the study, adolescents and caregivers in the physiorehabilitation with VR group complete Zoom (Zoom Video Communications)-based or in-person semistructured interviews to provide feedback regarding their treatment experience. Finally, clinicians complete an acceptability measure assessing their experiences integrating VR into patient sessions for each participant in the physiorehabilitation with VR arm and, subsequent to discharge of their final trial patient, will complete Zoom-based semistructured interviews to further assess PT perceptions of feasibility in integrating VR.

Follow-up Assessment

The follow-up assessment occurs at 3 months after discharge, at which time adolescents complete a set of self-reported questionnaires as well as 7 additional daily diaries. Caregivers complete 1 additional health cost diary. Adolescents receive the battery of self-report questionnaires via REDCap and respond to the daily diaries via LifeData. Caregivers receive their single health cost diary via REDCap.

Process Assessment

Following each PT session, the adolescent's clinician completes a brief series of questions regarding the adolescent's engagement in PT and exercise exertion as well as any adverse events that occurred during the session. Clinicians document and describe the HEP they prescribed to the adolescent to be completed between sessions.

Effectiveness Outcomes

The primary effectiveness outcome is physical function (adolescent), measured using the Lower Extremity Functional Scale (LEFS) and Upper Extremity Functional Index (UEFI). The secondary effectiveness outcome is pain-related fear and avoidance, measured using the FOPQ-SF, the Photographs of Daily Activities for Youth (PHODA-Youth), and the Tampa Scale for Kinesiophobia-17 (TSK-17).

LEFS Measure

The LEFS is a 20-item self-report survey that asks participants to report on their ability to perform everyday tasks using their lower extremities [44]. Participants rate the level of difficulty associated with a range of everyday activities on a 5-point Likert scale (0="extreme difficulty/unable to perform activity" to 4="no difficulty"). Summed scores indicate the level of function, with higher scores indicating more functionality.

UEFI Measure

The UEFI is a 20-item self-report survey that asks participants to report on their ability to perform everyday tasks using their upper extremities [45]. Participants rate the level of difficulty associated with a range of everyday activities on a 5-point Likert

scale (0="extreme difficulty/unable to perform activity" to 4="no difficulty"). For both the LEFS and UEFI, scores are summed, with a maximum score of 80 and where higher scores indicate better functioning. A minimum level of detectable change (confidence level=90%) is defined as a ≥9-point change based on the existing literature on patients with pain [46-48].

FOPQ-SF Measure

The FOPQ-SF consists of 10 items, with each item rated on a 5-point Likert scale (0="strongly disagree" to 4="strongly agree") [49]. The FOPQ-SF contains questions assessing both fear of pain and avoidance of activities in the context of pain. The total score is derived by summing the items, with higher scores indicating greater pain-related fear and avoidance of activities.

PHODA-Youth Measure

The PHODA-Youth is a 50-item measure assessing worry associated with activities of daily living (13 items), sports or exercise activities (15 items), school or social activities (13 items), and upper extremity activities (9 items) [50]. To complete each item, the patient is exposed to a photograph and label of the activity and asked to rate their worry "that this activity would be harmful to your pain" by dragging each photograph along a "worry thermometer" ranging from 0 to 10. Each photograph is given a rating according to its position on the thermometer. Patients then rate their anticipated pain if they engaged in the activity. The mean perceived harm and anticipated pain scores (ranging from 0 to 10) are calculated as the sum of each rating divided by the total number of pictures.

TSK-17 Measure

The TSK-17 is a 17-item self-report measure assessing fear of movement that has been implemented in a variety of pain conditions [51], including youth with chronic pain [52,53]. The 2 subscales assess activity avoidance and somatic focus, with higher total and subscale scores indicating a greater fear of movement, activity avoidance, and somatic focus.

Feasibility Outcomes

The primary feasibility outcomes are treatment satisfaction, acceptability, and engagement. The secondary feasibility outcomes are treatment expectations, treatment feedback, treatment fidelity, treatment adherence and retention, and adverse events.

Treatment Satisfaction

Treatment satisfaction is assessed using an adapted version of the Pain Service Satisfaction Test. The Pain Service Satisfaction Test is a 22-item measure that asks patients about their experiences in pain treatment, for instance, perceptions of the effectiveness of the intervention, the treatment team, and the impact on their own outcomes [54]. Scores are summed based on responses, with higher scores indicating greater satisfaction with treatment.

Acceptability

To evaluate the acceptability of the treatment intervention, the VR acceptability questionnaire is an 11-item measure completed by patients and clinicians at discharge. For patients, it asks about their enjoyment of VR, satisfaction with the VR treatment, perceived reduction of pain, and barriers experienced during the physiorehabilitation with VR intervention. For clinicians, it assesses their perceived difficulty associated with VR use, assessment of the games, ability of VR to facilitate engagement, overall satisfaction levels, and willingness to implement VR in the future for those in the physiorehabilitation with VR arm.

Treatment Engagement

To assess patient engagement in the physiorehabilitation with VR intervention, clinicians complete a postsession survey following every session, which includes the Pittsburgh Rehabilitation Participation Scale [55]. Clinicians rate the perceived patient's motivation. Engagement is rated on a 6-point Likert scale (1="none" to 6="excellent"). Clinicians do not fill out a survey if the patient did not attend their session. Clinicians are instructed to select a lower rating when in doubt, for instance, "good" rather than "very good." In addition, VR use is tracked via the ManageXR software (Mighty Immersion, Inc) preloaded onto each VR headset. Analytics regarding which VR games are played, duration of play per game, total play duration, and the number of application launches are displayed in the Oculus dashboard (Figure 2). The Oculus dashboard will be used to assess engagement in VR and fidelity to VR use for physiotherapy and HEPs.

Figure 2. Oculus analytics dashboard via ManageXR software (Mighty Immersion, Inc) capturing virtual reality engagement.
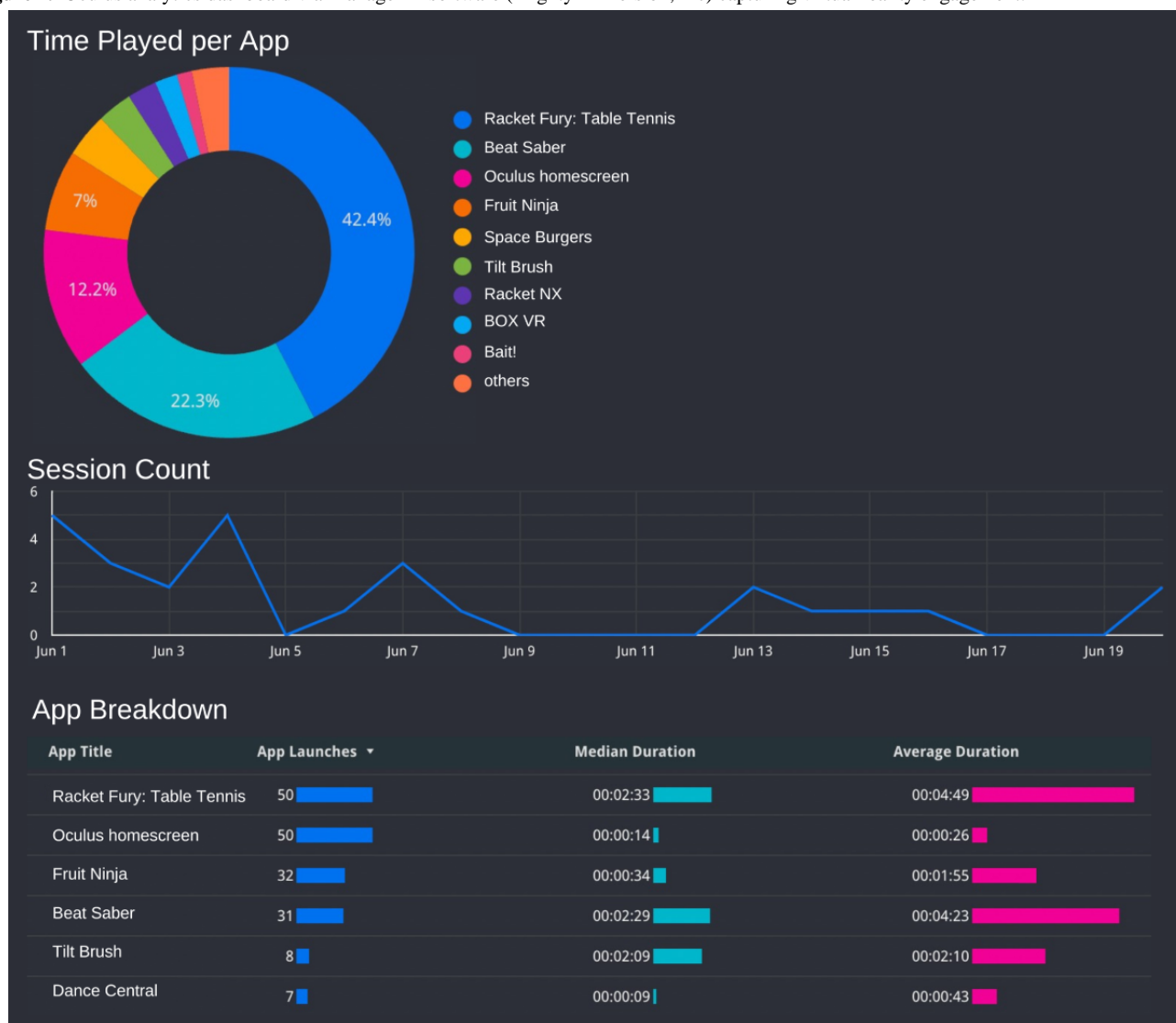
Treatment Expectancy

Treatment expectations are measured using the child Treatment Expectancy and Credibility measure (TEC-C) [56]. The TEC-C comprises 6 items assessing expectations related to the effectiveness of the current treatment. The TEC-C is completed by the patient after the first treatment session.

Treatment Feedback

Patient and clinician feedback regarding the VR intervention is collected via semistructured interviews. The goal of the interviews is to better understand the experience of using VR, strengths of the VR intervention, and barriers or considerations for future use.

Treatment Fidelity

Treatment fidelity is assessed by examining VR use analytics displayed on the ManageXR dashboard (Figure 2). For the physiorehabilitation with VR arm, clinicians aim for at least 8 minutes of the session to be dedicated to VR exercises and, therefore, the number of sessions reaching this benchmark can be tracked. In addition, at least 15 minutes of the HEP include VR in the physiorehabilitation with VR arm. HEPs across both

treatment arms are requested in the clinician postsession survey and, for the physiorehabilitation with VR arm, we can compare with VR use tracked in the ManageXR software.

Treatment Adherence and Retention

Adherence and retention are assessed by examining patient adherence to daily diaries, the percentage of patients who drop out before treatment completion, and the percentage of sessions completed on schedule.

Adverse Events

The clinician tracks adverse events related to VR use. Specifically, in the postsession survey, clinicians can indicate any adverse events of dizziness, nausea, or disorientation that occurred. As part of clinician orientation to the VR, important safety precautions are discussed to reduce the potential for accidents to occur.

Additional Outcomes

Additional outcomes of interest include changes in functional disability, mobility, pain interference in life, pain catastrophizing, pain intensity, self-efficacy while in pain, global impression of change, and perceived immersion in the VR

technology. Table 3 details the outcomes, measure names, respondents, and time of assessment.

Functional Disability

Functional disability is assessed using the FDI, a 15-item self-report measure of perceived difficulty in performing activities in the school, home, physical, and social contexts. Items are rated on a 5-point Likert scale (0="no trouble" to 4="impossible") [57]. Items are summed to obtain a total score, with higher scores indicating greater disability. The FDI is widely used in pediatric pain research and is recommended as the gold-standard measure of physical functioning in school-age children and adolescents for clinical trials in pediatric chronic pain.

Mobility

Mobility is assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS) Mobility measure, a subset of the PROMIS physical health function self-report outcomes [58]. This test is typically used in adult and pediatric populations with chronic conditions. The Mobility subscale measures perceived capabilities related to mobility tasks such as getting up from a chair or running. The PROMIS Mobility items are written in the past tense (eg, "I could..."), all use a standard recall of "in the past 7 days," and have a 5-point Likert scale (0="not able to do" to 4="with little to no trouble"). Scores are summed, with higher scores indicating greater mobility.

Pain Interference

The PROMIS Pain Interference instrument assesses patient perception of the impact of pain on their ability to engage across several life domains—namely, social, emotional, and recreational activities [58]. The PROMIS Pain Interference items use a standard recall of "in the past 7 days" with items such as "it was hard to have fun when I had pain." Responses are provided on a 5-point Likert scale (0="almost never" to 4="almost always"). PROMIS Pain Interference items are summed, with higher scores indicating more pain-related interference in a patient's life.

Pain Catastrophizing

The Pain Catastrophizing Scale-Children assesses negative cognitions associated with pain [59]. The Pain Catastrophizing Scale-Children comprises 13 items rated on a 5-point Likert scale (0="not at all true" to 4="very true"). A total score is obtained by summing the scores for all items. Higher scores indicate higher levels of catastrophic thinking.

Pain Intensity

Patients provide their pain rating when they complete their daily diary (Textbox 1) at the same scheduled time using a standard 11-point visual analog scale (0="no pain" to 10="most pain possible") [60]. Average pain intensity ratings are calculated for 7 days before the first treatment session (baseline average pain) and 7 days before the discharge assessment (discharge average pain).

Textbox 1. Daily diary items.

Engagement/fun

- I enjoyed my PT exercises

- How much *fun* did you have during your PT exercises?

Self-efficacy/confidence

- While doing your PT exercises, how *strong* did your body feel?

- While doing your PT exercises, how *easy and free* did your movement *feel*?

- While doing your PT exercises, how *worried* were you about *damaging* your body?

- *How confident* did you feel about *playing and doing physical things* after your PT?

Immersion/distraction

- I forgot everything around me during my PT exercises.

- How much *time* did you spend thinking about your pain during your PT exercises?

Lower Extremity Functional Scale/Upper Extremity Functional Index

- Today, because of my pain, I have _____ difficulty doing my usual work, chores, or school activities.

- Today, because of my pain, I have _____ difficulty doing my usual hobbies, recreational or sporting activities.

- Today, because of my pain, I have _____ difficulty going up or down 10 stairs (about 1 flight of stairs).

- Today, because of my pain, I have _____ difficulty lifting an object, like a bag of groceries, above my head.

Pain

- On a scale of 0 (no pain) to 10 (worst possible pain), tell us *how much pain you are feeling right now*.

Notable events

- Please make note of anything exciting or stressful that happened today.

Sleep

- What time did you get into bed last night?

- What time did you get out of bed this morning?

- How well did you sleep last night?

PT

- Did you have a physical therapy appointment today?

- How much time did you spend on your home exercise program today?

- Did you use VR today?

Self-efficacy

The Pain Self-Efficacy Scale-Children is a 7-item self-report questionnaire that measures patient beliefs about their ability to complete daily activities despite being in pain [61]. The Pain Self-Efficacy Scale-Children is scored on a 5-point Likert scale whereby patients rate their certainty about their ability to complete an activity (1="very sure" to 5="very unsure"), with higher scores indicating less self-efficacy in the context of pain.

Patients' Global Impression of Change

The self-report measure Patients' Global Impression of Change reflects a patient's belief about the efficacy of treatment [62]. The Patients' Global Impression of Change is a 7-point scale depicting a patient's rating of overall improvement. Patients

rate their change as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse."

VR Immersion

The child presence measure assesses the patients' perceived involvement or immersion, realism, and transportation while using the VR headset [63,64]. The measure comprises 12 items rated on a 3-point Likert scale (0="no" to 2="a lot"). A total score is obtained by summing the scores for all items. Higher scores indicate higher levels of immersion and engagement.

SCED Outcomes

The participant daily diary consists of 20 items assessing engagement or fun, self-efficacy, immersion or distraction,

function, pain, notable events, and sleep (Textbox 1). Daily diaries are collected via LifeData, an app that collects in-the-moment data from study participants by delivering push notifications to participants' smartphones [42].

Exploratory Outcomes

Modified Borg Dyspnea Scale

The Modified Borg Dyspnea Scale is completed by the patient after each appointment [65]. The Modified Borg Dyspnea Scale measures patient rate of perceived exertion to monitor and guide exercise intensity. The scale item states the following—"How much difficulty is your breathing causing you right now?"—and was slightly modified given the deliverance to state "How much difficulty did the patient's breathing cause them during today's therapy session?" Responses are provided on a 12-point scale (0="nothing at all," 0.5="very, very slight (just noticeable)," 5="severe," and 10="maximal").

Physical Assessment

To assess changes in physical ability and function, the 6-minute Walk Test [66], Single Leg Balance Test [67], and Closed Kinetic Chain Upper Extremity Stability Test [68] are performed at baseline and discharge. For the 6-minute Walk Test, patients walk back and forth in a straight line for 6 minutes, and the total distance covered is calculated. The Single Leg Balance Test consists of balancing on one leg at a time, and participants' scores reflect the amount of time they are able to balance within a 60-second time frame. The Closed Kinetic Chain Upper Extremity Stability Test assesses participants' upper body and core strength by asking them to start on their hands and knees or in a plank position and, while remaining in good form, continually tap the opposite hand that remains planted on the ground. The total score is the number of hand touches completed within the allotted time of 15 seconds. The Walk Test is recorded by a physiotherapist and research assistant. For the remaining 2 exercises, ViFive is used, a motion capture app that reads the patient's body and allows for automatized counting and timing (Figure 3). The ViFive technology can track additional informatics such as range of motion, balance, flexibility, and endurance metrics as well as real-time pose correction to the user. For example, ViFive captures the patient's body position during their Closed Kinetic Chain Upper Extremity Stability Test. Changes in performance from baseline to discharge across all 3 tests are assessed.

Figure 3. ViFive (ViFive, Inc) app screen showing 2 assessments delivered and captured by ViFive.
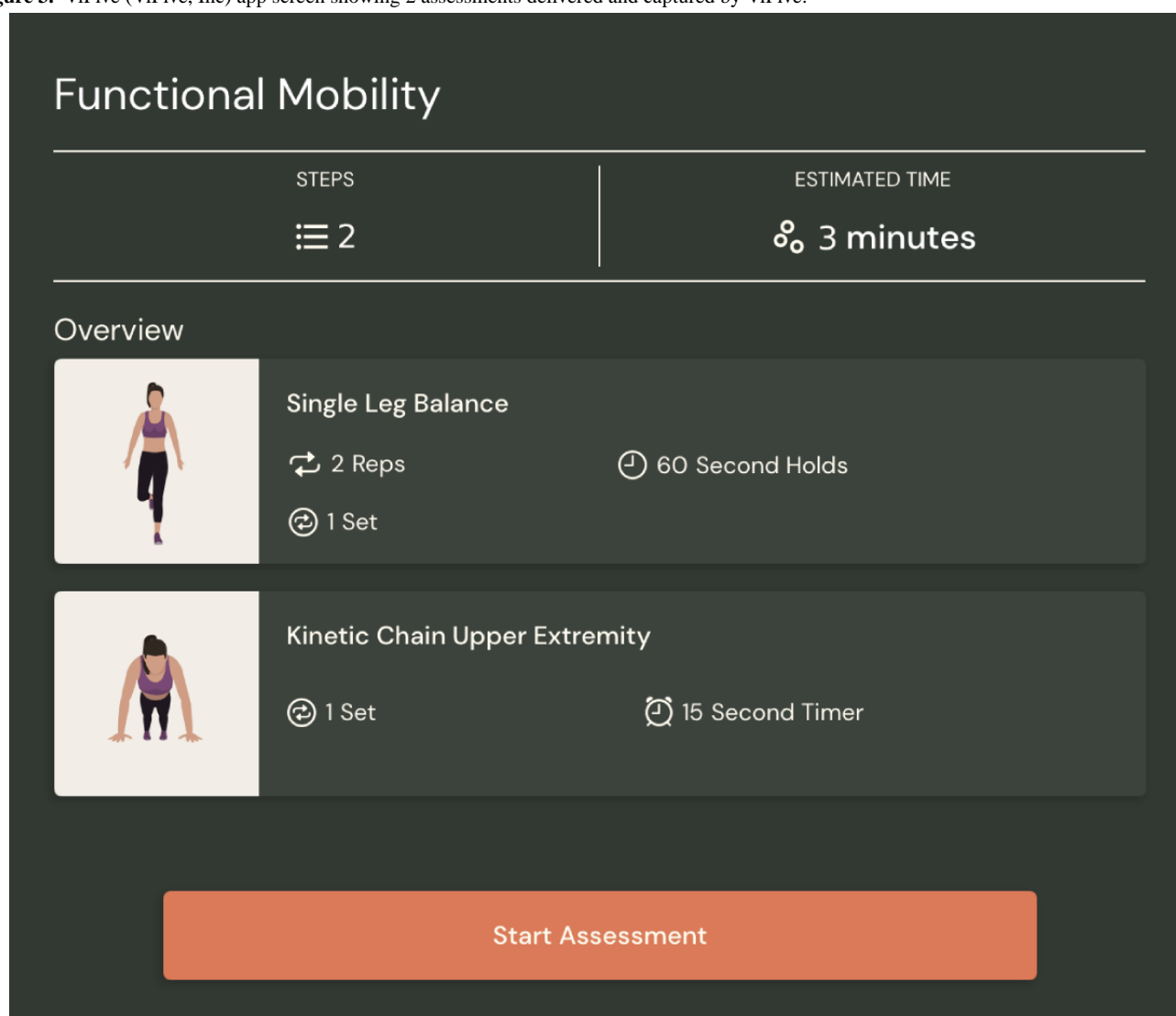
Physical Activity

To examine daily physical activity, the participants wear an ActiGraph watch for the duration of their study participation (baseline phase and across treatment). The ActiLife software (ActiGraph, LLC) will be used to extract data and calculate the mean and peak daily activity. Physical activity (mean and peak) is modeled at 2 time points, and the rate of change in physical activity from baseline to discharge will also be examined.

Health Cost Diary

Diaries on health care service use; personal costs; and support provided by family, friends, and professional carers are completed by parents once at baseline, on a weekly basis from pretreatment baseline to end of treatment, and once at the 3-month follow-up. Parents report on youths' health care service use—general and specialist medical practitioners, physiotherapists, alternative health care practitioners, medications, hospital admissions, and out-of-pocket costs—and other impacts on youth and parental activity—athletic extracurricular activities and parental days off work and sick leave.

Covariates

Medical History

Variables related to chronic pain, including pain onset, duration, and intensity of pain symptoms as well as course and medications, are collected.

Demographics

Demographic variables—namely, age, gender, sex, school grade, and ethnicity—are assessed via adolescent and parent reports at baseline.

Data Analysis

The study biostatisticians conduct all analyses. Covariates (age, pain variables, gender, and diagnosis) are examined for the primary, secondary, additional, and exploratory outcomes.

Primary, Secondary, and Additional Outcomes

Linear mixed effects models will be used to compare physiorehabilitation with VR with standard PT across all non-SCED outcomes. We will model our outcomes at 3 time points using a mixed effects linear model with fixed effects for treatment assignment, period, interaction between treatment and period, and baseline covariates, and a random effect for individual. The random effect will allow us to account for the correlation in the outcome within an individual over time.

Exploratory Outcomes

To examine biomechanical data, physical assessment metrics will be extracted. We will model physical assessment metrics of walk distance, single leg balance duration, and hand taps using mixed 2 (time)×2 (group) ANOVAs. If physical assessment metrics differ by pain site (upper, trunk, lower, or diffuse), this will be included as a covariate. To examine actigraphy data, the ActiLife software will be used to extract data and calculate the mean and peak daily activity. Published data reduction methods will be used [69]. We will model physical activity (mean and peak) at 2 time points using mixed 2 (time)×2 (group) ANOVAs. The rate of change in physical activity from baseline to discharge will also be examined using the randomization tests used for SCED outcomes described in the following sections. To examine health cost diary data, we will model health care cost variables using t tests and linear and mixed regression models.

Feasibility Outcomes

Mean satisfaction and acceptability scores will be examined for both patients and clinicians. To assess patient engagement, the mean adolescent daily diary completion, percentage of patient dropouts before treatment completion, and percentage of sessions with benchmark VR met will also be examined. To assess patient and clinician feedback regarding the feasibility and acceptability of the VR treatment, thematic analysis will be conducted of semistructured interviews to identify barriers, catalysts, and perceptions of integrating VR into clinical care. To evaluate engagement in the VR treatment, the mean clinician ratings on the Pittsburgh Rehabilitation Participation Scale will be examined. Acceptability of the VR treatment will be assessed using patient-reported treatment expectancy mean scores. Finally, adherence to the suggested benchmark VR engagement will be assessed by examining the mean time engaged in VR across participations (standard PT and physiorehabilitation with VR) as well as across VR game type (eg, Fruity Feet vs Vacation Simulator).

SCED Analyses

The data obtained from the randomized SCED used in this study have a hierarchical 2-level structure with observations (level 1) nested within patients (level 2). This nested structure induces dependency within the data—observations vary not only because of random sampling within a patient but also between different patients. For data analysis, we will use a *hierarchical linear model*, allowing us to combine all patients' data into a single multilevel model while also considering both the within- and between-patient dependencies. The within- and between-patient variability, as well as the overall effects of the treatment across patients, will be modeled. For conducting the multilevel analysis and obtaining inference results in R (R Foundation for Statistical Computing), MultiSCED will be used [70]. These daily individual data also allow for the use of randomization tests to assess the difference in daily diaries between baseline and discharge and between baseline and 3-month follow-up.

Sample Size and Power Analysis

The largest feasible sample size will be recruited to obtain as precise estimates as possible of improvement in adolescent function while also ensuring adequate power for the treatment difference in improvement in our primary outcome, physical function. In our primary power calculation, we assumed that we would observe a (medium) effect size of 0.70 for the effect of treatment on outcome (LEFS or UEFI), which corresponds to an absolute difference between physiorehabilitation with VR and standard PT at discharge of 11.9 points assuming an SD of 17 from the validation cohort. This difference of 11.9 equates to 1.32 times the minimal clinically important difference (9). Under this scenario, and accounting for a 20% attrition rate based on previous experience, we will have a power of 80%

with 68 participants (34 in each arm) at follow-up. Under more conservative assumptions, we will have a power of 80% with 40 participants (20 in each arm) at follow-up to detect an effect size of ≥0.90. For our secondary outcome, pain-related fear (FOPQ-SF), with 20 participants in each arm, we would have 80% power to detect a minimal clinically important difference between groups (8.6). A recent interoceptive exposure treatment for youth with chronic pain showed improvement in pain-related fear, with a medium effect (Cohen d=0.73), suggesting a sample size of 31 per group to achieve 80% power, suitably within the range of these estimates.

Monitoring

The study is monitored by Navitas Clinical Research for the executive secretary of the National Institute of Arthritis and Musculoskeletal and Skin Diseases. A safety monitoring committee of 3 experts, approved by the National Institute of Arthritis and Musculoskeletal and Skin Diseases via Navitas Clinical Research, meets quarterly to review overall participant enrollment status, accrual, adherence, protocol deviations, and adverse events.

Results

The physiorehabilitation with VR RCT was prospectively registered at ClinicalTrials.gov (NCT04636177). Analysis of results from the main clinical trial will begin as recruitment progresses, and results are expected in early 2024.

Discussion

Overview

Improving treatment outcomes for adolescents with chronic pain requires engagement in gold-standard treatment and notably progressive physical activity as guided by a physiotherapist. Given existing barriers to engaging in this treatment, innovative and engaging technologies may offer an important option for improving engagement and reducing fear and avoidance of pain, thus allowing for the optimal benefit of PT support. A critical element of engagement in PT is the HEP, which requires patients and families to be diligent in completing daily stretching as well as strength and endurance training, all of which can be difficult and uncomfortable and even more so in the context of chronic pain. Improving engagement in PT as well as adherence to at-home exercise programs are important opportunities for potentially accelerating improvements in PT.

Although we know that the use of VR equipment can be helpful in several contexts, we still do not know if it can facilitate improved functioning and reduced pain-related fear and avoidance in the context of PT in a pediatric pain population. These results will add to this growing body of literature by providing a rigorous assessment of the feasibility of physiorehabilitation with VR in outpatient PT for MSK pain and, thus, support or refute the feasibility of disseminating physiorehabilitation with VR for large-scale implementation.

The findings of this study will also illuminate the feasibility of integrating VR technology into current clinical practice across diverse clinical settings, from private to academic medical PT. Engagement and feasibility outcomes will support the understanding of the feasibility of implementing VR within the PT session as well as how VR can augment HEPs for adolescents. Qualitative interview results will further the existing literature [37] in identifying barriers and catalysts to initiating implementation of VR in practice from the perspective of clinicians responsible for intervention implementation.

The addition of the SCED will further highlight the potential of VR to operate as a tailored treatment intervention through the identification of individual experiences and outcomes associated with the use of VR in physiotherapy. Through analysis of individual daily diary data, these findings will support a greater understanding of what elements of the intervention are most impactful and how that may differ across individuals engaged in the study as well as when inclusion of the VR intervention may be most helpful during PT for MSK pain. Together, the results of this RCT, including the SCED and feasibility elements, may support a large hybrid effectiveness-dissemination RCT serving as the basis for potential large-scale implementation of physiorehabilitation with VR and ultimately expand effective, tailored treatment options for adolescents struggling with persistent MSK pain and related fear and disability.

Study Strengths

This study has several strengths. This is the first pragmatic trial to implement VR in busy and diverse clinical settings, including academic medicine at a major children's hospital as well as private PT clinics. This offers important information regarding the feasibility of VR in distinct real-world care settings. The embedded single-case design within the RCT study is also a strength as it allows for the evaluation of individual treatment responses (responder or nonresponder) within a small cohort of individuals.

Study Limitations

With regard to limitations, an emphasis on integration into the flow of clinical care may result in less control in the implementation of the intervention and, thus, create variability in the VR dose. Importantly, we have metrics to assess the degree of use for each participant so that this factor can be adequately accounted for in the analysis. This study is also being implemented within primarily private clinical settings and, thus, generalizability to other settings is limited. Future research should examine the utility of VR in physical therapy settings in more diverse clinical contexts and geographical locations and in populations of diverse patients. Finally, this study relies on the researchers' ability to engage and support implementation in the care setting, and ongoing evaluation of integration is warranted following the end of the trial as clinics may require the support of the research team to maintain engagement.

Acknowledgments

Data Availability

The information and mentioned materials are available from the corresponding author upon reasonable request. Once data are collected and analyzed, they will be posted on ClinicalTrials.gov and will be available from the corresponding author upon reasonable request.

Conflicts of Interest

TJC is a recipient of philanthropic donations from Meta, Inc and Magic Leap, Inc.

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Abbreviations

FDI: Functional Disability Inventory
FOPQ-SF: Fear of Pain Questionnaire-Short Form
HEP: home exercise program
IRB: Institutional Review Board
LEFS: Lower Extremity Functional Scale
MSK: musculoskeletal
PHODA-Youth: Photographs of Daily Activities for Youth
PROMIS: Patient-Reported Outcomes Measurement Information System
PT: physiotherapy
RCT: randomized controlled trial
SCED: single-case experimental design
TEC-C: child Treatment Expectancy and Credibility
TSK-17: 17-item Tampa Scale for Kinesiophobia
UEFI: Upper Extremity Functional Index
VR: virtual reality

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Protocol

Clinic-Integrated Mobile Health Intervention ("JomPrEP" App) to Improve Uptake of HIV Testing and Pre-exposure Prophylaxis Among Men Who Have Sex With Men in Malaysia: Protocol for an Intervention Development and Multiphase Trial

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Abstract

Background: Men who have sex with men (MSM) are disproportionately affected by the HIV epidemic in Malaysia and globally. Cross-cutting prevention strategies such as mobile health (mHealth), particularly smartphone apps, hold great promise for HIV prevention efforts among Malaysian MSM, especially when linked to HIV testing and pre-exposure prophylaxis (PrEP).

Objective: This study aims to adapt an existing app to create and test a clinic-integrated app (JomPrEP), a virtual platform to deliver HIV testing and PrEP services for MSM in Malaysia.

Methods: The JomPrEP project involves developing and testing an app-based platform for HIV prevention among Malaysian MSM and will be conducted in 2 phases. In phase I (development phase), we will adapt an existing mHealth app (HealthMindr) to create a new clinic-integrated app called "JomPrEP" to deliver holistic HIV prevention services (eg, HIV testing, PrEP, support services for mental health and substance use) among MSM in Malaysia. During phase II (testing phase), we will use a type I hybrid implementation science trial design to test the efficacy of JomPrEP while gathering information on implementation factors to guide future scale-up in real-world settings.

Results: As of September 2022, we have completed phase I of the proposed study. Based on a series of formative work completed during phase I, we developed a fully functional, clinic-integrated JomPrEP app, which provides a virtual platform for MSM in Malaysia to facilitate their engagement in HIV prevention in a fast and convenient manner. Based on participant feedback provided during phase I, we are currently optimizing JomPrEP and the research protocols for a large-scale efficacy trial (phase II), which will commence in January 2023.

Conclusions: Scant HIV prevention resources coupled with entrenched stigma, discrimination, and criminalization of same-sex sexual behavior and substance use hamper access to HIV prevention services in Malaysia. If found efficacious, JomPrEP can be easily adapted for a range of health outcomes and health care delivery services for MSM, including adaptation to other low- and middle-income countries.

Trial Registration: ClinicalTrials.gov NCT05325476; https://clinicaltrials.gov/ct2/show/NCT05325476

Introduction

Reductions in HIV incidence and mortality have not translated uniformly on a global scale, especially in many Southeast Asian countries and among sexual minority groups, where stigma and discrimination are high [1-3]. In Malaysia, same-sex sexual behavior is illegal in both secular and Sharia laws, translating to high levels of stigma and discrimination. With over 100,000 cumulative HIV cases, Malaysia's rapidly expanding HIV epidemic is the fifth largest in the Asia-Pacific region and has now transitioned into men who have sex with men (MSM). From 2008 to 2018, MSM accounted for an increasing proportion of incident HIV cases (10%-21.6%), with trends among this population projected to rise even more in the coming years, making MSM the primary key population with the highest HIV prevalence in Malaysia through 2030 [4,5]. Central to this expanding HIV epidemic among MSM is condomless sex, sexually transmitted infections, and co-occurring psychiatric and substance use disorders [6-9].

Modeling studies for MSM suggest that pre-exposure prophylaxis (PrEP) is a highly effective strategy to avert new HIV infections [10-18]. PrEP uptake, however, is low among Malaysian MSM despite acknowledged high risk and strong interest in taking it [19,20]. Multilevel factors undermine the scale-up of HIV testing and subsequent linkage to PrEP services among Malaysian MSM. Patient-level factors are MSM's hesitancy to disclose their sexuality or risk behaviors in-person to providers, primarily due to fear of stigma, discrimination, or criminalization. Furthermore, findings from other studies expanded these factors to include additional patient- (eg, mental illness, negative experiences with clinicians, low perceived HIV risk), provider- (eg, stigma and discrimination), and structural-level (eg, multiple clinic visits, long waits, lack of after-hour clinic visits) barriers [21-29]. Therefore, the scale-up of HIV testing and PrEP to individuals most at risk for HIV infection requires innovations to support this marginalized group.

Mobile health (mHealth) interventions represent an innovative strategy to transform health service delivery and personal health management [23-26]. In particular, online-to-offline (O2O) models integrating emerging technologies in HIV service delivery are recommended for highly stigmatized persons with or at risk for HIV [30,31]. The O2O models represent powerful resources and opportunities to tailor online outreach as well as identify and engage key populations with a seamless transition to offline HIV clinical services. O2O, however, has often been limited by the requirement to transition to offline services, mostly in-person. Recommended innovations in O2O service delivery are the incorporation of real-time online counseling (e-Counseling) and instant text/video support via 1 platform to deliver 1 seamless, cross-channel journey experience [30].

Findings from recent studies [32,33] with MSM in Malaysia indicate that nearly the entire subgroup (>97%) owns a smartphone, with higher (89.4%) internet penetration mostly through smartphones [34]. Importantly, most MSM prefer to interface with "apps," instead of face-to-face interaction with a clinician, to access HIV prevention and other support services (eg, substance use, mental health) [33]. Although app-based platforms are evolving to increase uptake and adherence to PrEP, most, if not all, are limited to high-income countries. In addition, no mHealth apps that provide comprehensive HIV prevention services are clinically integrated. Innovations through these apps that provide the entire clinical experience, from risk assessment, HIV self-testing, and assessing PrEP eligibility and prescription, expand the benefits of these apps, especially in settings where MSM are highly stigmatized and discriminated against [35,36]. We, therefore, aimed to adapt and test an existing app that integrates clinical services, which we call "JomPrEP," to promote the HIV prevention cascade among MSM in Malaysia.

Methods

Multiphase Study Design

The proposed study, which involves developing and testing JomPrEP among Malaysian MSM, will be conducted in 2 phases. In phase I (development phase), we will adapt an existing mHealth app (HealthMindr) [37,38] to create a new clinic-integrated app called "JomPrEP" to deliver holistic HIV prevention services (eg, HIV testing, PrEP, support services for mental health and substance use) among MSM in Malaysia. During phase II (testing phase), we will utilize a type I hybrid implementation science trial design [39] to test the efficacy of JomPrEP while gathering additional information on its implementation to guide future scale-up in real-world settings. JomPrEP is being adapted to the Malaysian context from the HealthMindr app [30], developed to improve HIV testing and PrEP uptake among MSM in the United States.

Theoretical Framework

The HealthMindr app is based on the Social Cognitive Theory (SCT) [40], which asserts that cognition, behavior, and environmental influences interact with and reinforce one another to impact health behavior. It specifies goal setting, self-efficacy, outcome expectations, and self-regulation as essential influences of health behavior. Features in HealthMindr fit the framework for several health behaviors such as making HIV testing plans, consistently using condoms, screening for PrEP, and seeking PrEP (if eligible). For each health behavior, there are specific app features designed to promote goal setting, self-efficacy, outcome expectations, and self-regulation. For example, for HIV testing, the "Make a Plan" feature promotes goal setting. The presentation of several testing options and information

promotes self-efficacy, while information about the benefits of testing promotes positive outcome expectations, and a customizable reminder is used for testing self-regulation. HealthMindr has shown preliminary acceptability and usability among MSM in the United States [37], and HealthMindr combined with in-app prevention messages doubled HIV testing and PrEP uptake in a randomized trial among MSM in the United States [41]. As JomPrEP will be adapted from HealthMindr, its main domains will coincide with the core elements of the SCT framework.

Community Advisory Board

We have instituted a community advisory board (CAB; n=8) comprising representatives from rural and urban settings, including researchers, MSM, clinical providers, and leaders of MSM-serving community-based organizations. The CAB is instrumental in collaborative work in the region and is heavily engaged in JomPrEP development and dissemination. Specifically, the CAB meets quarterly to assist in the design and content development of the platform. In addition, the CAB guides and assists the research team with (1) community outreach and study promotion; (2) fostering cross-collaboration between stakeholders and other disciplines working to improve MSM health outcomes; (3) ensuring cultural competency throughout various aspects of the study; (4) encouraging community participation in the proposed project; and (5) assistance in developing dissemination strategies, including communication of results in community forums, and feedback on adaptations to inform a future trial.

Phase I: Development of JomPrEP

Overview

We will use the modified Intervention Mapping Adapt model [42] to adapt the HealthMindr app to create JomPrEP for optimal use among MSM in the Malaysian context. The modified Intervention Mapping Adapt model consists of the following sequential steps.

Phase IA: Theater Testing

We will conduct theater testing to examine attitudes toward the format, content, and features of HealthMindr and to receive feedback for improving the acceptability and feasibility of the newly created app. We will also explore preferences for additional features to facilitate and improve self-care, peer support, and screening and referrals for psychiatric and substance use disorder. We will conduct focus groups (FGs) with 25 MSM and 10 stakeholders. Eligibility criteria for MSM will include being (1) 18 years of age or older; (2) self-identified as MSM; and (3) able to understand English or Bahasa Malaysia. Participants will be recruited using advertisements on geosocial networking apps for MSM (eg, Grindr, Hornet) and popular social networking websites (eg, Facebook). Stakeholders will include doctors, nurses, pharmacists, mental health counselors, community outreach workers, and nongovernmental organization (NGO) staff involved in providing HIV-related services to the target population. We will start with 5 FGs (with 6-8 participants per group), each lasting approximately 60 minutes [43]. We will recruit further if saturation is not achieved.

An interview guide will be created by the investigator team. At the beginning of the theater testing session, participants will interact with HealthMindr with guidance from facilitators. Feedback will be elicited on the overall appearance and functionality of HealthMindr interface, appeal, and usability; components they like or dislike; and areas for improvement. Furthermore, participants will provide insight into the potential functionalities and content for JomPrEP in terms of addressing barriers and facilitators to HIV testing, PrEP, and substance use disorder screening and related services. For example, we intend to incorporate elements that allow participants to use the app to access HIV prevention services virtually (PrEPxpress). We will, therefore, explore options to simplify the process of accessing PrEP through a proposed "PrEPxpress" pathway that involves replacing in-person clinician interactions with virtual or home-based ones (eg, app-based risk assessment, scheduling appointments, electronic consultations [e-consults], mail-in-order for HIV testing kits, and PrEP medication).

Using findings from the theater testing, we will carefully adapt, expand, and refine the content and functionalities of the HealthMindr app to create an interactive prototype of the JomPrEP app (alpha version) while maintaining fidelity to its core elements and underlying conceptual framework. The app development team will update the interactive wireframe through multiple iterations, which will act as a skeleton for JomPrEP.

Phase IB: Alpha Testing

In this phase, we will conduct alpha testing of the interactive prototype developed from the previous phase to identify use-related issues that are due to the original design and missing content. Participants will also provide feedback on how each function can be used, their willingness to use it, and suggestions for improvement. It is a widely used user-centered design methodology incorporating an iterative process of testing an app's user preferences and then applying the results to redesign the prototype to meet user needs.

We will conduct individual 1-on-1 sessions with 10 MSM and 10 stakeholders. Screening, eligibility criteria, and enrollment will be identical to procedures used for phase IA (ie, theater testing). During each session, video recordings will be made of the participant's use of the app wireframe and voice. Each participant will be asked to complete prespecified tasks (eg, set up a profile, complete an HIV risk assessment, send a message to the clinical staff via the app, order an HIV self-testing kit, schedule an appointment for a PrEP consultation, set up a reminder for PrEP, and complete a PrEP medication order) on the app wireframe while "thinking aloud" and narrating their thoughts. Participants will then be asked to complete a questionnaire on 2 main aspects: (1) experiences with the testing; and (2) experiences completing the given tasks using the wireframe. Besides, a series of open-ended questions related to ease and experience of use, recommendations for modifications, and feasibility will be asked after completing the assigned tasks. The app developer will review the video to assist with interface changes based on participant feedback.

Based on the findings from the alpha testing, recommendations for modifications will be compiled and discussed with the app developer. The prototype will then be modified to address the

key usability barriers and participant preferences. Following wireframing and alpha testing, the user interface (ie, colors and branding) will be applied to the prototype, followed by the final development of JomPrEP (beta version).

Expected Elements of JomPrEP (Beta Version)

Core and Additional Features

JomPrEP will minimally include core features (refined for the Malaysian context) present in HealthMindr (eg, risk assessment, HIV testing plan, reminders, ordering of testing kits) plus additional features to virtually access HIV prevention services (ie, PrEPxpress—a clinic-integrated enhancement), such as appointment booking for HIV testing and PrEP services, a chat function to communicate with clinical staff, and a test result feature that enables participants to access their laboratory results. More features embedded in the app include e-consults, health product ordering, discrete door-to-door delivery, and notification customization. Upon downloading the app, the user completes an onboarding process, which includes creating log-in credentials. Participants are then taken to the JomPrEP landing screen with icons for key functions of the app. In addition, we will work with a few local clinics to integrate the JomPrEP platform into their existing clinical care setting. This will enable the JomPrEP users to access HIV prevention services via the app.

Phase IC: Beta Testing

After adaptation and refinement as described in phase IA (theater testing) and phase IB (alpha testing), beta testing of JomPrEP will be conducted to assess its usability and acceptability with Malaysian MSM. Beta testing of the app (n=50) will also help identify potential bugs and ensure its usability in a real-world setting [43]. Screening, eligibility criteria, and enrollment will be identical to the procedures used for phase IA (ie, theater testing).

All enrolled participants will be given a brief overview of the purpose of the study, followed by a survey that focuses on participant characteristics and barriers to accessing HIV testing, PrEP, and psychiatric and substance use disorder support services. The participants will then be observed downloading JomPrEP and instructed with a brief tutorial about the onboarding process. To restrict access to JomPrEP during beta

testing, a single-use registration code will be provided to study participants that will need to be entered to gain access to the app. The participants will be told to keep the app for 30 days and encouraged to use all the app's features. On day 30, the participants will be asked to provide a synthesis of issues that have emerged regarding the app and will complete a postsurvey, which will include the same questions as the presurvey and the Systems Usability Scale [44], a validated measure that assesses the subjective usability of an app. We will also collect app analytics, such as the number of log-ins, session duration, pages visited, and frequency and duration of use for each app's components. In addition, participants will be asked to provide qualitative feedback on functionality, performance, errors encountered, motivation to use the app, overall experiences using the app, input for further refinement, and subjective impact of the app on HIV prevention outcomes. The findings from the beta testing will allow us to make final refinements to JomPrEP before the initiation of the efficacy trial (testing phase).

## Phase II: Testing of JomPrEP

Overview

We will conduct a type I hybrid implementation science trial [39] that involves an assessment of the efficacy of JomPrEP while assessing contextual implementation factors to guide its future adoption and scale-up. While assessing efficacy outcomes for JomPrEP, we will interview stakeholders (eg, patients, clinicians, counselors, administrative staff) to understand barriers and facilitators to JomPrEP adoption and scale-up, especially for applicability to new sites in low- and middle-income countries (LMICs).

Phase IIA: Efficacy Trial of JomPrEP

Study Design

We will conduct a prospective randomized controlled trial to evaluate the efficacy of JomPrEP versus treatment as usual (TAU) among MSM in Malaysia for primary (ie, HIV testing and PrEP uptake) and secondary (ie, PrEP adherence and persistence) outcomes over 9 months of observation. We will enroll 268 participants who will be randomized (1:1) to receive either JomPrEP or TAU and will be followed for 9 months (assessments at 3, 6, and 9 months; Figure 1).

Figure 1. Study design of the JomPrEP efficacy trial (phase IIA). PrEP: pre-exposure prophylaxis; TAU: treatment as usual.
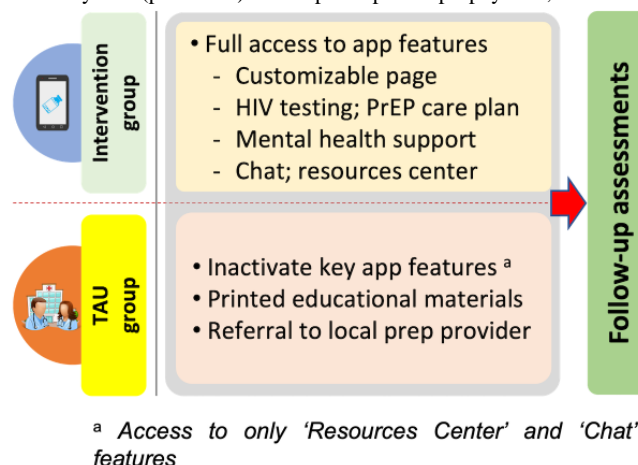
Study Settings and Participants

Eligibility screening and recruitment will be identical to procedures used for phase I. We will partner with the Centre of Excellence for Research in AIDS (CERiA) at the University of Malaya, Kuala Lumpur, Malaysia. Eligibility criteria will include the following: (1) age ≥18 years; (2) cis-gender men; (3) laboratory-confirmed HIV negative status; (4) no existing use of PrEP; (5) own a smartphone; and (6) ability to understand, read, and speak English. Participants will be discontinued from the study under any of these circumstances: (1) acquisition of HIV infection (will be referred to appropriate care); (2) participant voluntarily chooses to leave the study; and (3) the provider thinks the study is no longer in the best interest of the participant.

Participants will be recruited using both in-person and online recruitment strategies. For in-person recruitment, flyers will be given out to potential participants as well as posted at local community-based organizations. In addition, various general and MSM-specific social media and other online platforms will be chosen as venues for participant recruitment. These include placing advertisements in geosocial networking apps popular among MSM in Malaysia (eg, Grindr, Hornet) as well as posting study flyers on Malaysian MSM–focused Facebook pages. The recruitment materials will include brief information about the study and contact information (and a link to the study website) where potential participants could receive more information.

Procedures

After meeting eligibility, participants will provide written consent and complete a baseline assessment. Participants will then be randomized (1:1) to either JomPrEP or TAU. Participants in both groups will have JomPrEP installed on their phones and be guided through its use. However, participants in the TAU group will receive JomPrEP with major intervention features inactivated. They will have access to only the resources center with information on HIV testing and PrEP, mental health, and addiction support services, and the chat function to contact the research staff. The research staff will assist in downloading the app and provide a tutorial on how to use the app.

Participants in the JomPrEP group will be provided with full app access, including a customizable page (*visual representation using avatars and pseudonyms*); visual dashboard (*tracking PrEP adherence, daily mood tracker*); HIV testing plan (*ordering self-testing kits, testing site locator*); PrEP Care Plan (*PrEPxpress—HIV risk assessment, scheduling and managing appointments, e-consult, an electronic script for PrEP medicine, discrete door-to-door delivery, accessing test results*); mental health support (*screening for psychiatric and substance use disorder, referral to mental health support services*), chat function (*ability to chat with clinical and research staff*); tailored notifications (*automated reminders for follow-up care*); and

resources center (*multimedia library on information and resources on HIV testing, PrEP, risks, relationships, and psychiatric and substance use disorder*). The research staff will use an onboarding checklist to orient participants to download JomPrEP and its use. Participants will be encouraged to explore and use all components of JomPrEP. Participants can earn points for completing specific tasks on JomPrEP (ie, gamification) and personalize the frequency, timing, and content for reminder notifications and follow-up PrEP services. They can also contact the research or clinical staff using the chat function for support. Anyone identified at baseline who seroconverts during the study period will be referred to appropriate HIV treatment services.

Primary Outcomes

All structured interviews will be assessed online via Qualtrics (Qualtrics XM). Primary outcomes are those along the HIV prevention cascade, including uptake of HIV testing (ie, ordering of HIV self-testing kit and uploading the result via the app or HIV testing as part of the PrEP clinical care) and PrEP (ie, current use of PrEP; yes/no). Both HIV testing and PrEP uptake will be assessed at each follow-up time point (3, 6, and 9 months) using self-report and medical record review for confirmation.

Secondary Outcomes

Secondary outcomes include adherence and persistence on PrEP (for those who initiated PrEP). PrEP adherence will be assessed using (1) dried blood spot testing at 3-, 6-, and 9-month follow-ups, which will quantify tenofovir-diphosphate and emtricitabine-triphosphate in red blood corpuscles [45-48]. Tenofovir-diphosphate ≥700 fmol/punch will be defined as optimal adherence; and (2) self-reported adherence, which will be measured using the validated Visual Analog Scale [49]. Persistence on PrEP will be measured based on the completion of quarterly PrEP visits (recorded on the app).

Other Outcomes

Consistent with the SCT framework, we will collect measures related to its constructs, which are (1) self-regulation (frequency of use of app components, perceived HIV risk), (2) self-efficacy (related to PrEP use and adherence, condom use, substance use, and utilization of mental health support), and (3) goal setting and environmental influences (frequency of use of HIV testing, PrEP care plans, and notification reminders). Given the importance of moderating factors that may influence the uptake of prevention strategies, we will use the Socioecological Theoretical model, which links individual (eg, sociodemographic, sexually transmitted infection incidence, sexual/drug use behavior, mental health), social (eg, social support, peer norms), and structural (eg, stigma, discrimination, incarceration) factors as they relate to linkage to HIV prevention services in Malaysian MSM (Table 1).

Table 1. Study activity and measures (phase II).

Study activity	Timeline				
	Prebaseline	Baseline	3 Months	6 Months	9 Months
Enrollment					
Eligibility screen	✓				
Informed consent		✓			
Randomization		✓			
Interventions					
App onboarding		✓			
Access to the app					
JomPrEP group	✓	✓	✓	✓	
TAU[a] group	✓	✓	✓	✓	
Assessments					
Questionnaires	✓	✓	✓	✓	
PrEP[b] adherence[c]					
Dried blood spot testing			✓	✓	✓
Visual Analog Scale			✓	✓	✓
Online PrEP script[c,d]			✓	✓	✓
PrEP persistence[c]			✓	✓	✓
Focus groups					✓
Payment		✓	✓	✓	✓

[a]Treatment as usual (restricted access to the JomPrEP app features).

[b]PrEP: pre-exposure prophylaxis.

[c]Only applies to those who initiated PrEP.

[d]Only applies to the JomPrEP group.

Analytical Plan

To test the hypothesis that the intervention group (I=JomPrEP) will be significantly more effective than the TAU group for HIV testing and PrEP uptake, we will compare the proportion for both outcomes. The null hypothesis is that the proportion of HIV testing and PrEP uptake in the intervention group and TAU is equal, expressed as follows: H_0: $p_I = p_{TAU}$, where p_I and p_{TAU} are the proportion of HIV testing and PrEP uptake in the JomPrEP and TAU groups, respectively. Our alternative hypothesis is H_1: $p_I > p_{TAU}$. We will use both intent-to-treat (ITT) and on-treatment analyses, with ITT used for efficacy. Baseline characteristics will be tested for homogeneity across the 2 groups using a *t* test or Wilcoxon rank sum test for continuous variables and chi-square test or Fisher exact test for categorical variables. Any baseline variable showing a significant difference at $P<.05$ between the 2 groups will be put into the model for adjustment. For all outcome variables assessed over a 9-month follow-up period, plots of longitudinal data over time will be provided. Prior to the primary analysis, the distribution of the missing data pattern will be examined across the 2 groups. For a subgroup of those starting PrEP, we will compare PrEP adherence using the same method and PrEP persistence using time-to-discontinuation and Cox proportional hazards ratios.

The framework for testing the study hypotheses will compare the differences between the 2 groups (JomPrEP vs TAU) over time. To test our primary hypotheses on binary outcomes of HIV testing and PrEP uptake, a generalized linear mixed model [50] with random subject effects will be built to account for the correlation in repeated measurements within participants. Treatment assignment, time, the interaction between time and treatment assignment, and any other hypothesized confounders will be included as covariates. HIV testing and PrEP uptake proportion at the 9-month follow-up will be estimated and compared using a linear contrast statement in SAS PROC GLIMMIX. Similar analyses will be conducted for the secondary binary outcomes: optimal adherence and PrEP persistence. As an alternative analytical plan for assessing the impact of the 2 groups on adherence to PrEP, continuous adherence variables will be analyzed using a linear mixed model [50] with the same set of covariates as the binary adherence outcome and percent changes in adherence between the different assessment points will be estimated and compared between the 2 arms using the linear contrast statement in SAS PROC MIXED. For the aforementioned model, the covariance structure will be selected based on the fit statistics (eg, Akaike information criterion and the Bayesian information criterion) [51]. Given the several strategies by which PrEP adherence will be measured, we will utilize Spearman correlation coefficients and scatterplots to

assess the associations between the biomedical measure (dried blood spot) [45-48] and self-report measure (Visual Analog Scale) [49].

Sample Size

We calculated the sample size based on the difference we expect in the primary outcome (ie, PrEP uptake) by month 9. A sample size of 121 per group achieves 90% power to detect a 10% increase in PrEP uptake for the JomPrEP group compared with the TAU group, assuming 50% PrEP uptake in the TAU group at the 1-sided .05 significance level. A sample of 268 participants will be enrolled and randomized to the JomPrEP and TAU groups to accommodate a 10% dropout. Assuming 60% of PrEP uptake in the JomPrEP group, this sample size provides 85% power in detecting a standardized effect size of 0.5 for the secondary outcomes of adherence and persistence.

Plan for Missing Data

Several strategies will be deployed to accommodate the possibility that missing data will occur. This protocol will perform both per-protocol and ITT analyses; thus, we will follow all randomized participants regardless of the treatment received [52]. Our primary analysis is valid under the assumption that missing data are missing completely at random, using the Little missing completely at random test [53]. We will evaluate the plausibility of this assumption by determining the extent and pattern of missing data and using logistic regression to identify factors associated with dropout [54]. Sensitivity analysis will be performed under the assumption of missing not at random using a selection model, pattern mixture model, or semiparametric methods [55] to examine the robustness of conclusions from the primary analysis.

Minimizing Contamination Across Groups

Contamination will be minimized in several ways: (1) only individuals enrolled in the project will be provided with a single-use code to access the app; (2) couples and housemates will be randomized together; and (3) participants will be assessed at follow-up about their observation of others using the app. We will disguise these questions by asking (1) "Have you seen a different version of the app?"; (2) "Do you have a buddy who is also in the study but uses a different version of the app?"; and (3) "Did you find how different is your app from others?"

Phase IIB: Explore Multilevel Implementation Factors

We will use the Consolidated Framework for Implementation Research (CFIR) to gather multilevel implementation factors. We selected CFIR because it provides a structured menu of constructs associated with effective implementation and can be used flexibly at any phase, and has been used to guide PrEP implementation in other settings [56-58]. It consists of 5 domains with 39 underlying constructs [56]. As recommended [56], we have identified 11 constructs based on the relevancy to our trial (Table 2).

Table 2. Constructs of CFIR[a] to explore multilevel implementation factors.

CFIR domains and constructs	Sample questions
Intervention	
Relative advantage	• How does the JomPrEP app compare with other alternatives?
Adaptability	• What changes will be needed for the JomPrEP app to work effectively?
Design quality and packaging	• What is your perception of bundling HIV and mental health support services in the JomPrEP app?
Internal Context	
Structural characteristics	• What kinds of infrastructure changes will be needed to accommodate the intervention?
Readiness for implementation	• What level of endorsement or support have you seen or heard from leaders?
External Context	
Patient needs and resources	• What barriers will the users face while participating in the JomPrEP intervention?
Participants	
Knowledge and beliefs about the intervention	• How do you feel about integrating the JomPrEP app into your clinical setting?
	• Do you have any feelings of anticipation? Stress? Enthusiasm? Why?
Self-efficacy	• How confident do you think your colleagues feel about using the JomPrEP app?
Process	
Planning	• What have you done (or what do you plan to do) to implement the JomPrEP program?
Engaging	• What steps have been taken to encourage people to use the JomPrEP app?

[a]CFIR: Consolidated Framework for Implementation Research.

We will conduct FGs with participants randomized to the JomPrEP group (n=16-20) and stakeholders (eg, clinicians and administrative staff from NGOs, clinics, and hospitals; those who do and do not participate in the trial; n=16-20), where we will measure implementation and process measures, existing and potential barriers and facilitators, as well as identify available resources and key facilitating stakeholders. For stakeholders, we will have 2 groups of matched clinicians (who do and do not participate in the trial). Administrative personnel will include supervisory personnel at the clinics, hospitals, and NGOs. The same process will occur when we start, and then again at the end of the project, where we will share results and assess changes from the baseline. During the FG sessions, participants will be asked about the multilevel implementation factors based on the sample guide available elsewhere [59] (Table 2) but tailored for the Malaysian context.

Ethics Approval

The institutional review board at the University of Connecticut approved this protocol (H22-0049) with an institutional reliance agreement with the University of Malaya. This study is registered at ClinicalTrials.gov (NCT05325476).

Results

As of September 2022, we have completed phase I of the proposed study. Based on a series of formative work completed during this phase, we have developed a fully functional, clinic-integrated JomPrEP app [60], which is available to download for free on both iOS and Android platforms (Multimedia Appendix 1). JomPrEP provides a virtual platform for MSM in Malaysia to facilitate their engagement in HIV prevention in a fast and convenient manner. It offers a range of HIV prevention (ie, HIV testing and PrEP) and other support services (eg, referral to mental health services), including several on-demand features (Figure 2). We have also developed a web-based "JomPrEP Clinic Dashboard," which will provide role-based access to clinical staff from affiliated clinics to facilitate patient care for JomPrEP app users. Without an electronic health record in the local setting, our JomPrEP Clinic Dashboard functions more like an electronic health record system.

Figure 2. Features included in JomPrEP. PrEP: pre-exposure prophylaxis; P/SUD: psychiatric and substance use disorders.
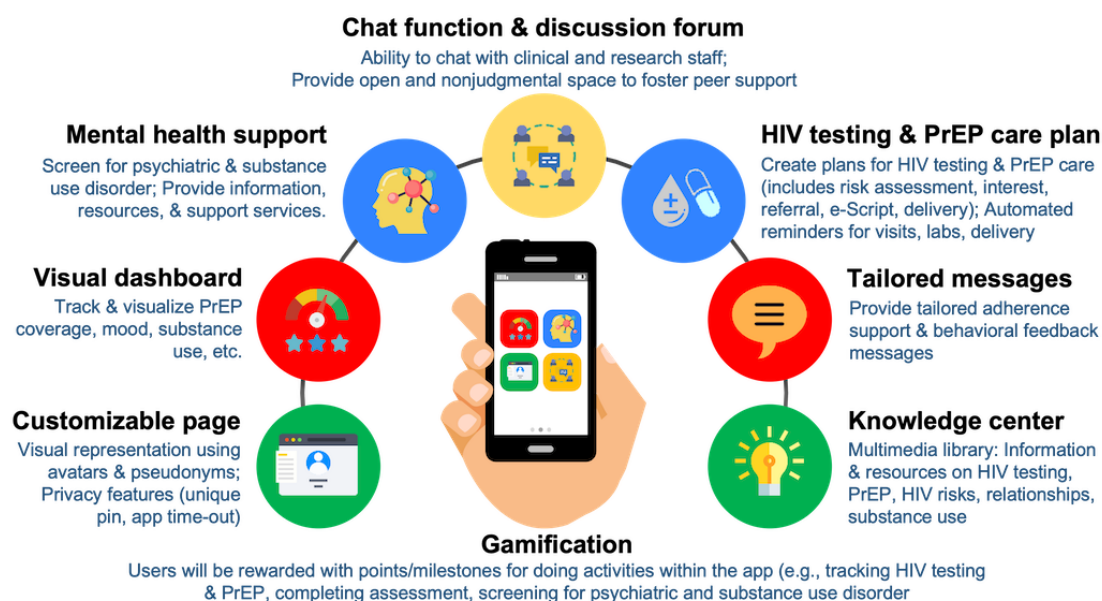
Data from beta testing (phase IC) demonstrated JomPrEP to be highly feasible and acceptable for HIV prevention efforts among MSM in Malaysia. Based on participant feedback provided during beta testing exit interviews, we are currently optimizing the app and the research protocols for a large-scale efficacy trial (phase II), which will commence in January 2023. Data collection for phase II will be completed in Spring 2025, followed by data analysis.

Discussion

Expected Findings

In this study, we propose to develop and test the efficacy of a clinic-integrated app (ie, "JomPrEP"). JomPrEP will be designed to virtually deliver an integrated HIV prevention intervention that will promote HIV testing and linkage to PrEP. We hypothesize that JomPrEP will be significantly more effective in improving uptake of HIV testing and PrEP among MSM in Malaysia. We also anticipate that the results and qualitative feedback from participants and stakeholders will inform the refinement of JomPrEP for a future implementation trial.

JomPrEP will help to reduce some of the individual- (eg, lack of information, psychiatric and substance use disorder, negative experiences with clinicians, low perceived risk) and structural-level barriers (eg, long waits and multiple visits, stigma, and discrimination from physicians) to HIV testing and PrEP care in multiple ways, by (1) offering relevant information and resources on PrEP, HIV risk reduction, and psychiatric and substance use disorder support services; (2) incorporating on-demand features with real-time e-Counseling, tracking, and monitoring linked and integrated with clinical services within 1 platform to deliver seamless transition without any in-person interaction with the clinicians. This enhancement on the traditional O2O service delivery model ensures open and nonjudgmental virtual space for MSM to discuss various issues with the clinicians without fear of stigma and discrimination [30,31]; (3) decreasing long clinic wait times and reducing the number of clinical visits; and (4) collaborating with local clinics

and other stakeholders to deliver seamless, integrated HIV prevention services care as well as to ensure sustainability and further expansion of JomPrEP. If successful, JomPrEP will be among the first clinic-integrated apps to deliver comprehensive HIV prevention services for MSM in LMICs, including Malaysia. Furthermore, the app could be an innovative platform to link online service utilization and subsequent offline clinical services uptake (eg, HIV treatment services, psychiatric care).

Planned Next Step

As part of the next step, we propose to conduct a type I hybrid implementation science trial [39] that involves an assessment of the efficacy of JomPrEP while assessing contextual implementation factors to guide its future adoption and scale-up.

Limitations

Threat to internal validity includes retention and differential loss to follow-up. We will utilize established procedures to increase compliance with follow-up assessments, including minimal wait time for follow-up appointments, reminder messages between visits and prior to follow-up surveys, and incentives for completing study activities. If a participant misses a follow-up assessment, research staff will make additional outreach to support engagement. Additional threats to internal validity are issues around quality assurance during data collection. Possible technological difficulties with the app and server are additional concerns.

In addition, a number of strategies will be in place during different stages of the project to ensure the sustainability and scalability of JomPrEP. First, as part of the JomPrEP development process, we used the user-centered design approach that incorporated individual preferences at the center of the app design and grounded on continuous and structured interaction with end users. Second, we propose to use the hybrid effectiveness-implementation design to gather information on its potential for implementation in real-world settings while testing JomPrEP. This will help to simultaneously answer many questions (eg, client-, clinicians-, and administrative-level

factors) important for transitioning to app implementation in real-world settings more comprehensively, accurately, and certainly earlier. Third, as part of the planning process, we met with several key local stakeholders, yielding an in-depth understanding of capacities and priorities that helped shape this project. Many clinics (mostly private clinics) across Malaysia have signaled interest in incorporating JomPrEP into their clinical care. Importantly, we will work with the local stakeholder to identify an organization to take ownership of JomPrEP and use it as a tool for scaling-up PrEP uptake across Malaysia at the end of the grant cycle.

Conclusions

Limited HIV prevention resources and entrenched stigma, discrimination, and criminalization of same-sex behavior and substance use hamper access to HIV prevention services in Malaysia. Introducing a new app-based platform to deliver holistic HIV prevention services represents a paradigm shift in HIV prevention because it can deliver effective prevention in a confidential, less stigmatizing, and convenient manner. If found efficacious, JomPrEP can be adapted for a range of health outcomes and health care services delivery in these populations and other LMICs.

Data Availability

The data sets generated during or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
JomPrEP app screenshots.
[PNG File , 776 KB - resprot_v11i12e43318_app1.png]

Multimedia Appendix 2
Peer review report by NCI-J - Center for Scientific Review Special Emphasis Panel - Mobile Health: Technology and Outcomes in Low and Middle Income Countries - (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 164 KB - resprot_v11i12e43318_app2.pdf]

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Abbreviations

CAB: community advisory board
CERiA: Centre of Excellence for Research in AIDS
CFIR: Consolidated Framework for Implementation Research
FG: focus group
ITT: intent-to-treat
LMICs: low- and middle- income countries
mHealth: mobile health
MSM: men who have sex with men
NGO: nongovernmental organization
O2O: online-to-offline
PrEP: pre-exposure prophylaxis
SCT: Social Cognitive Theory
TAU: treatment as usual

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