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Protocol

Web-Based Eye Movement Desensitization and Reprocessing for Adults With Suicidal Ideation: Protocol for a Randomized Controlled Trial

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Abstract

Background: Adversity and traumatic experiences increase the likelihood of suicidal thoughts and behaviors. Eye Movement Desensitization and Reprocessing (EMDR) is an evidence-based, trauma-focused psychotherapy that desensitizes painful memories, so that reminders in the present no longer provoke overwhelming emotional responses. Preliminary evidence suggests that EMDR can be used as an acute intervention in suicidal patients, including those with major depressive disorder. In addition, because of social distancing restrictions during the COVID-19 pandemic, clinicians have been using EMDR on the web and, in the absence of formal evaluations of web-based EMDR, informal reports indicate good results.

Objective: The primary aim of this randomized controlled trial is to investigate whether remotely delivered EMDR (targeting experiences associated with suicidal thinking) reduces suicidal thoughts. Secondary aims include examining the impact of remotely delivered EMDR on symptoms of depression, anxiety, posttraumatic stress, emotional dysregulation, and dissociation. We will also report on adverse events in the EMDR group to explore whether targeting suicidal ideation with EMDR is safe. Finally, we will compare dropout rates between the treatment groups.

Methods: In this randomized controlled trial, 80 adults who express suicidal ideation and meet the study criteria will receive either 12 sessions of twice weekly EMDR plus treatment as usual or treatment as usual alone. EMDR sessions will focus on the most distressing and intrusive memories associated with suicidal ideation. Data for primary and secondary objectives will be collected at baseline, 2 months, and 4 months after enrollment. A subsequent longer-term analysis, beyond the scope of this protocol, will examine differences between the groups with respect to the number of posttreatment emergency room visits, hospitalizations, and overall health care use in the year before and after therapy.

Results: The protocol was approved by the University of Alberta Research Health Ethics Board (protocol ID Pro00090989). Funding for this study was provided by the Mental Health Foundation (grant RES0048906). Recruitment started in May 2021, with a projected completion date of March 2023.

Conclusions: The results of this trial will contribute to knowledge on whether web-based delivery of EMDR is a safe and effective treatment for reducing suicidal ideation and potentially reducing the incidence of suicide attempts in this patient population.

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International Registered Report Identifier (IRRID): DERR1-10.2196/30711

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KEYWORDS

suicide; trauma; eye movement desensitization and reprocessing (EMDR); telemedicine; psychotherapy; digital health; eHealth; remote delivery; virtual care

Introduction

Trauma, Suicide, and Psychopathology

Suicide is the second leading cause of death among those aged 10-29 years and the ninth leading cause of death overall, with reports of 4000 completed suicides per year in Canada [1]. Psychiatric disorders that most strongly predict subsequent suicide attempts are bipolar disorder, posttraumatic stress disorder (PTSD), and major depressive disorder (MDD) [2]. Epidemiological evidence also indicates that adverse or traumatic experiences increase the likelihood of developing both suicidal ideation (SI) and a range of psychiatric disorders [3-9]. Among over 30 psychological risk and protective factors identified for suicidal behavior, the strongest associations were with depression, hopelessness, impulsivity, adverse childhood experiences (ACEs), and trauma [2-9].

The psychological and neurobiological consequences of adverse or traumatic experiences may moderate the development of suicidal thoughts and behaviors [10]. The neurobiological and psychological basis of suicidal thoughts and behaviors is outlined in reviews by van Heeringen and Mann [11] and O'Connor and Nock [12]. ACEs are associated with a strong, graded relationship to later suicide attempts, which may be moderated through stress sensitivity and emotion dysregulation, and expressed as substance use, risky sexual behavior, depressed mood, or anxiety [8,13,14]. Childhood adversity has been associated with deficits in executive function, including attention, working memory, cognitive flexibility, inhibitory control, and emotion regulation. These factors, particularly inhibitory control and emotion dysregulation, are associated with an increased risk for the development of psychopathology and suicidality later in life [15,16].

Eye Movement Desensitization and Reprocessing

Eye Movement Desensitization and Reprocessing (EMDR) is evidence-based therapy, initially developed for PTSD, that desensitizes painful memories, so that present reminders no longer provoke overwhelming emotional responses [17]. EMDR is effective for treating a variety of conditions, including anxiety, depression, trauma, substance misuse, and trauma in patients with severe mental illnesses such as psychosis or bipolar disorder [18-20]. During a typical EMDR session, the client focuses on emotionally disturbing material while bilateral stimulation is applied, either in the form of alternating eye movements, a tactile stimulus such as alternating bilateral tapping, or auditory tones. Standard EMDR uses an 8-phase protocol, including history-taking, preparation, assessment and treatment-planning, desensitization, installation of a positive cognition, body scan, closure, and re-evaluation [21].

EMDR is guided by the Adaptive Information Processing (AIP) model, in which present symptoms are seen as unprocessed explicit and implicit memories stored in the brain that lead to maladaptive information processing and present as posttraumatic and other psychiatric symptoms. In theory, EMDR facilitates the accessing and processing of traumatic memories to an adaptive resolution, after which the disturbing affective distress is relieved, physiological arousal is reduced, negative beliefs are reformulated, and alternative ways of responding to future similar situations are considered [21].

EMDR and Suicidality

Suicide researchers have hypothesized that suicidal thoughts and behaviors may emerge when environmental triggers activate dimensions of risk in individuals who have been exposed to past adverse experiences and trauma. Two relevant theories include the Escape Theory and the Fluid Vulnerability Theory [22,23]. The Escape Theory suggests that stressful life events activate painful affective states, leading to urges to escape the negative affect and self-awareness. The urge to escape painful affect may lead to reduced self-inhibition, increased passivity, disconnect from emotions, or increased negative thoughts such as suicidal thinking. In this context, SI becomes more accessible and acceptable over time. The more frequent and distressing the suicidal intrusions, the more likely the person is to see them as the best solution to the unescapable, intensely negative state [22].

The Fluid Vulnerability Theory, which focuses on the process of suicide risk rather than risk factors, posits that each person has both a baseline risk state and potential for at least one *suicidal mode*, a time-limited suicidal state with individual characteristic features related to the person's suicidal belief (cognitive) system, affective system, physiological system, and behavioral (motivational) system, which together work in synchrony. This theory proposes that the risk state and suicidal mode can be activated by either external or internal triggers, and usually ends in a state "characterized by specific or core cognitive themes (i.e., unlovability, helplessness, poor distress tolerance, and perceived burdensomeness), acute dysphoria and related physiological arousal (ie, Axis I symptomatology), and associated death-related behaviors" [23]. During these *suicidal modes*, motivational and behavioral systems may be engaged which activate specific motoric and physiologic responses, for example, fight, flight, or freeze, along with preparatory urges or behaviors. Sometimes, these states are misinterpreted cognitively as a threat in themselves, leading to escalation of distress. These modes are based on the original cognitive therapy model by Beck [24] and defined as "specific suborganizations within the personality organization (that) incorporates the relevant components of the basic systems of personality:

cognitive (or information processing), affective, behavioral, and motivational." Beck [24] described a mode as an "integrated cognitive-affective-behavioral network [that] produces a synchronous response to external demands and provides a mechanism for implementing internal dictates and goals" [23]. The Fluid Vulnerability Theory also assumes that a person's baseline level of risk is determined by historical and developmental factors that predict why activation of a suicidal state might occur in a particular context and with a particular intensity. This vulnerability also has cognitive, affective, physiological, and behavioral aspects, and improvements in any one area can reduce vulnerability across the system. This theory emphasizes the cognitive *suicidal belief system*, which may stem from historical factors such as adversity. Rudd [23] proposed that the suicidal belief system is "potentially amenable to change during periods of activation, [and] activation is critical to treatment progress and success."

Both the Escape Theory and the Fluid Vulnerability Theory are compatible with the AIP model and the Working Memory Model of EMDR and may provide theoretical support for why EMDR could reduce suicidality [21,25]. In the AIP model, stressful and especially overwhelming experiences are conceptualized as affectively laden memories with explicit and implicit components that are incompletely processed. Multiple stressful experiences may be associated within networks linked by common themes, cognitions, emotions, implicit states, urges, or other similarities. These memories include a cognitive component, which may be the consequence of dysfunctional learning or overgeneralization, that may contribute to core beliefs. Activation of these memory networks, along with their cognitive, emotional, sensory, physiological, and behavioral components, represent the basis for symptomatology [21]. The Working Memory Theory posits that memories are transferred to working memory during EMDR and that eye movements function to reduce the vividness and intensity of memory-related imagery, partly because they *tax* working memory by using processing resources in the visuospatial sketchpad, which reduces the emotionality of the memory. This is corroborated by research showing reduced amygdala activation during EMDR [26]. At the same time, while the experience is held in awareness in working memory, it is amenable to change and is ultimately reconsolidated into a different form, with altered and more adaptive meta-cognitive interpretations [25].

Standard EMDR begins with accessing past associations to a current presenting problem by asking the participant about their current cognitions, emotions, or sensations. Holding all these elements together in awareness, the therapist then directs the person to *float back* to earlier times in life when these elements were experienced together, thus finding implicit past associations with the presenting problem. Alternatively, patients are asked to provide experiences that have *proven* their core beliefs, for example, *I am unlovable*, which are likewise processed. The targeted memory is desensitized and then paired with a positive core belief, which allows the person to access more adaptive information. Once the past experience is processed, present reminders and future fears of when a similar experience may happen are found in a similar fashion and then again processed. The Escape Theory would suggest that if EMDR desensitizes distressing memories associated with painful affective states fueling suicidal intrusions, SI would decrease. From the Fluid Vulnerability Model perspective, EMDR may address multiple aspects of the *suicidal mode*, as well as baseline risk, by targeting all 4 components (cognitive, affective, physiological, and behavioral) of the experiences contributing to risk. As the suicidal belief system shifts and internal and external cues no longer provoke arousal, vulnerability to activating future suicidal states may decrease. As cognitive, affective, and sensory (somatic or physiologic) aspects are addressed, in past, present, and future time frames, we hypothesize that EMDR will be able to uniquely access and address multiple dimensions of risk for suicidality concurrently in an individualized manner.

Preliminary evidence indicates that EMDR may be an effective intervention for SI [27-29]. With populations experiencing suicidal thoughts, EMDR may decrease SI, even when SI is not addressed directly, as is the case when PTSD, anxiety, or depression are primary treatment targets [27,28,30,31]. Most recently, Fereidouni reported a reduction in the Beck Scale for Suicide Ideation (BSS) scores in a randomized controlled trial (RCT) using intensive EMDR in 70 adult inpatients with MDD. Participants in the intervention group received individual EMDR for 45 to 90 minutes 3 times per week for 9 sessions. In that study, the mean BSS score dropped significantly from 26.48 to 11.11 in the EMDR group compared with no change in the control group. However, no other outcome measures were reported, and the participants were limited to those with depression [28]. Currently, most psychotherapeutic treatments target a specific diagnosis. Examples include EMDR treatment for PTSD and Dialectical Behavioral Therapy for borderline personality disorder (BPD), and changes in SI are usually reported as secondary outcomes [17,32]. Given the increasing public health need to improve treatment options for suicidality, this pragmatic real-world study was designed to assess the impact and safety of using EMDR to target SI across a wide spectrum of diagnoses.

Web-Based Delivery of EMDR

The COVID-19 pandemic has forced a rapid shift from in-person psychotherapy to remotely delivered psychotherapy services, both to reduce the spread of COVID-19 and to maintain service accessibility. This rapid shift to web-based care has raised concerns about whether therapy delivered via the web is as safe and effective as in-person therapy. A recent systematic review reported level 1a evidence that remote access, digitally delivered trauma therapies such as prolonged exposure therapy, cognitive processing therapy, and therapeutic exposure can be as effective as in-person treatment and may improve access to care [33]. Although there is a paucity of research on the safety and effectiveness of web-delivered EMDR, remotely delivered EMDR has been adopted clinically around the world [34]. This project will contribute to this area by exploring, with a focus on SI, whether remotely delivered EMDR can be delivered safely and effectively in a routine clinical practice setting. Remote access, rather than a face-to-face approach, has been chosen for our study as, locally in Edmonton, Alberta, Canada, the COVID-19 pandemic resulted in an increase in demand for mental health services at the same time as a reduction in the

availability of in-person mental health support. Furthermore, public health measures have necessitated periodic self-isolation, leading to clinic cancelations. For these reasons, this project will deliver EMDR via end-to-end encrypted Zoom videoconferencing (Zoom Video Communications, Inc), rather than in person.

Objectives

This study aims to examine whether web-based delivery of EMDR reduces the intensity of SI in adults, as measured by the BSS and the Columbia Suicide Severity Rating Scale (CSSRS). We hypothesize that targeting memories that are associated with SI, including addressing the associated suicidal belief system, will reduce distress and emotional dysregulation driving SI.

SI is often associated with mood, anxiety, and posttraumatic symptoms, and emotion dysregulation and dissociation are common in populations experiencing intense negative emotional states and those at risk of SI, such as PTSD and BPD [35-37]. The secondary study objectives, therefore, include measuring the impact of our modified EMDR treatment on symptoms of depression, anxiety, posttraumatic stress, emotional dysregulation, and dissociation. Measuring these symptoms will allow better characterization of our study sample and allow comparison with previous literature. In addition, we wish to learn if focusing on SI-associated experiences specifically leads to improvement in these common comorbid symptoms. Previous literature indicates that reductions in SI that occur during PTSD treatment, for example, may be mediated by improvements in PTSD or depressive symptoms [38]. It is unknown whether focusing specifically on SI, rather than a specific diagnosis such as PTSD, would also result in decreases in mood, anxiety, and PTSD symptoms.

A further objective is to report on the history of ACEs and the level of dissociative symptoms experienced by study participants (EMDR vs treatment as usual [TAU] group), as these may be markers of complexity [39,40]. Dissociative symptoms have been linked to increased comorbidity, exposure to childhood adversities, clinical severity, and lower response to trauma-focused therapies (TFTs) [39-42]. There is controversy as to whether dissociation is a barrier to using TFTs, such as EMDR [43]. The dissociative subtype of PTSD has been associated with midline prefrontal inhibition of limbic regions involved in emotion regulation, leading to emotional overmodulation [42]. One possible clinical implication is that such patients may have difficulty improving with TFTs because of impaired emotional regulation capacities and a tendency to dissociate upon exposure to distressing cues inherent in the processing of the trauma. This could impair the ability to adequately activate the fear network, leading to reduced effectiveness of TFTs [42]. Therefore, measuring dissociation at baseline and after treatment will provide important information about whether EMDR impacts dissociation, or if dissociative symptoms adversely impact treatment response.

We will compare dropout rates between treatment groups and report on any adverse events that arise in the EMDR group to explore the safety of using EMDR to target SI. Experts in the field of trauma have long believed that survivors of trauma should be treated using a phased approach [44-46]. The first phase focuses on stabilization and the introduction of coping skills to reduce self-harm and suicidality. Once phase 1 is completed and the person is no longer a risk to themselves or others, phase 2 may begin, with TFTs such as EMDR, which focus on distressing memories directly. However, this phased approach emphasizing stabilization before trauma processing has been criticized as lacking evidence [47]. Therefore, studies reporting on the safety of TFTs, such as EMDR, in patients with SI can help address this controversy.

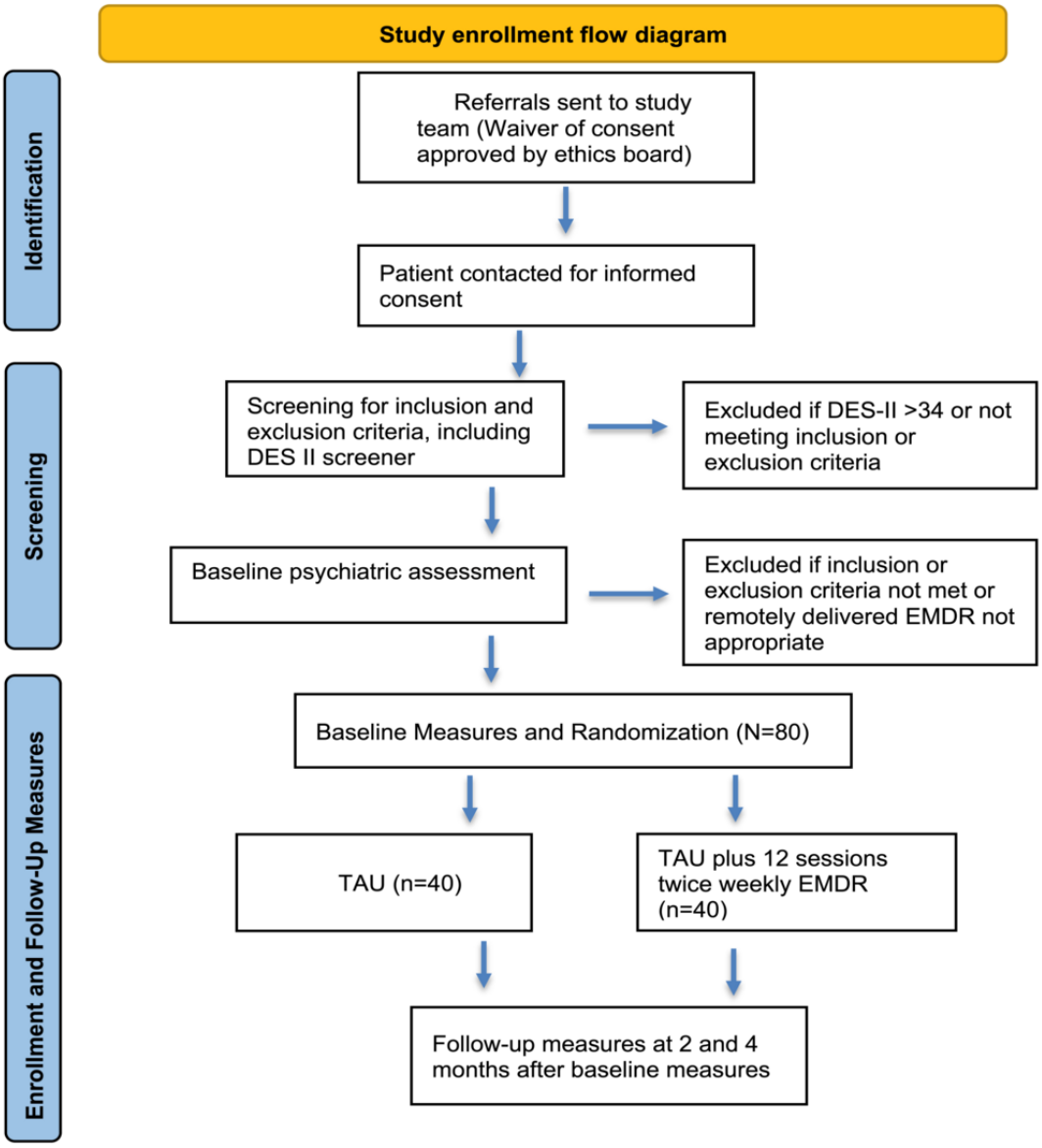
Methods

Study Design

The study is a nonblinded RCT that will evaluate the effects of remotely delivered EMDR in combination with TAU, compared with TAU alone for adult patients with SI. Owing to the nature of EMDR, trial blinding to the research team and clinical staff is not possible. All clinical contact will occur on the web via a health care–level encrypted Zoom platform. The anticipated flow of participant enrollment is shown in Figure 1, and details are included in the *Study Procedure* section. Participants will be randomized (by computer-generated random allocation) to receive either intensive 90-minute EMDR sessions twice per week plus TAU or TAU alone. A pilot study by Proudlock et al [29] and an RCT by Fereidouni et al [28] used a similar design, with intensive EMDR provided 2 to 3 times per week. In the study by Proudlock et al [29], most of the participants were outpatients with an acute mental health crisis with SI. In the RCT, the participants were inpatients with major depression and suicidal thoughts [28]. The literature suggests that intensive (ie, multiple sessions per week) therapy is safe and effective and may reduce attrition [28,29,48,49].

The primary outcome is the intensity of SI in adults, as measured by the BSS and the CSSRS. Secondary outcomes include mood (Beck Depression Inventory-II and Patient Health Questionnaire 9), anxiety (Generalized Anxiety Scale-7), posttraumatic symptoms (Impact of Events Scale Revised), dissociation symptoms (Dissociative Experiences Scale-II [DES-II]), and emotion dysregulation (Difficulties in Emotional Regulation Scale). Secondary outcomes include adverse events and dropout rates. A subsequent longer-term analysis, beyond the scope of this protocol, will examine differences between groups with respect to the number of emergency room visits, hospitalizations, and overall health care use in the year before and after therapy.

Figure 1. Flow diagram. DES-II: Dissociative Experiences Scale-II; EMDR: Eye Movement Desensitization and Reprocessing; TAU: treatment as usual.



Ethics

The Health Research Ethics Board at the University of Alberta approved the study protocol (protocol ID number: Pro00090989). The study is registered at ClinicalTrials.gov (ID number: NCT04181047). Although EMDR is a gold standard, evidence-based treatment for trauma [17,18], current practice guidelines do not generally endorse EMDR specifically for the treatment of suicidal thinking, and data on remote delivery of EMDR are limited [33]. Some providers believe that trauma therapy should not be attempted in patients with SI, based on fears that exposure to traumatic memories may increase emotional dysregulation or worsen suicidality. EMDR may, in some cases, lead to temporarily increased PTSD symptoms, anxiety, nightmares, or distress during treatment. The web-based nature of the treatment may also add privacy and safety risks because of the use of electronic communications and the fact that the therapist is not in the same location as the participant. Therefore, clinical safety procedures were developed to monitor and manage increased SI and adverse events, in addition to ensuring informed consent from participants. These considerations were discussed with the Health Research Ethics Review Board, which approved the study.

Participants

Adults (aged 18-65 years) with SI in the last week are eligible for this study. SI may be chronic or acute and of any intensity as long as it is not accompanied by an active plan with intent, given the concerns about immediate safety and the need for stabilization in this population. As SI can occur across various diagnoses, participants are not limited to having one main diagnosis. Participants with suicidal thoughts and any or all of

the following primary diagnoses: mood and anxiety disorders, trauma and stress-related disorders, or personality disorders as primary diagnoses are eligible for this study. Participants must also be willing and able to volunteer to participate in the study, provide informed consent, and follow up twice weekly for EMDR sessions if they are randomized to the EMDR group (a total of 12 desensitization sessions). Participants must have a primary service provider, either a physician or a mental health professional, who they can access for care outside of EMDR sessions. Participants must have access to their own laptop or desktop computer that enables bilateral stimulation with a working screen, camera, and microphone, as well as access to a quiet, private, well-lit space for therapy. Participants must be willing to refrain from benzodiazepine, cannabis, or illicit substance use in the 24 hours before or after EMDR sessions to avoid interference with EMDR and memory consolidation. Participants must also be willing to adhere to the study safety precautions (see the *Clinical Safety Procedures* section).

Participants will be excluded from the study if, at the time of the baseline assessment, SI is accompanied by intent or a plan to follow through with suicide. The rationale is that those with intent or a plan may be more at risk of imminently following through with acting on the ideation. Clinical guidelines recommend that this warrants inpatient stabilization to ensure immediate safety [50]. Participants will be excluded if they score above 34 on the DES-II or report severe dissociative symptoms during the baseline psychiatric assessment interview in keeping with a separate dissociative disorder, such as hearing internal voices, amnestic episodes, dissociative fugue states, passivity experiences, first rank symptoms under stress, the subjective experience of having alter personality self-states, or severe isolation of affect, with the inability to feel body sensations or emotions. Clinical experience and the scientific literature suggest that severe dissociative symptoms signal a poor response to standard EMDR therapy or require special techniques or extensive stabilization. Participants with manic or psychotic symptoms will be excluded to reduce heterogeneity, as are those undergoing electroconvulsive therapy, which may have an impact on memory. Participants undergoing or planning to undergo another trauma-focused psychotherapy in the 4-month study period will also be excluded to reduce bias. Participants who are known to be pregnant will be excluded, as there is limited information about the impact of EMDR in pregnancy.

Study Sample Size and Duration

The only analogous trial published, to our knowledge, is an RCT by Fereidouni et al [28], which also used the BSS to measure changes in SI, but in a depressed inpatient population. They reported a required sample size of 31 per arm, which was increased to 35 to account for attrition, calculated using a CI of 95%, a statistical power of 80%, and a minimum clinically significant difference of 5%. This previous trial enrolled 70 participants and had no dropouts.

In this study, the overall target sample size is 80 participants (40 in each group). To detect a within-group change (pre- and posttreatment changes in rating scale measures) of Cohen d=0.50, applying a 2-tailed α level of .05 and power at 0.80 (0.75 for between-group changes), the study will require 32 participants in each group. Our target sample size of 40 participants per group was chosen to account for an anticipated attrition rate of 20%, resulting in samples no smaller than 32. The attrition rate is based on clinical experience, as well as the literature reporting a mean dropout rate of approximately 18% in previous EMDR trials [29,51].

Clinical Safety Procedures

To ensure participant safety during the study, the following measures have been instituted:

1. All participants must have access to a health professional, such as a family physician or psychiatrist, during the course of this trial, who is willing to provide general mental health care, as necessary. If a safety concern arises during the study, the participant's provider will be informed.
2. Before commencing EMDR, the participant will confirm their address, phone number, email address, and emergency contact person. This is necessary so that an emergency response can be activated if clinically indicated.
3. If the participant is enrolled in the EMDR treatment group, the study therapist will ensure that a written safety plan has been completed before treatment is initiated. This safety plan will include helping the participant to identify their warning signs for crisis, their internal coping resources, sources of helpful distraction, and helpful others, including professional resources, from whom they can access assistance in a crisis. Contact information for Edmonton crisis services will also be provided.
4. To ensure safety during EMDR sessions, participants will be asked to ensure that there is a supportive person who will be available to assist within 5 minutes, in the unlikely case of an emergency.
5. If there is a significant worsening in SI, the study therapist may pause EMDR and focus on crisis stabilization and the institution of the individualized safety plan.
6. The study research assistant (RA) was trained in a protocol for enrolling participants, which includes a safety protocol to manage any unanticipated situations in which a participant spontaneously expresses worsening or active SI (Multimedia Appendix 1). Consent for EMDR therapy includes an understanding that in the case of imminent risk of harm to self or others, the therapist or RA may need to activate the safety plan or call emergency services.
7. For the EMDR group, adverse events will be queried and recorded at the beginning of each EMDR session, along with recording a self-report of the intensity of various symptoms, including SI, on a 0-10 scale. As therapy is taking place in the context of clinical care, progress will be documented in the electronic health record, which may be accessed by the participants' treatment team (see Multimedia Appendix 2 for the items captured regarding adverse events). In addition, serious adverse events will be directly reported to the participants' treatment team. Each person participating in the study must agree to maintain a relationship with his or her community treatment team during the study to avoid a situation where the person has no access to care during or immediately after participating in the study.

Participant confidentiality and web-based security:

1. Informed consent for web-based EMDR therapy also includes an agreement that the patient will disclose their physical location, keep a working telephone with them in the case of internet disconnection, and connect in a private area. Health service–level encrypted Zoom, as authorized by Alberta Health Services, will be used for videoconferencing therapy to minimize security concerns. The participants will also be encouraged to use their own private computer and Wi-Fi.
2. Encryption will be used in the case that email is needed to send potentially identifying information, in accordance with Alberta Health Services policy.

Study Procedure

This study is being conducted in partnership with the outpatient mental health clinics of the Alberta Health Services Addiction and Mental Health, Edmonton Zone. Figure 1 shows the anticipated flow of subject enrollment and assessments.

1. Community clinicians will make a referral through email, fax, or phone to the RA. The research ethics board at the University of Alberta approved a waiver of consent to allow the RA to receive and screen referrals and contact the potential participants to set up a Zoom meeting to explain the study and obtain informed consent. If necessary, the RA can aid the potential participant in setting up Zoom and instructing the person on its use. During this initial Zoom meeting, the RA will obtain informed consent for participation in the study, which will be collected and managed using REDCap (Research Electronic Data Capture) tools hosted by the Women & Children's Health Research Institute at the University of Alberta, using a 2-factor authorization process [52]. Participants will be informed that they may withdraw their consent and opt out of the study at any time during the 4-month study period, whereas participant data may be withdrawn at any point before treatment begins.
2. After obtaining consent, the RA will send a link from REDCap to the participant to complete the DES-II electronically. A DES-II score ≥34 will exclude a person from the study. If enrollment screening criteria are met, the participants will receive a psychiatric assessment by the study psychiatrist. The purpose of the psychiatrist assessment is to complete an in-depth assessment to rule out contraindications to web-based EMDR and to ensure eligibility criteria are met, including ruling out severe dissociation not apparent on the DES-II screening questionnaire. The psychiatrist will also perform a baseline diagnostic assessment according to *Diagnostic and Statistical Manual of Mental Disorders - 5* criteria to evaluate the baseline diagnoses. If the person appears suitable for the study, baseline self-report measures will be completed electronically (Table 1). Once the baseline measures are complete, REDCap will randomly assign the person to either the EMDR group or the TAU group using random computerized allocation.
3. All patients will complete baseline and follow-up measures electronically through REDCap, as shown in Table 1.
4. Patients in the EMDR treatment group will receive live, twice weekly EMDR through Zoom videoconferencing. The study therapist will take a relevant history, provide limited psychoeducation, and explain EMDR to the patient. After developing a safety plan with the participant, up to 5 standard preparation exercises will be completed before therapy (container, safe state, internal meeting place, safe place for parts, and updating the emotional circuits [53]). Patients will then receive EMDR, targeting the experiences or core beliefs associated with the SI. The standard EMDR protocol will generally be used, with the modification that the *future template* will be a *flashforward* of the *worst-case scenario future when suicide would again seem like an option*. Although the standard *future template* involves running a mental movie about the future, a *flashforward* targets the person's mental representation of future events in a similar fashion as past events are targeted (see the paper by Logie and De Jongh [54] for details about this strategy).

Table 1. Timing and content of study measures.

Measure	Content of measure	Timing of measures		
		Baseline	2 months after enrollment	4 months after enrollment
Demographic questionnaire	Demographics	✓[a]		
ACES[b]	Adverse childhood experiences	✓		
DES-II[c]	Dissociative symptoms	✓		✓
BSS[d]	Suicidal ideation	✓	✓	✓
CSSRS[e]—clinician rated	Suicidal ideation	✓		
CSSRS—past week (self-rated)	Suicidal ideation	✓	✓	✓
BDI-II[f]	Depressive symptoms	✓	✓	✓
PHQ-9[g]	Depressive symptoms	✓	✓	✓
GAD-7[h]	Anxiety	✓	✓	✓
IES-R[i]	PTSD symptoms	✓	✓	✓
DERS[j]	Emotional dysregulation	✓		✓

[a]Indicates the timing of the respective measures.
[b]ACES: Adverse Childhood Experiences Scale.
[c]DES-II: Dissociative Experiences Scale.
[d]BSS: Beck Scale for Suicide Ideation.
[e]CSSRS: Columbia Suicide Severity Rating Scale.
[f]BDI-II: Beck Depression Inventory-II.
[g]PHQ-9: Patient Health Questionnaire-9.
[h]GAD-7: Generalized Anxiety Disorder-7.
[i]IES-R: Impact of Events Scale Revised.
[j]DERS: Difficulties in Emotional Regulation Scale.

Some other modifications to the standard protocol are allowed. Specifically, intrusive or distressing memories may be targeted initially, if needed, instead of the first, worst, current, and future order of the standard protocol. If there is apprehension about doing EMDR, a flashforward of the worst thing that could happen may be used to address this resistance before targeting memories. This was reported as a successful strategy in an intensive treatment program [49]. In addition, therapists can use the EMDR early trauma protocol if there are significant attachment problems, add additional dual attention tasks to load working memory, or use shorter sets of bilateral stimulation if the standard protocol is not tolerated [55,56]. Strategies in the Jim Knipe EMDR Toolbox can also be used as needed [57]. Modifications to the standard protocol will be recorded in REDCap and reported on.

EMDR will specifically target the traumatic memories or core beliefs associated with the SI. These targets may be easily identified by the patient in some cases. Alternatively, the standard floatback method may be used to identify memory targets, or therapists may target the somatic urge or state associated with suicidal thoughts. This strategy of targeting states or urges has been utilized in EMDR protocols such as the *DeprEnd protocol* for depression and the *DeTUR protocol* for urges associated with substance use disorders [58,59]. Other possible targets for EMDR include memory of the circumstances surrounding the first occurrence of SI, memories at the origin of the negative beliefs associated with SI, or memories related to hopelessness and despair [21,58,60]. If escape fantasies, including the fantasy of escaping through suicide, emerge during memory processing, the participant may be encouraged to notice the fantasy rather than avoid or suppress it. In addition, if nightmares arise during the course of treatment, they can also be targeted directly using EMDR if clearly related to SI or the experiences being reviewed in therapy sessions.

Participants will be seen twice weekly until the therapy is completed (12 desensitization sessions in total). Symptoms and any adverse reactions will be recorded at the beginning of each session using a standard EMDR session progress note form.

Measures

Primary Outcome Measures

Beck Scale for Suicide Ideation

The BSS is a 21-item questionnaire on SI and behavior over the past week. The score ranges from 0 to 42, with higher scores indicating worse outcomes. Questions 6 through 19 are not completed if answers to both questions 4 and 5 indicate that the person has no suicidal desire and would try to save their life if in a life-threatening situation. Question 20 asks about previous suicide attempts, and question 21 asks about the wish to die during any such attempt [61] (Digital adaptation 2021 NCS

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Columbia Suicide Severity Rating Scale

The CSSRS is a questionnaire used for suicide assessment, developed by multiple institutions including Columbia University. Several versions exist; this study will use the clinician-rated version that assesses lifetime and recent SI (last week) and suicidal behavior at baseline. In addition, a self-report version will be used at baseline, 2 months, and 4 months to assess SI in the *past 1 week*, which includes 5 questions about SI and 2 questions about suicidal behavior [62].

Secondary Outcome Measures

Adverse Childhood Experiences Scale

The Adverse Childhood Experiences Scale is a standard 10-item questionnaire that assesses the presence or absence of adversities experienced in the first 18 years of life, including emotional, physical, or sexual abuse, neglect, parental divorce, domestic abuse, familial substance abuse, incarceration, or mental illness. Higher scores are indicative of more childhood adversity and have been consistently associated with an increased risk of psychiatric illness, substance abuse, and physical illness [63].

Dissociative Experiences Scale-II

The DES-II is a 28-item questionnaire that includes questions about common dissociative symptoms, which are scored based on the frequency of experiencing the symptom, from 0% of the time to 100% of the time. A higher score (range 0-100) indicates more severe dissociative pathology. The mean scores for PTSD, Dissociative Disorder Not Otherwise Specified, and Dissociative Identity Disorder in a previous study were 31, 36, and 48, respectively [64].

Beck Depression Inventory-II

The Beck Depression Inventory-II is a 21-item questionnaire focusing on symptoms of MDD, including one question on SI or wishes. Each question is scored on a 0-3 scale, with higher scores indicating a higher likelihood of MDD [65] (digital adaptation 2021 NCS Pearson Inc. All rights reserved. Adapted and used under license #LSR-262494).

Patient Health Questionnaire-9

The Patient Health Questionnaire-9 Self-Report is a self-report questionnaire for assessing depressive symptoms during the previous 2 weeks, using a 4-point Likert scale to indicate symptom frequency for each item (0=not at all; 3=nearly every day). Higher scores (range 0-27) indicate more severe depressive symptoms. Included is also a question about how difficult the symptoms made it for the participant to work, take care of things at home, or get along with people (rated from not difficult to extremely difficult, on a 4-point scale) [66].

Generalized Anxiety Disorder 7

The Generalized Anxiety Scale-7 is a 7-item self-report scale for anxiety symptoms, with each symptom rated for the past 2 weeks on a 4-point scale. The scale ranges from 0 (not at all) to 3 (nearly every day), with higher scores indicating worse anxiety symptoms. There is also a question about how difficult the problems endorsed made it for the participant to work, take care of things at home, or get along with people (rated from not difficult to extremely difficult, on a 4-point scale) [67].

Impact of Events Revised

The Impact of Events Scale Revised is a 22-item questionnaire, which rates the intensity of distress over the past 7 days, related to a past event. Symptoms related to distress are rated on a 5-point scale, from 0 for *not at all* to 4 for *extremely* distressing, with scores ranging from 0 to 88. Questions include symptoms generally indicative of posttraumatic stress, with a higher score indicating more severe symptoms [68].

Difficulties in Emotional Regulation Scale

The Difficulties in Emotional Regulation Scale is a 35-item questionnaire focusing on symptoms related to emotion regulation. Questions are rated on a 5-point scale, and participants rate how often the statements apply to them by providing a number, where 1 indicates *almost never* (0%-10% of the time) and 5 indicates *almost always* (91%-100% of the time) [69].

Session Forms

For the EMDR group, session forms will be used to track weekly progress. These forms include a scale of 0 to 10 (ranging from no difficulties to highest intensity) to record the intensity of suicidal thoughts, self-harm urges, and the following symptoms: worry thoughts, anxiety, guilt or shame, anger, sadness, flashbacks, sleep problems, substance use, suicidal thoughts or impulses, self-harm urges, concentration difficulties, lethargy or fatigue, appetite problems, and repetitive thoughts. These forms will also capture the session focus and any deviations from the standard EMDR protocol.

Statistical Analysis

Treatment groups will be compared for differences in demographics or clinical severity that may be relevant to differences in outcomes. The number of desensitization sessions will be reported, along with any adverse events.

The main statistical contrast will compare measures for the EMDR versus the TAU group; particular emphasis will be placed on the primary outcome variables of severity of SI before and after treatment in each group. Pre- and posttreatment effects on rating scales will be analyzed using parametric (2-tailed *t* tests and analysis of variance [ANOVA]) or nonparametric (Mann-Whitney and Wilcoxon and Friedman or Kruskal-Wallis ANOVA) tests, where appropriate. For multiple comparisons in the analysis, the error rates will be adjusted appropriately using Bonferroni corrections. ANOVA followed by multiple comparison tests will be applied where the number of within-subject test times k>2 (Table 1). For single time measures, for example, Adverse Childhood Experiences Scale or clinician-rated suicide ratings, simple contrasts will be assessed with *t* tests or nonparametric equivalents, as appropriate. The statistical criterion for type one errors will be a 2-tailed probability of $P \geq .05$, after appropriate adjustment for multiple comparisons.

Results

It is anticipated that the active recruitment, psychotherapy treatment, and data collection phase of this study will take 18 months to complete. We expect to report the primary and secondary outcomes by mid-2023. The primary outcome will be changes in SI; secondary outcomes will include changes in reported depressive, anxious, dissociative, and PTSD symptoms, as well as changes in emotional dysregulation. In addition, we will report on dropout rates and adverse effects that emerge during EMDR treatment. Study participants will be informed about the trial results via a plain language summary that will be sent to them. Academic papers and summary reports will be provided to the Mental Health Foundation for knowledge dissemination. Evidence regarding the safety and efficacy of EMDR in the context of SI will be discussed with Alberta Health Services and presented in clinical academic settings to support knowledge translation and knowledge implementation.

Discussion

Principal Hypotheses

There exists a significant body of literature demonstrating that childhood and adult adverse experiences are strongly associated with SI, suicide attempts, self-injurious behavior, and the development of a wide range of psychiatric illnesses [3-9]. If the AIP model of EMDR is correct, experiences lead to the development of explicit and implicit memories that drive or contribute to painful core beliefs or overwhelming affect. We hypothesize that targeting these memories directly will provide a direct treatment for emotional dysregulation and suicidal thinking.

Current treatment of SI usually focuses on treating comorbidities such as depression and teaching new ways of coping, thinking, or behaving. None of the currently recommended treatments for suicidality target memories directly. EMDR desensitizes the emotionality of traumatic memories, followed by reprocessing the associated negative core belief with a more adaptive one. A recent RCT using EMDR for suicidal thoughts in inpatients with depression offers the first RCT evidence that EMDR can specifically reduce suicidal thoughts [28]. This adds to the uncontrolled data that suggest that EMDR can reduce suicidality in patients in crisis or those with suicidal thinking [27,29]. This study aims to target SI from a transdiagnostic perspective, focusing on the memories driving or associated with the SI across a broad spectrum of diagnoses.

Implications for the Future

If the study results support the use of EMDR as a safe and effective treatment for people with SI, it would challenge current clinical norms. The PTSD literature suggests that treating PTSD with TFTs reduces SI, even after controlling for depression and hopelessness [70,71]. However, clinicians are often reluctant to offer TFT in suicidal patients for fear of worsening their suicide risk. Therefore, patients' trauma symptoms may go untreated or be addressed solely with medications, and they may experience repeated bouts of crisis or hospitalization, leading to further demoralization. This study may provide evidence to support clinicians in using TFTs for patients with SI earlier, potentially preventing the vicious cycle of repeated hospitalizations, suffering, and chronic psychiatric morbidity.

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Authors' Contributions

LB, OW, SP, AG, KO and AA: conceptualization, design, and methodology. LB and OW: drafting of original manuscript. All authors: review and revision of manuscript for important intellectual content. LB: project administration.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Safety protocol for a research assistant.
[PDF File (Adobe PDF File), 235 KB - resprot_v10i11e30711_app1.pdf]

Multimedia Appendix 2
Questions regarding adverse events and dropouts.
[PDF File (Adobe PDF File), 71 KB - resprot_v10i11e30711_app2.pdf]

References

1. The Federal Framework for Suicide Prevention – Progress Report 2018. Public Health Agency of Canada, Government of Canada. URL: https://www.canada.ca/en/public-health/services/publications/healthy-living/federal-framework-suicide-prevention-progress-report-2018.html#fn16 [accessed 2021-03-13]
2. Klonsky ED, May AM, Saffer BY. Suicide, suicide attempts, and suicidal ideation. Annu Rev Clin Psychol 2016;12:307-330. [doi: 10.1146/annurev-clinpsy-021815-093204] [Medline: 26772209]
3. Afifi TO, Enns MW, Cox BJ, Asmundson GJ, Stein MB, Sareen J. Population attributable fractions of psychiatric disorders and suicide ideation and attempts associated with adverse childhood experiences. Am J Public Health 2008 May;98(5):946-952. [doi: 10.2105/AJPH.2007.120253] [Medline: 18381992]
4. Afifi TO, Boman J, Fleisher W, Sareen J. The relationship between child abuse, parental divorce, and lifetime mental disorders and suicidality in a nationally representative adult sample. Child Abuse Negl 2009 Mar;33(3):139-147. [doi: 10.1016/j.chiabu.2008.12.009] [Medline: 19327835]
5. Afifi TO, Taillieu T, Zamorski MA, Turner S, Cheung K, Sareen J. Association of child abuse exposure with suicidal ideation, suicide plans, and suicide attempts in military personnel and the general population in Canada. JAMA Psychiatry 2016 Mar;73(3):229-238. [doi: 10.1001/jamapsychiatry.2015.2732] [Medline: 26817953]
6. Ásgeirsdóttir HG, Valdimarsdóttir UA, Þorsteinsdóttir Þ, Lund SH, Tomasson G, Nyberg U, et al. The association between different traumatic life events and suicidality. Eur J Psychotraumatol 2018;9(1):1510279 [FREE Full text] [doi: 10.1080/20008198.2018.1510279] [Medline: 30220981]
7. de Araújo RM, Lara DR. More than words: the association of childhood emotional abuse and suicidal behavior. Eur Psychiatry 2016 Sep;37:14-21. [doi: 10.1016/j.eurpsy.2016.04.002] [Medline: 27442978]
8. Dube SR, Anda RF, Felitti VJ, Chapman DP, Williamson DF, Giles WH. Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: findings from the adverse childhood experiences study. J Am Med Assoc 2001 Dec 26;286(24):3089-3096. [doi: 10.1001/jama.286.24.3089] [Medline: 11754674]
9. Kisely S, Abajobir AA, Mills R, Strathearn L, Clavarino A, Najman JM. Child maltreatment and mental health problems in adulthood: birth cohort study. Br J Psychiatry 2018 Dec;213(6):698-703. [doi: 10.1192/bjp.2018.207] [Medline: 30475193]
10. Shapero BG, Farabaugh A, Terechina O, DeCross S, Cheung JC, Fava M, et al. Understanding the effects of emotional reactivity on depression and suicidal thoughts and behaviors: moderating effects of childhood adversity and resilience. J Affect Disord 2019 Feb 15;245:419-427. [doi: 10.1016/j.jad.2018.11.033] [Medline: 30423470]
11. van Heeringen K, Mann JJ. The neurobiology of suicide. Lancet Psychiatry 2014 Jun;1(1):63-72. [doi: 10.1016/S2215-0366(14)70220-2] [Medline: 26360403]
12. O'Connor RC, Nock MK. The psychology of suicidal behaviour. Lancet Psychiatry 2014 Jun;1(1):73-85. [doi: 10.1016/S2215-0366(14)70222-6] [Medline: 26360404]
13. Petruccelli K, Davis J, Berman T. Adverse childhood experiences and associated health outcomes: a systematic review and meta-analysis. Child Abuse Negl 2019 Nov;97:104127. [doi: 10.1016/j.chiabu.2019.104127] [Medline: 31454589]
14. Herzog JI, Schmahl C. Adverse childhood experiences and the consequences on neurobiological, psychosocial, and somatic conditions across the lifespan. Front Psychiatry 2018;9:420 [FREE Full text] [doi: 10.3389/fpsyt.2018.00420] [Medline: 30233435]
15. Lund JI, Toombs E, Radford A, Boles K, Mushquash C. Adverse childhood experiences and executive function difficulties in children: a systematic review. Child Abuse Negl 2020 Aug;106:104485. [doi: 10.1016/j.chiabu.2020.104485] [Medline: 32388225]
16. Dvir Y, Ford JD, Hill M, Frazier JA. Childhood maltreatment, emotional dysregulation, and psychiatric comorbidities. Harv Rev Psychiatry 2014;22(3):149-161 [FREE Full text] [doi: 10.1097/HRP.0000000000000014] [Medline: 24704784]
17. Navarro PN, Landin-Romero R, Guardiola-Wanden-Berghe R, Moreno-Alcázar A, Valiente-Gómez A, Lupo W, et al. 25 years of eye movement desensitization and reprocessing (EMDR): the EMDR therapy protocol, hypotheses of its mechanism of action and a systematic review of its efficacy in the treatment of post-traumatic stress disorder. Rev Psiquiatr Salud Ment (Engl Ed) 2018;11(2):101-114. [doi: 10.1016/j.rpsm.2015.12.002] [Medline: 26877093]
18. Wilson G, Farrell D, Barron I, Hutchins J, Whybrow D, Kiernan MD. The use of eye-movement desensitization reprocessing (EMDR) therapy in treating post-traumatic stress disorder-a systematic narrative review. Front Psychol 2018;9:923 [FREE Full text] [doi: 10.3389/fpsyg.2018.00923] [Medline: 29928250]
19. Carletto S, Malandrone F, Berchialla P, Oliva F, Colombi N, Hase M, et al. Eye movement desensitization and reprocessing for depression: a systematic review and meta-analysis. Eur J Psychotraumatol 2021 Apr 09;12(1):1894736 [FREE Full text] [doi: 10.1080/20008198.2021.1894736] [Medline: 33889310]
20. Valiente-Gómez A, Moreno-Alcázar A, Treen D, Cedrón C, Colom F, Pérez V, et al. EMDR beyond PTSD: a systematic literature review. Front Psychol 2017;8:1668 [FREE Full text] [doi: 10.3389/fpsyg.2017.01668] [Medline: 29018388]
21. Shapiro F. Eye Movement Desensitization and Reprocessing (EMDR) Therapy: Basic Principles, Protocols, and Procedures. New York, NY: Guildford Press; Jan 19, 2018:87-88.
22. Baumeister RF. Suicide as escape from self. Psychol Rev 1990 Jan;97(1):90-113. [doi: 10.1037/0033-295x.97.1.90] [Medline: 2408091]

23. Rudd MD. Fluid vulnerability theory: a cognitive approach to understanding the process of acute and chronic suicide risk. In: Ellis TE, editor. Cognition and Suicide: Theory, Research, and Therapy. Washington D.C: American Psychological Association; 2006:355-368.
24. Beck AT. Beyond belief: a theory of modes, personality, and psychopathology. In: Salkovskis P, editor. Frontiers of Cognitive Therapy. New York, United States: Guilford Press; 1996:1-25.
25. Andrade J, Kavanagh D, Baddeley A. Eye-movements and visual imagery: a working memory approach to the treatment of post-traumatic stress disorder. Br J Clin Psychol 1997 May;36(2):209-223. [doi: 10.1111/j.2044-8260.1997.tb01408.x] [Medline: 9167862]
26. de Voogd LD, Kanen JW, Neville DA, Roelofs K, Fernández G, Hermans EJ. Eye-movement intervention enhances extinction via amygdala deactivation. J Neurosci 2018 Oct 03;38(40):8694-8706 [FREE Full text] [doi: 10.1523/JNEUROSCI.0703-18.2018] [Medline: 30181134]
27. Proudlock S, Hutchins J. EMDR within crisis resolution and home treatment teams. J EMDR Prac Res 2016 Jan 01;10(1):47-56. [doi: 10.1891/1933-3196.10.1.47]
28. Fereidouni Z, Behnammoghadam M, Jahanfar A, Dehghan A. The effect of eye movement desensitization and reprocessing (EMDR) on the severity of suicidal thoughts in patients with major depressive disorder: a randomized controlled trial. Neuropsychiatr Dis Treat 2019;15:2459-2466 [FREE Full text] [doi: 10.2147/NDT.S210757] [Medline: 31695382]
29. Proudlock S, Peris J. Using EMDR therapy with patients in an acute mental health crisis. BMC Psychiatry 2020 Jan 09;20(1):14 [FREE Full text] [doi: 10.1186/s12888-019-2426-7] [Medline: 31918684]
30. Jamshidi F, Rajabi S, Dehghani Y. How to heal their psychological wounds? Effectiveness of EMDR therapy on post-traumatic stress symptoms, mind-wandering and suicidal ideation in Iranian child abuse victims. Couns Psychother Res 2020 Jul 22;21(2):412-421. [doi: 10.1002/capr.12339]
31. van den Berg DP, de Bont PA, van der Vleugel BM, de Roos C, de Jongh A, Van Minnen A, et al. Prolonged exposure vs eye movement desensitization and reprocessing vs waiting list for posttraumatic stress disorder in patients with a psychotic disorder: a randomized clinical trial. JAMA Psychiatry 2015 Mar;72(3):259-267. [doi: 10.1001/jamapsychiatry.2014.2637] [Medline: 25607833]
32. May JM, Richardi TM, Barth KS. Dialectical behavior therapy as treatment for borderline personality disorder. Ment Health Clin 2016 Mar;6(2):62-67 [FREE Full text] [doi: 10.9740/mhc.2016.03.62] [Medline: 29955449]
33. Jones C, Miguel-Cruz A, Smith-MacDonald L, Cruikshank E, Baghoori D, Chohan AK, et al. Virtual trauma-focused therapy for military members, veterans, and public safety personnel with posttraumatic stress injury: systematic scoping review. JMIR Mhealth Uhealth 2020 Sep 21;8(9):e22079 [FREE Full text] [doi: 10.2196/22079] [Medline: 32955456]
34. Lenferink LI, Meyerbröker K, Boelen PA. PTSD treatment in times of COVID-19: a systematic review of the effects of online EMDR. Psychiatry Res 2020 Nov;293:113438 [FREE Full text] [doi: 10.1016/j.psychres.2020.113438] [Medline: 32905864]
35. Korzekwa MI, Dell PF, Links PS, Thabane L, Fougere P. Dissociation in borderline personality disorder: a detailed look. J Trauma Dissociation 2009;10(3):346-367. [doi: 10.1080/15299730902956838] [Medline: 19585341]
36. Carlson EB, Dalenberg C, McDade-Montez E. "Dissociation in posttraumatic stress disorder Part I: Definitions and review of research": correction to Carlson, Dalenberg, and McDade-Montez (2012). Psychol Trauma 2012;4(5):489. [doi: 10.1037/a0030230]
37. Choi H, Kim S, Yun KW, Kim YC, Lim W, Kim E, et al. A study on correlation between anxiety symptoms and suicidal ideation. Psychiatry Investig 2011 Dec;8(4):320-326 [FREE Full text] [doi: 10.4306/pi.2011.8.4.320] [Medline: 22216041]
38. Brown LA, Zang Y, Benhamou K, Taylor DJ, Bryan CJ, Yarvis JS, STRONG STAR Consortium. Mediation of suicide ideation in prolonged exposure therapy for posttraumatic stress disorder. Behav Res Ther 2019 Aug;119:103409. [doi: 10.1016/j.brat.2019.103409] [Medline: 31176888]
39. Rafiq S, Campodonico C, Varese F. The relationship between childhood adversities and dissociation in severe mental illness: a meta-analytic review. Acta Psychiatr Scand 2018 Dec;138(6):509-525. [doi: 10.1111/acps.12969] [Medline: 30338524]
40. Lyssenko L, Schmahl C, Bockhacker L, Vonderlin R, Bohus M, Kleindienst N. Dissociation in psychiatric disorders: a meta-analysis of studies using the dissociative experiences scale. Am J Psychiatry 2018 Jan 01;175(1):37-46. [doi: 10.1176/appi.ajp.2017.17010025] [Medline: 28946763]
41. Bae H, Kim D, Park YC. Dissociation predicts treatment response in eye-movement desensitization and reprocessing for posttraumatic stress disorder. J Trauma Dissociation 2016;17(1):112-130. [doi: 10.1080/15299732.2015.1037039] [Medline: 26156867]
42. Lanius RA, Vermetten E, Loewenstein RJ, Brand B, Schmahl C, Bremner JD, et al. Emotion modulation in PTSD: clinical and neurobiological evidence for a dissociative subtype. Am J Psychiatry 2010 Jun;167(6):640-647 [FREE Full text] [doi: 10.1176/appi.ajp.2009.09081168] [Medline: 20360318]
43. Lynch SM, Forman E, Mendelsohn M, Herman J. Attending to dissociation: assessing change in dissociation and predicting treatment outcome. J Trauma Dissociation 2008;9(3):301-319. [doi: 10.1080/15299730802139063] [Medline: 19042780]
44. Herman J. Recovery from psychological trauma. Psychiatry Clin Neurosci 1998;52:98-103 [FREE Full text] [doi: 10.1046/j.1440-1819.1998.0520s5s145.x]

45. Cloitre M, Courtois CA, Charuvastra A, Carapezza R, Stolbach BC, Green BL. Treatment of complex PTSD: results of the ISTSS expert clinician survey on best practices. J Trauma Stress 2011 Dec;24(6):615-627. [doi: 10.1002/jts.20697] [Medline: 22147449]
46. van der Kolk B. Posttraumatic stress disorder and the nature of trauma. Dialogues Clin Neurosci 2000 Mar;2(1):7-22 [FREE Full text] [Medline: 22034447]
47. De Jongh A, Resick PA, Zoellner LA, van Minnen A, Lee CW, Monson CM, et al. Critical analysis of the current treatment guidelines for complex PTSD in adults. Depress Anxiety 2016 May;33(5):359-369. [doi: 10.1002/da.22469] [Medline: 26840244]
48. Méndez MZ, Nijdam MJ, Heide FJ, van der Aa N, Olff M. A five-day inpatient emdr treatment programme for PTSD: pilot study. Eur J Psychotraumatol 2018;9(1):1425575 [FREE Full text] [doi: 10.1080/20008198.2018.1425575] [Medline: 29441152]
49. Van Woudenberg C, Voorendonk EM, Bongaerts H, Zoet HA, Verhagen M, Lee CW, et al. Effectiveness of an intensive treatment programme combining prolonged exposure and eye movement desensitization and reprocessing for severe post-traumatic stress disorder. Eur J Psychotraumatol 2018;9(1):1487225 [FREE Full text] [doi: 10.1080/20008198.2018.1487225] [Medline: 30013726]
50. Jacobs DG, Baldessarini RJ, Conwell Y, Fawcett JA, Horton L, Meltzer H, et al. Practice guideline for the assessment and treatment of patients with suicidal behaviors. Am J Psychiatry 2003 Nov;160(11 Suppl):1-60. [Medline: 14649920]
51. Lewis C, Roberts NP, Gibson S, Bisson JI. Dropout from psychological therapies for post-traumatic stress disorder (PTSD) in adults: systematic review and meta-analysis. Eur J Psychotraumatol 2020;11(1):1709709 [FREE Full text] [doi: 10.1080/20008198.2019.1709709] [Medline: 32284816]
52. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 Apr;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
53. O'Shea K. EMDR friendly preparation methods for adults and children. In: Shapiro R, editor. EMDR Solutions II: For Depression, Eating Disorders, Performance, and More. New York, United States: W. W. Norton & Company; 2009:289-312.
54. Logie RD, Jongh AD. The "flashforward procedure": confronting the catastrophe. J EMDR Prac Res 2014 Jan 01;8(1):25-32. [doi: 10.1891/1933-3196.8.1.25]
55. O'Shea K. The EMDR early trauma protocol. In: Shapiro R, editor. EMDR Solutions II: For Depression, Eating Disorders, Performance, and More. New York, United States: W. W. Norton & Company; 2009:313-334.
56. Matthijssen SJ, Verhoeven LC, van den Hout MA, Heitland I. Auditory and visual memories in PTSD patients targeted with eye movements and counting: the effect of modality-specific loading of working memory. Front Psychol 2017;8:1937 [FREE Full text] [doi: 10.3389/fpsyg.2017.01937] [Medline: 29163311]
57. Knipe J. EMDR Toolbox: Theory and Treatment of Complex PTSD and Dissociation. New York, United States: Springer Publishing Co Inc; 2015.
58. Hofmann A, Hase M, Liebermann P, Ostacoli L, Lehnung M, Ebner F, et al. DeprEnd – EMDR Therapy Protocol for the Treatment of Depressive Disorders. New York, United States: Springer Publishing Co Inc; 2016:290-323.
59. Popky A. DeTUR, an Urge Reduction Protocol for Addictions and Dysfunctional Behaviors. New York, United States: W. W. Norton and Company; 2005:167-188.
60. Mosquera D. Treating personality disorders with EMDR Therapy. Clin Neuropsychiatry 2018;15(3):151-157 [FREE Full text]
61. Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the scale for suicide ideation. J Consult Clin Psychol 1979 Apr;47(2):343-352. [doi: 10.1037//0022-006x.47.2.343] [Medline: 469082]
62. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The columbia-suicide severity rating scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011 Dec;168(12):1266-1277 [FREE Full text] [doi: 10.1176/appi.ajp.2011.10111704] [Medline: 22193671]
63. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The adverse childhood experiences (ACE) study. Am J Prev Med 1998 May;14(4):245-258. [doi: 10.1016/s0749-3797(98)00017-8] [Medline: 9635069]
64. Carlson E, Putnam F. An update on the dissociative experiences scale. Dissociation 1993;6(1):16-27. [doi: 10.1037/t07472-000]
65. Beck AT, Steer RA, Carbin MG. Psychometric properties of the beck depression inventory: twenty-five years of evaluation. Clin Psychol 1988 Jan;8(1):77-100. [doi: 10.1016/0272-7358(88)90050-5]
66. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001 Sep;16(9):606-613 [FREE Full text] [doi: 10.1046/j.1525-1497.2001.016009606.x] [Medline: 11556941]
67. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097. [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
68. Weiss DS, Marmar CR. The impact of event scale-revised. In: Wilson JP, Keane TM, editors. Assessing Psychological Trauma and PTSD: A Practitioner's Handbook. New York: Guilford Press; 1997:399-411.

69. Gratz KL, Roemer L. Multidimensional assessment of emotion regulation and dysregulation: development, factor structure, and initial validation of the difficulties in emotion regulation scale. J Psychopathol Behav Assess 2004 Mar;26(1):41-54. [doi: 10.1023/B:JOBA.0000007455.08539.94]
70. Cox KS, Mouilso ER, Venners MR, Defever ME, Duvivier L, Rauch SA, et al. Reducing suicidal ideation through evidence-based treatment for posttraumatic stress disorder. J Psychiatr Res 2016 Sep;80:59-63. [doi: 10.1016/j.jpsychires.2016.05.011] [Medline: 27295122]
71. Gradus JL, Suvak MK, Wisco BE, Marx BP, Resick PA. Treatment of posttraumatic stress disorder reduces suicidal ideation. Depress Anxiety 2013 Oct;30(10):1046-1053. [doi: 10.1002/da.22117] [Medline: 23636925]

Abbreviations

AIP: Adaptive Information Processing
ANOVA: analysis of variance
BSS: Beck Scale for Suicide Ideation
CSSRS: Columbia Suicide Severity Rating Scale
DES-II: Dissociative Experiences Scale-II
EMDR: Eye Movement Desensitization and Reprocessing
MDD: major depressive disorder
PTSD: posttraumatic stress disorder
RA: research assistant
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SI: suicidal ideation
TAU: treatment as usual
TFT: trauma-focused therapy

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Protocol

An App-Based Intervention for Adolescents Exposed to Cyberbullying in Norway: Protocol for a Randomized Controlled Trial

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Abstract

Background: Adolescents exposed to negative online events are at high risk to develop mental health problems. Little is known about what is effective for treatment in this group. NettOpp is a new mobile app for adolescents who have been exposed to cyberbullying or negative online experiences in Norway.

Objective: The aim of this paper is to provide a description of the content of the intervention and about a randomized controlled trial that will be conducted to examine the effectiveness of NettOpp. This protocol is written in accordance with the Spirit 2013 Checklist.

Methods: An effectiveness study with a follow-up examination after 3 months will be conducted to evaluate the mobile app. Adolescents will be recruited through schools and will be randomly assigned to the intervention (NettOpp) group and a waiting-list control group. The adolescents (aged 11 to 16 years) will respond to self-report questionnaires on the internet. Primary outcomes will be changes in mental health assessed with the Strengths and Difficulties Questionnaire, the WHO-Five Well-being Index, and the Child and Adolescent Trauma Screen.

Results: Recruitment will start in January 2022. The results from this study will be available in 2023.

Conclusions: There are few published evaluation studies on app-based interventions. This project and its publications will contribute new knowledge to the field.

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KEYWORDS

cyberbullying; intervention; mobile app; adolescents; NettOpp; mental health; adolescents; health care

Introduction

Background

The technological revolution has led to most young people being able to now use the internet and mobile phones daily to communicate with others, socialize, entertain themselves, and find information. This development goes hand in hand with many new challenges and possibilities also when it comes to aversive behavior among children and youth. On the one hand, cyberbullying and other negative online experiences affect many children and youth. On the other hand, this technological development opens up for new innovative technologies to help and support young people exposed to such behavior.

Cyberbullying can be defined as an "aggressive, intentional act carried out by a group or individual, *using electronic forms of contact*, repeatedly and over time against a victim who cannot easily defend him or herself" [1]. Electronic forms can be the internet and other digital technologies including mobile phones that are used to, for example, call, write emails, instant, and text messages, chats, blogs, or web posts to say mean things, insult, threaten, or make fun of somebody, to spread rumors, lies, embarrassing information, or pictures [2]. Cyberbullying can take on many different forms, from passively ignoring or excluding somebody from a group to more active actions such as sending or posting cruel or embarrassing messages about someone [2,3].

Cyberbullying prevalence rates among 12-to-18-year-old individuals vary from 5% to 74% with a median of 23%, as reported in a review by Hamm et al [4]. Some of this variation can probably be explained by age group and country differences in the prevalence of cyberbullying. Nonetheless, we believe it is likely that this huge variation is also due to the use of different definitions, perceptions, and interpretation for cyberbullying across studies; that is, does cyberbullying have to occur repeatedly or is one occurrence enough [3-6] and what are the different types of scales used to measure the phenomenon? The annual conducted Norwegian school survey among 10-to-18-year-old students reported a cyberbullying rate of 2% in 2017 with a peak (2.6%) in junior high school [7]. This is the proportion of adolescents who report that they have been cyberbullied 2-3 times a month or more. The proportion increases to 10% if adolescents who have experienced one negative online event are included.

The consequences of bullying victimization in adolescence are serious. Meta-analyses have found that bullying, both traditionally and on the internet, is related to mental health problems such as depression, anxiety, and poor general health [8,9]. Furthermore, there is an association between bullying victimization and psychosomatic health complaints such as stomach ache, sleeping difficulties, and headache and social functioning including social isolation, loneliness, and low self-esteem [2,8,10].

Given the seriousness of bullying or cyberbullying victimization, interventions that aim at preventing cyberbullying and helping and supporting those exposed to cyberbullying are important. A recently published meta-analysis found that intervention and prevention programs for cyberbullying can reduce cyberbullying victimization [11]. Furthermore, some traditional antibullying programs have also proven to have an effect on cyberbullying [12,13].

A review found that there are more preventive antibullying programs compared to interventions for adolescents who have been exposed to cyberbullying [10]. However, such studies suggest that cognitive measures appear to be effective [10]. A systematic review of digital bullying from the Norwegian Institute of Public Health did not identify any available interventions in Norway, except for 2 anticyberbullying campaigns [14]. Those campaigns were neither theoretically grounded nor evaluated. The report encourages using technology and being innovative when developing measures to prevent cyberbullying [14] as adolescents spend a lot of their time on the internet and with their mobile phones [15]. Furthermore, many adolescents find it difficult to tell their parents or other adults about their experiences of being bullied or cyberbullied [16,17]. Therefore, a mobile app may be a useful resource as they are always accessible, easy to use, and they offer anonymity.

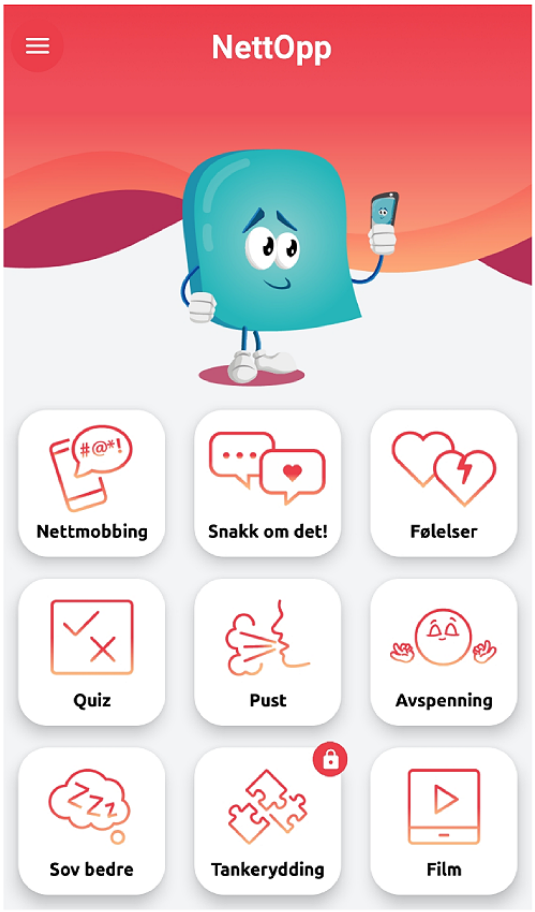
Several health-promoting apps aimed at youth have been developed. Many of them aim to promote health by monitoring or motivating the user to adopt healthier diets or increase their physical activity [18]. Other apps are more supportive in which the purpose is to learn how to cope with, for example, chronic diseases such as diabetes, asthma, or cancer [19]. Overall, two reviews concluded that apps may have the potential to be feasible health interventions for young people, but that more studies are needed to assess their effectiveness [19,20]. In addition to this, Shieh (2016) has found 9 anticyberbullying apps with different focus [21]. However, none of these apps have been empirically evaluated or adapted to Norwegian conditions, indicating the need for the development and evaluation of an app against cyberbullying in Norway.

The Cyberbullying Coping Intervention

NettOpp is a mobile app for adolescents who have been exposed to cyberbullying or other negative online experiences in Norway (Figure 1). NettOpp directly translated means "exactly" in English but "Nett" refers also to the internet and "Opp" comes from "Opplysning," which means information or enlightenment. The target group of the cyberbullying coping intervention was adolescents in elementary school and junior high school, between 11 to 16 years of age. According to Jacobs et al [22] (2014), a cyberbullying coping intervention should do more than just increase awareness about internet threats. Ideally, an intervention should reduce the risks for getting victimized, combat cyberbullying once it occurred, and buffer the negative impact of the event [23].

The primary aim of this intervention is (1) to reduce mental health problems related to cyberbullying; the secondary aims are to (2) increase adolescents coping skills with cyberbullying, (3) increase knowledge about cyberbullying, (4) increase the help-seeking behavior of the adolescents, (5) increase their self-esteem, (6) increase their sleeping quality, and finally, (7) reduce cyberbullying. Below a description of why it is important to focus on the aforementioned aims.

Figure 1. NettOpp start page.



A previously conducted user survey (N=15) showed that most users found NettOpp easy to use, appealing, and would recommend the mobile app to a friend. A total of 14 out of 15 adolescents agreed that NettOpp would probably increase knowledge about cyberbullying and 5 out of 15 believed that NettOpp would reduce cyberbullying [24].

Reduce Mental Health Problems

Adolescents exposed to cyberbullying are at high risk for developing mental health problems. The intensity and duration of the cyberbullying may determine how serious the consequences are [25]. Giving the adolescents advice on how to cope with cyberbullying might have a buffering impact and can reduce mental health problems. A study found that, for example, help-seeking behavior buffered the negative impact of cyber victimization on depressive symptoms [26] and internalizing problems [27]. In addition, learning how to deal with a cyberbullying event may shorten the cyberbullying episode and thereby prevent serious consequences that could affect the health of the adolescents.

Increase Adolescents' Coping Skills With Cyberbullying

How an adolescent copes with a cyberbullying event can determine whether he/she experiences long-term consequences [22]. A study found that among the most helpful coping strategies to stop cyberbullying were technical strategies (eg, blocking or deleting the person or profile), help-seeking behavior, and behavioral avoidance (eg, stopping visiting the webpages where the event happened) [28].

Furthermore, cyberbullying is emotionally distressing and young people exposed to it can feel upset, hurt, embarrassed, helpless, isolated, and scared for their safety [29]. Teaching adolescents about normal emotional reactions to a cyberbullying event and how to cope with the feelings could be emotionally helpful. Healthy coping strategies (eg, help-seeking and talking about the problem or using relaxation techniques, listening to music, or thinking positive thoughts) could replace unhealthy coping strategies (eg, social withdrawal, self-harm, aggression, or skipping school), and buffer the negative impact of the cyberbullying event [23]. A study found that among the most emotionally helpful coping strategies for cyberbullying victims were support-seeking, technical strategies, behavioral avoidance, and reframing the situation (eg, "whoever is doing this to me is not worth my time") [28].

Increase Knowledge About Cyberbullying

Increasing knowledge about what cyberbullying is, what consequences are associated with it, rights and laws, security advice, and what can be done in the case of a cyberbullying event is an important part of the psychoeducation adolescents should receive [25,30]. It will increase awareness of the problem, its seriousness, and help the adolescent to act safer on the internet and thus reduce the risk of being victimized in the future. Providing information on how to deal with an event

might help the adolescent to combat cyberbullying once it occurred.

Increase Help-Seeking Behavior Among Adolescents

Some studies that examined help-seeking behavior among individuals exposed to traditional bullying have found that telling an adult made things worse for some adolescents [27,31,32]. Regarding cyberbullying, Price and Dalgleish [33] found that the majority (approximately 60%-70%) of adolescents who sought help found this helpful to some degree. For the remaining individuals, help-seeking did not change the situation. Price and Dalgleish [33] concluded, "a critical response to effectively addressing cyberbullying relies on both increasing the help-seeking behaviour of victimized young people and improving the efficacy of those they speak to." Seeking support was also found to be emotionally helpful for the majority of victims of cyberbullying and helped to stop cyberbullying for some adolescents in another study [28]. However, some adolescents do not have a trusted adult around, or they are too ashamed or afraid to tell somebody they know and may prefer to contact someone anonymously [23]. Encouraging adolescents to seek help, provide information about whom to contact (eg, also about online resources and helplines), how to seek help, and what should happen when adolescents have sought help at school are important [22].

Increase the Self-esteem of the Adolescents

Low self-esteem in adolescence has been found to predict negative consequences such as poor physical and mental health during adulthood [34]. Studies have found a negative relationship between cyberbullying victimization and self-esteem [35-37]. Interventions that aim to increase self-esteem are therefore important. Most of the studies that aim at increasing self-esteem use physical exercise as the intervention [38].

Increase the Sleeping Quality

Insufficient sleep among adolescents is related to physiological and mental health risks such as cardiometabolic dysfunction, poor academic performance, or mood disturbances such as increased suicidal ideation [39], and it was found to be a precursor to depression [40]. A meta-analysis found that peer victimization like bullying among children and adolescents was related to sleeping problems [41]. Healthy lifestyles including longer sleep duration, on the other hand, was associated with less suicidal ideation among individuals exposed to cyberbullying [42]. In general, a review and meta-analysis found that cognitive-behavioral sleep interventions for adolescents are effective in improving sleeping quality [43].

Reduce Cyberbullying

Cyberbullying rates can be reduced by increasing the knowledge and skills about how to handle cyberbullying [25]. The knowledge adolescents will acquire about what cyberbullying is, what consequences are associated with it, and rights and laws may lead to increased awareness of the problem. By teaching the adolescents how to reduce risks of being victimized and how to better cope with a cyberbullying event might help to stop cyberbullying and prevent new occurrences and thus reduce cyberbullying rates.

The Mobile App

The app will consist of 2 modules. Module 1 will be psychoeducational including information about cyberbullying, its consequences, rights and laws, practical and technical advice about how to cope with a cyberbullying event (eg, blocking or deleting a person). This will hopefully increase adolescents' knowledge about cyberbullying. The app will also provide tips about what the adolescents can do to reduce new occurrences of cyberbullying events (eg, "Don't add 'Friends' that you don't know who is," "Be critical of which images you share with others," and "Check your privacy settings on social media"). In addition, the adolescents will learn about normal emotional reactions when exposed to cyberbullying (eg, fear, helplessness, shame, and sadness) and how to cope with them. This will contribute to increased coping skills with cyberbullying. Further, the psychoeducational information focuses on motivating adolescents to seek help from a trusted adult. Adolescents are advised to contact a trusted adult who they think can help in case of cyberbullying or a negative online experience. The app further informs about how one can talk about difficult things to someone else and about what should happen once the adolescent has told an adult. In addition, there is information about available professional online resources including chats and helplines the adolescents can contact in case they do not know with whom to talk or prefer to stay anonymous. This might increase help-seeking behavior among adolescents.

Module 2 will be a resource module that provides exercises and techniques on how to cope with emotional distress related to cyberbullying. These exercises include relaxation techniques (breathing and guided meditation exercises) that aim at increasing the adolescents' coping skills with the cyberbullying event. The exercises also include sleep hygiene–related advice and exercises to increase the sleep quality of adolescents that have, for example, difficulties to fall asleep because of worries. The adolescents will be encouraged to create a bedroom where they feel safe, enjoy themselves, and relax. They will also be encouraged to relate to their concerns and quarry thoughts during daytime.

The app also includes an exercise based on cognitive behavioral therapy, which aims at helping the adolescents to reframe the situation [44]. The aim is to make the adolescents aware of the connection between thoughts and feelings, and at increasing awareness about negative thoughts the adolescents might have because of the cyberbullying event and replacing these thoughts with alternative thoughts. The adolescents will be guided through this exercise by giving them the opportunity to choose between different statements. First, they can choose a statement that fits best to their situation (eg, "Someone has posted a picture or video of me that I don't like"). Then, they can identify the negative thoughts (eg, "I'm thick/ugly/stupid" and "Everyone is going to think I look stupid") and rate how strongly they believe in this thought on a scale from 0 to 10. In a third step, they can identify the negative feelings they are experiencing (eg, "I feel sad and tired" and "I'm ashamed") and rate how strongly they experience this feeling on a scale from 0 to 10. Thereafter, they will be shown a list of alternative thoughts. They will be instructed to pick out alternative thoughts or advice on what they could do, what they can say to themselves, and

what they would have said to a friend who was in a similar situation. They can select up to 3 statements (eg, "It's not my fault that I'm being exposed to this," "I can ask for help [e.g., from parents, teachers, health nurses]," and "There are many people that like and care about me"). In a last step, the adolescents can rate how strong the original, negative thought and the feelings are and rate once more if they feel better, the same, or worse. The overall aim of this and the other exercises is to increase coping skills with a cyberbullying event and thus to prevent the development of mental health problems.

Furthermore, every second day, the adolescents will receive a push-message in the app, which will either say something nice (eg, "Do something nice for yourself") or motivate the adolescents to do an exercise (eg, "Relax and do a breathing exercise").

Information will be displayed in the app through text, sound recordings, and short movies, to keep the adolescents engaged with the app. In addition, rights and laws associated with cyberbullying will be communicated to the adolescents through quizzes.

User Involvement

The users, in our case Norwegian elementary and junior high school students, have been involved in the project from the development of the intervention to its evaluation. The app was developed in collaboration with the users in terms of what the intervention should contain, but also in terms of functionality and format of the app. The 8 adolescents in the user group were involved through workshops. A larger reference group consisted of teachers, school health nurses, nurses from the health care station for adolescents, community psychologists, and the local antibullying professional.

The aim of the current paper is to provide a description of the content of the intervention and the randomized controlled trial that will be conducted to examine the effectiveness of NettOpp.

Methods

Eligibility Criteria and Setting of the Effectiveness Study

Adolescents from the 6th to 10th grade (11-16 years old) are eligible for participation in the effectiveness study. Adolescents will be recruited through schools in Norway. To recruit enough participants, the schools need to be big enough; that is, they should have at least 20 students in each class.

Inclusion and Exclusion Criteria

Adolescents between the ages of 11 and 16 years, whose guardians have given consent and who agree to take part in the study, will be included. To use the app, adolescents need a smartphone and be able to read and understand Norwegian. Furthermore, android users must provide a Gmail address, and iPhone users must first download the free app TestFlight to be able to download a test version of NettOpp. Adolescents who may not benefit from an app-based intervention because of, for example, severe developmental or cognitive challenges will be excluded from the study.

Intervention

NettOpp is a self-help tool that aims at supporting adolescents who have been exposed to cyberbullying or a negative online event. Adolescents can install the app on their mobile phone and use it as much as they want and whenever they want. The intervention focuses on psychoeducation, on motivating the adolescents to seek help from a trusted adult, and on strategies to better cope with stress related to cyberbullying or negative online experiences.

Control

The waiting-list control group will receive access to the app after study completion; that is, when the follow-up assessment is conducted after approximately 3 months.

Randomization

The effectiveness study will be conducted as a randomized controlled trial with an intervention group and a waiting-list control group. Randomization will be conducted after baseline measures have been collected at the school level by a statistician. A random number between 0 and 1 will be generated using SPSS and assigned to each school. Half of the schools with the highest value on the random variable will be assigned to the intervention group and half of the schools with the lowest value will be assigned to the waiting-list control group.

Blinding

Adolescents are randomized to the intervention or waiting-list control group and are blinded to the allocation prior to the baseline assessment, and their schools will also not receive information about their allocation. The information letters include information about study content and purpose, but guardians and students were both blinded to the allocation to the intervention or waiting-list control group prior to offering their consent or before the baseline assessment.

Outcomes

Data will be collected at baseline (T_1, preintervention) and after approximately 2 weeks of the intervention (T_2, postintervention) through self-report measures that the adolescents fill in using Nettskjema, a secure online tool to conduct surveys [45]. A follow-up evaluation (T_3) will be conducted after approximately 3 months to examine if the effects were stable over time.

Primary Outcomes

Mental health will be assessed with the Strengths and Difficulties Questionnaire (SDQ) [46], the WHO-Five Well-being Index (WHO-5) [47], and the Child and Adolescent Trauma Screen (CATS) [48]. The null hypothesis of this study is that there will not be significant differences in changes in mental health scores between the waiting-list control and the intervention group.

Secondary Outcomes

How the adolescents cope with cyberbullying will be measured with the Cyberbullying Coping Questionnaire [49]. Help-seeking behavior will be assessed with 3 questions; for example, "Have you told someone about your experiences so they can help you?" Health problems will be assessed using 7 items asking the

respondent how often he/she has, for example, experienced headaches. Self-esteem will be measured with the Norwegian Version of the Self-liking and Competence Scale [50,51]. Sleeping quality will be measured with 6 questions (eg, "At what time do you usually go to bed?") from the Bergen Child Study [52]. Cyberbullying and bullying experiences will be assessed using 4 questions based on the Olweus questionnaire [5].

Power Calculations

Power calculations were conducted using the software PASS 16 [53]. Using multilevel analysis, it will require a total sample of 400 participants (200 in each group: 20 schools with 20 students per group) to detect an effect size of at least Cohen *d*=0.30, when the expected interclass correlation at school level is 0.01, with a power of 0.79, and a significance level of .05.

Data Management

Data collection, data cleaning, and statistical analyses will be performed by members of the research team. The statistical analyses will be conducted on anonymized data and only members of the research team will have access to the data. Data will be stored on a secure server.

Planned Statistical Analysis

A linear mixed model will be used for analyzing the outcomes in the effectiveness study. Missing data will be handled using multiple imputation.

Ethics Approval and Consent to Participate

The effectiveness study is approved by the regional Research Ethics Committee (reference number 161212). The studies are approved by the Norwegian Centre for Research Data (NSD) (reference number 545417). Since the study participants are between 11 to 16 years old, study participation requires consent from an authorized guardian. The consent form and information letter to the guardians and study participants are approved by the regional Research Ethics Committee and by the NSD. Changes to the project, which may impact study participants will be reported to the regional Research Ethics Committee and to the NSD.

Results

The study has been approved by the regional Research Ethics Committee and by the NSD. The mobile app NettOpp has been developed, and enrollment for the study will begin in January 2022. The results of the study will be published in 2023.

Discussion

Expected Outcomes

Adolescents who have been exposed to cyberbullying are vulnerable to mental health problems and other harmful effects of the stressful events. In addition to the negative effects that cyberbullying can have for those who have been exposed to it, there may be a considerable financial burden to the society, which is associated with the consequences of mental health problems in adolescence and over the lifespan [8,54,55]. The threshold for telling and seeking help from a trusted adult might be too high and as such, there is a need for a low-threshold intervention against cyberbullying for adolescents.

NettOpp is a mobile app for adolescents who have been exposed to cyberbullying or a negative online experience in Norway. Its evaluation will contribute unique knowledge to the field as there are very few interventions targeting adolescents who have been exposed to cyberbullying. The aim of this paper is to provide a description of the content of the intervention and about its evaluation. The results of the evaluation will be presented in other studies. If the intervention is found to be effective, it will be free of charge and available to all adolescents in Norway.

Challenges

The intervention and its evaluation have several limitations. First, the intervention may be too comprehensive, aim at too many areas (ie, knowledge, coping, self-esteem, sleep, mental health, and reduce cyberbullying rates), and may partly contain too much information. In particular, the exercise where the adolescent learns about unhelpful or inappropriate thoughts and reframing the situation is long and is based on written information. This might not be appealing to adolescents and that they will therefore not use it. However, it is difficult to redesign this exercise to make it more attractive. Furthermore, we find that the exercise is too important to exclude it from the intervention. The questionnaire to evaluate the intervention is long and may lead to dropping out, response fatigue, or saying no or yes [22]. However, it is necessary to assess these measures to evaluate the effectiveness of the intervention. Both working with the intervention and filling in the questionnaire can be potentially distressing for the adolescents as they are confronted with the seriousness of the cyberbullying event and their thoughts, feelings, and consequences of the event. Therefore, we inform the adolescents about possible contact persons such as school nurses and provide a number to a helpline in the information letter and in the online questionnaire. However, in general, we expect the benefits of the intervention to exceed its disadvantages.

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Authors' Contributions

All authors provided substantial contributions to the intervention and the study protocol. SK wrote the first draft of the manuscript. HK is the principal investigator of the study. MM, FA, KB, and HK read, edited, and approved the final manuscript.

Conflicts of Interest

None declared.

References

1. Smith PK, Mahdavi J, Carvalho M, Fisher S, Russell S, Tippett N. Cyberbullying: its nature and impact in secondary school pupils. J Child Psychol Psychiatry 2008 Apr;49(4):376-385. [doi: 10.1111/j.1469-7610.2007.01846.x] [Medline: 18363945]
2. Kowalski RM, Giumetti GW, Schroeder AN, Lattanner MR. Bullying in the digital age: a critical review and meta-analysis of cyberbullying research among youth. Psychol Bull 2014 Jul;140(4):1073-1137. [doi: 10.1037/a0035618] [Medline: 24512111]
3. Smith PK. The nature of cyberbullying and what we can do about it. J Res Spec Educ Needs 2015 Jul 14;15(3):176-184. [doi: 10.1111/1471-3802.12114]
4. Hamm MP, Newton AS, Chisholm A, Shulhan J, Milne A, Sundar P, et al. Prevalence and Effect of Cyberbullying on Children and Young People: A Scoping Review of Social Media Studies. JAMA Pediatr 2015 Aug;169(8):770-777. [doi: 10.1001/jamapediatrics.2015.0944] [Medline: 26098362]
5. Olweus D. Bullying at School: What We Know and What We Can Do. Hoboken, NJ: Wiley; 1993:1-152.
6. Hellevik P, Øverlien C. Digital mobbing blant barn og ungdom i Norge – En kunnskapsoversikt 2013. Oslo: Nasjonalt kunnskapssenter om vold og traumatisk stress. 2013. URL: https://www.nkvts.no/rapport/digital-mobbing-blant-barn-og-ungdom-i-norge-en-kunnskapsoversikt-2013/ [accessed 2021-10-15]
7. Wendelborg C. Mobbing og arbeidsro i skolen Analyse av Elevundersøkelsen skoleåret 2017/18. Trondheim: NTNU Samfunnsforskning AS; 2018:1-34.
8. Moore SE, Norman RE, Suetani S, Thomas HJ, Sly PD, Scott JG. Consequences of bullying victimization in childhood and adolescence: A systematic review and meta-analysis. World J Psychiatry 2017 Mar 22;7(1):60-76 [FREE Full text] [doi: 10.5498/wjp.v7.i1.60] [Medline: 28401049]
9. Gini G, Card NA, Pozzoli T. A meta-analysis of the differential relations of traditional and cyber-victimization with internalizing problems. Aggress Behav 2018 Mar;44(2):185-198. [doi: 10.1002/ab.21742] [Medline: 29160943]
10. Breivik K, Bru E, Hancock C, Idsøe E, Idsøe T, Solberg M. Å bli utsatt for mobbing – en kunnskapsoppsummering om konsekvenser og tiltak. 2017. URL: https://www.udir.no/tall-og-forskning/finn-forskning/rapporter/a-bli-utsatt-for-mobbing--en-kunnskapsoppsummering-om-konsekvenser-og-tiltak/ [accessed 2021-10-15]
11. Gaffney H, Farrington DP, Espelage DL, Ttofi MM. Are cyberbullying intervention and prevention programs effective? A systematic and meta-analytical review. Aggress Violent Behav 2019 Mar;45:134-153. [doi: 10.1016/j.avb.2018.07.002]
12. Olweus D, Limber SP, Breivik K. Addressing Specific Forms of Bullying: A Large-Scale Evaluation of the Olweus Bullying Prevention Program. Int J Bullying Prev 2019 Mar 11;1(1):70-84. [doi: 10.1007/s42380-019-00009-7]
13. Williford A, Elledge LC, Boulton AJ, DePaolis KJ, Little TD, Salmivalli C. Effects of the KiVa antibullying program on cyberbullying and cybervictimization frequency among Finnish youth. J Clin Child Adolesc Psychol 2013;42(6):820-833. [doi: 10.1080/15374416.2013.787623] [Medline: 23659182]
14. Ulriksen R, Knapstad M. Digital mobbing-Kunnskapsoversikt over forskning på effekter av tiltak. Norwegian Institute of Public Health, Norway. 2016. URL: https://www.fhi.no/publ/2016/digital-mobbing.-kunnskapsoversikt-over-forskning-pa-effekter-av-tiltak/ [accessed 2021-10-15]
15. Norwegian MA. Barn & medier 2016 - 9-16 åringer bruk og opplevelser av medier. URL: https://docplayer.me/19307521-Barn-medier-2016-9-16-aringers-bruk-og-opplevelser-av-medier.html [accessed 2021-10-15]
16. Dooley JJ, Gradinger P, Strohmeier D, Cross D, Spiel C. Cyber-Victimisation: The Association Between Help-Seeking Behaviours and Self-Reported Emotional Symptoms in Australia and Austria. J Psychol Couns Sch 2012 Feb 23;20(2):194-209. [doi: 10.1375/ajgc.20.2.194]
17. Scott E, Dale J, Russell R, Wolke D. Young people who are being bullied - do they want general practice support? BMC Fam Pract 2016 Aug 22;17(1):116 [FREE Full text] [doi: 10.1186/s12875-016-0517-9] [Medline: 27550153]
18. Schoffman DE, Turner-McGrievy G, Jones SJ, Wilcox S. Mobile apps for pediatric obesity prevention and treatment, healthy eating, and physical activity promotion: just fun and games? Transl Behav Med 2013 Sep;3(3):320-325 [FREE Full text] [doi: 10.1007/s13142-013-0206-3] [Medline: 24073184]
19. Majeed-Ariss R, Baildam E, Campbell M, Chieng A, Fallon D, Hall A, et al. Apps and Adolescents: A Systematic Review of Adolescents' Use of Mobile Phone and Tablet Apps That Support Personal Management of Their Chronic or Long-Term Physical Conditions. J Med Internet Res 2015 Dec 23;17(12):e287 [FREE Full text] [doi: 10.2196/jmir.5043] [Medline: 26701961]
20. Punukollu M, Marques M. Use of mobile apps and technologies in child and adolescent mental health: a systematic review. Evid Based Ment Health 2019 Nov;22(4):161-166. [doi: 10.1136/ebmental-2019-300093] [Medline: 31358537]

21. Shieh B. CyberPAL: a mobile resource for cyberbullying. Pepperdine University. 2016. URL: https://digitalcommons.pepperdine.edu/cgi/viewcontent.cgi?article=1621&context=etd [accessed 2021-10-15]
22. Jacobs NC, Völlink T, Dehue F, Lechner L. Online Pestkoppenstoppen: systematic and theory-based development of a web-based tailored intervention for adolescent cyberbully victims to combat and prevent cyberbullying. BMC Public Health 2014 Apr 24;14:396 [FREE Full text] [doi: 10.1186/1471-2458-14-396] [Medline: 24758264]
23. Perren S, Corcoran L, Cowie H, Dehue F, Garcia D, Mc Guckin C, et al. Tackling Cyberbullying: Review of Empirical Evidence Regarding Successful Responses by Students, Parents, and Schools. Int J Confl Violence 2012;6(2):283-292 [FREE Full text]
24. Kaiser S, Martinussen M, Breivik K, Adolfsen F, Kyrrestad H. En brukerundersøkelse av mobilappenNettOpp. In: A user survey of the mobile appNettOpp. 2020 Dec 02 Presented at: Barn og Unge Kongressen; December 2, 2020; Bergen p. 1.
25. Wölfer R, Schultze-Krumbholz A, Zagorscak P, Jäkel A, Göbel K, Scheithauer H. Prevention 2.0: targeting cyberbullying @ school. Prev Sci 2014 Dec;15(6):879-887. [doi: 10.1007/s11121-013-0438-y] [Medline: 24122481]
26. Machmutow K, Perren S, Sticca F, Alsaker FD. Peer victimisation and depressive symptoms: can specific coping strategies buffer the negative impact of cybervictimisation? Emotional and Behavioural Difficulties 2012 Sep;17(3-4):403-420. [doi: 10.1080/13632752.2012.704310]
27. Shaw T, Campbell MA, Eastham J, Runions KC, Salmivalli C, Cross D. Telling an Adult at School about Bullying: Subsequent Victimization and Internalizing Problems. J Child Fam Stud 2019 Jul 19;28(9):2594-2605. [doi: 10.1007/s10826-019-01507-4]
28. Machackova H, Cerna A, Sevcikova A, Dedkova L, Daneback K. Effectiveness of coping strategies for victims of cyberbullying. Cyberpsychology 2013 Dec 01;7(3). [doi: 10.5817/cp2013-3-5]
29. Nixon C. Current perspectives: the impact of cyberbullying on adolescent health. Adolesc Health Med Ther 2014;5:143-158 [FREE Full text] [doi: 10.2147/AHMT.S36456] [Medline: 25177157]
30. Camelford KG, Ebrahim C. The Cyberbullying Virus: A Psychoeducational Intervention to Define and Discuss Cyberbullying Among High School Females. J Creat Ment Health 2016 Dec 09;11(3-4):458-468. [doi: 10.1080/15401383.2016.1183545]
31. Mendez JJ, Bauman S, Sulkowski ML, Davis S, Nixon C. Racially-focused peer victimization: Prevalence, psychosocial impacts, and the influence of coping strategies. Psychol Violence 2016;6(1):103-111. [doi: 10.1037/a0038161]
32. Smith PK, Shu S. What Good Schools can Do About Bullying. Childhood 2016 Jul 24;7(2):193-212. [doi: 10.1177/0907568200007002005]
33. Price M, Dalgleish J. Cyberbullying-Experiences, impacts and coping strategies as described by Australian young people. Youth Stud Aust 2010;29(2):51-59.
34. Trzesniewski KH, Donnellan MB, Moffitt TE, Robins RW, Poulton R, Caspi A. Low self-esteem during adolescence predicts poor health, criminal behavior, and limited economic prospects during adulthood. Dev Psychol 2006 Mar;42(2):381-390. [doi: 10.1037/0012-1649.42.2.381] [Medline: 16569175]
35. Brewer G, Kerslake J. Cyberbullying, self-esteem, empathy and loneliness. Comput Hum Behav 2015 Jul;48:255-260. [doi: 10.1016/j.chb.2015.01.073]
36. Cénat JM, Hébert M, Blais M, Lavoie F, Guerrier M, Derivois D. Cyberbullying, psychological distress and self-esteem among youth in Quebec schools. J Affect Disord 2014 Dec;169:7-9 [FREE Full text] [doi: 10.1016/j.jad.2014.07.019] [Medline: 25128859]
37. Patchin J, Hinduja S. Cyberbullying and self-esteem. J Sch Health 2010 Dec;80(12):614-21; quiz 622-4. [doi: 10.1111/j.1746-1561.2010.00548.x] [Medline: 21087257]
38. Liu M, Wu L, Ming Q. How Does Physical Activity Intervention Improve Self-Esteem and Self-Concept in Children and Adolescents? Evidence from a Meta-Analysis. PLoS One 2015;10(8):e0134804 [FREE Full text] [doi: 10.1371/journal.pone.0134804] [Medline: 26241879]
39. Owens JA, Weiss MR. Insufficient sleep in adolescents: causes and consequences. Minerva Pediatr 2017 Aug;69(4):326-336. [doi: 10.23736/S0026-4946.17.04914-3] [Medline: 28211649]
40. Lovato N, Gradisar M. A meta-analysis and model of the relationship between sleep and depression in adolescents: recommendations for future research and clinical practice. Sleep Med Rev 2014 Dec;18(6):521-529. [doi: 10.1016/j.smrv.2014.03.006] [Medline: 24857255]
41. van Geel M, Goemans A, Vedder PH. The relation between peer victimization and sleeping problems: A meta-analysis. Sleep Med Rev 2016 Jun;27:89-95. [doi: 10.1016/j.smrv.2015.05.004] [Medline: 26140869]
42. Rodelli M, De Bourdeaudhuij I, Dumon E, Portzky G, DeSmet A. Which healthy lifestyle factors are associated with a lower risk of suicidal ideation among adolescents faced with cyberbullying? Prev Med 2018 Aug;113:32-40. [doi: 10.1016/j.ypmed.2018.05.002] [Medline: 29729287]
43. Blake MJ, Sheeber LB, Youssef GJ, Raniti MB, Allen NB. Systematic Review and Meta-analysis of Adolescent Cognitive-Behavioral Sleep Interventions. Clin Child Fam Psychol Rev 2017 Sep;20(3):227-249. [doi: 10.1007/s10567-017-0234-5] [Medline: 28331991]
44. Ariso J, Reyero D. Reconsidering the Scenario of Cyberbullying: Promoting the Internalization of the Locus of Control in Adolescents through Cognitive Restructuring. APS 2014 Jul 31;4(2):98-103. [doi: 10.2174/22106766046661404251120 47]
45. Nettskjema. Universitetet i Oslo. URL: https://www.uio.no/tjenester/it/adm-app/nettskjema/ [accessed 2021-10-15]

46. Goodman R. The Strengths and Difficulties Questionnaire: a research note. J Child Psychol Psychiatry 1997 Jul;38(5):581-586. [doi: 10.1111/j.1469-7610.1997.tb01545.x] [Medline: 9255702]
47. WHO. Wellbeing Measures in Primary Health Care/The Depcare Project. World Health Organization Regional Office for Europe. 1998. URL: https://www.euro.who.int/__data/assets/pdf_file/0016/130750/E60246.pdf [accessed 2021-10-15]
48. Sachser C, Berliner L, Holt T, Jensen TK, Jungbluth N, Risch E, et al. International development and psychometric properties of the Child and Adolescent Trauma Screen (CATS). J Affect Disord 2017 Mar 01;210:189-195. [doi: 10.1016/j.jad.2016.12.040] [Medline: 28049104]
49. Jacobs N, Völlink T, Dehue F, Lechner L. The Development of a Self-Report Questionnaire on Coping with Cyberbullying: The Cyberbullying Coping Questionnaire. Societies 2015 May 18;5(2):460-491. [doi: 10.3390/soc5020460]
50. Silvera DH, Neilands T, Perry JA. A Norwegian translation of the self-liking and competence scale. Scand J Psychol 2001 Dec;42(5):417-427. [doi: 10.1111/1467-9450.00254] [Medline: 11771811]
51. Tafarodi R, Swann W. Two-dimensional self-esteem: theory and measurement. Pers Individ Dif 2001 Oct;31(5):653-673. [doi: 10.1016/s0191-8869(00)00169-0]
52. Hysing M, Harvey A, Stormark K, Pallesen S, Sivertsen B. Precursors of delayed sleep phase in adolescence: a population-based longitudinal study. Sleep 2018 Nov 01;41(11):1-7. [doi: 10.1093/sleep/zsy163] [Medline: 30203021]
53. NCSS. PASS 16 Power Analysis and Sample Size Software. URL: https://www.ncss.com/software/pass/ [accessed 2021-10-15]
54. Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. Dialogues Clin Neurosci 2015 Sep;17(3):327-335 [FREE Full text] [Medline: 26487813]
55. Bodden D, Stikkelbroek Y, Dirksen C. Societal burden of adolescent depression, an overview and cost-of-illness study. J Affect Disord 2018 Dec 01;241:256-262. [doi: 10.1016/j.jad.2018.06.015] [Medline: 30138810]

Abbreviations

CATS: Child and Adolescent Trauma Screen
NSD: Norwegian Centre for Research Data
SDQ: Strengths and Difficulties Questionnaire
UiT: The Arctic University of Norway
WHO-5: WHO-Five Well-being Index

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Protocol

An In Situ, Child-Led Intervention to Promote Emotion Regulation Competence in Middle Childhood: Protocol for an Exploratory Randomized Controlled Trial

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Abstract

Background: Emotion regulation is a key transdiagnostic risk factor for a range of psychopathologies, making it a prime target for both prevention and treatment interventions in childhood. Existing interventions predominantly rely on workshops or in-person therapy-based approaches, limiting the ability to promote emotion regulation competence for children in everyday settings and at scale. Purrble is a newly developed, inexpensive, socially assistive robot—in the form of an interactive plush toy—that uses haptic feedback to support in-the-moment emotion regulation. It is accessible to children as needed in their daily lives, without the need for a priori training. Although qualitative data from previous studies show high engagement in situ and anecdotal evidence of the robot being incorporated into children's emotion regulation routines, there is no quantitative evidence of the intervention's impact on child outcomes.

Objective: The aim of this study is to examine the efficacy of a new intervention model for child-led emotion regulation—Purrble—that can be deployed across prevention and treatment contexts.

Methods: Overall, 134 children aged 8 to 10 years will be selected from an *enriched* nonclinical North American population; for inclusion, the cutoff for the parents' rating of child dysregulation will be ≥10 points in the total difficulties score on the Strengths and Difficulties Questionnaire. This cutoff was selected to obtain a measurable, but not necessarily clinical, level of the child's emotion regulatory difficulties. The selected families will be randomly assigned with .5 probability to receive either a Purrble or an active control (noninteractive plush toy). The primary outcome will be a daily ecological momentary assessment measure of child emotion regulation capability (as reported by parents) over a period of 4 weeks. Exploratory analyses will investigate the intervention impact on secondary outcomes of child emotion regulation, collected weekly over the same 4-week period, with follow-ups at 1 month and 6 months postdeployment. Quantitative data will be analyzed on an intent-to-treat basis. A proportion of families (approximately 30% of the sample) will be interviewed after deployment as part of the process analysis.

Results: The study is funded by the UKRI Future Leaders Fellowship (MR/T041897/1) and an in-kind contribution from the Committee for Children. This study received ethical approval from the Pearl institutional review board (#18-CFC-101). Participant recruitment started in February 2021, with the 1-month deployment in April-May 2021. The results of this analysis will be published in 2022.

Conclusions: This study will be the first quantitative evaluation of the efficacy of an innovative, proof-of-concept intervention model for an in situ, child-led emotion regulation intervention. Insights into the trajectory of daily changes, complemented with weekly questionnaire batteries and postdeployment interviews, will result in an in-depth understanding of whether and how the hypothesized intervention logic model works, leading to further intervention optimization.

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International Registered Report Identifier (IRRID): PRR1-10.2196/28914

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KEYWORDS

randomized controlled trial; children; emotion regulation; in situ intervention; intervention; emotion; protocol; exploratory; efficacy; model; prevention; treatment; risk factor

Introduction

Maladaptive emotion regulation in childhood is associated with an increased incidence of both internalizing and externalizing mental health disorders [1-4]. In contrast, adaptive emotion regulation in childhood is associated with better mental [5-7] and physical health [8-10]. For these reasons, emotion regulation in childhood is a crucial target for treatment and prevention programs to reduce the societal and personal burden of mental health disorders [11,12].

Although emotion regulation (ER) skills are malleable, and a range of predominantly adult-focused interventions have started to appear in clinical settings (eg, Emotion Regulation Therapy [13] and the Unified Protocol for Transdiagnostic Treatment of Emotional Disorders [14,15]), existing work shows that children's ER skills are difficult to shape and maintain without detailed guidance and support [16-18]. This work has also shown that parenting strategies play a key role in shaping and maintaining children's patterns of ER [19-27], but requiring parents' involvement in existing training, such as in-person workshops, represents yet another barrier to treatment because of well-known issues with access, reach, and cost of parent training programs.

However, the field lacks evidence-based intervention mechanisms to deliver cost-effective ER interventions for children directly in situ, relying instead on extensive in-person workshops (prevention context) or clinical sessions for children and parents (treatment context). Existing approaches thus lead to high costs that disproportionately disadvantage underprivileged families, who would likely benefit most; such families face access- and time-based challenges to take part in available intervention programs [28], although children from low socioeconomic status populations are at risk of low emotion-regulation competencies already at an early age [29], and the gap further widens over the school years [30].

To address the challenges outlined, we developed a proof-of-concept intervention platform to deliver in situ support for child ER during everyday emotionally charged situations, such as the child feeling angry, anxious, or sad. On the basis of a 2-year-long development [31,32], we worked with children, parents, and prevention science experts to co-design an intervention that would support children in strengthening their ER skills. The research prototype was then produced by the Committee for Children (a US-based nonprofit developer of socioemotional learning programs) and Sproutel [33], resulting in a commercial-grade therapeutic toy called Purrble [34].

The initial research prototypes were designed as the first instantiation of a novel *situated* intervention model, which is delivered through an interactive, socially assistive robot sent home with the child or used in schools, without any previous training for either the child or their parent or caregiver. As such, the psychological effects of Purrble are assumed to arise from repeated *bottom-up* support in situ, instead of relying on the traditional *top-down* training contexts delivered through workshops or therapy sessions. In particular, the intervention logic model relies on a 3-stage approach: (1) enabling the child to downregulate emotional moments in situ can (2) provide a preferred alternative to maladaptive emotion regulatory strategies (eg, rumination or suppression) and, over time, (3) lead to shifts in child ER competence [31]. For a detailed description of the hypothesized mechanisms and their links to the intervention design choices, see the *Intervention* section.

To date, 2 qualitative deployment studies have investigated the engagement and acceptability of the prototype in young children's homes, as well as subjective indicators of effects on emotion regulatory practices (whether positive or negative), as reported by parents and children [31,32]. Findings from these studies have been very positive: all 25 children engaged with the prototype throughout the deployments, all wanted to keep it for longer, and all described how they naturally incorporated it into their everyday routines and gravitated toward it when they needed to downregulate their emotions, including anger, anxiety, or just needing to relax.

Although these early data are promising, we lack quantitative data on the impact of the intervention on child outcomes. In particular, evidence is needed to (1) evaluate the efficacy of Purrble in delivering measurable changes in emotion regulatory practices of children over time and (2) start validating the hypothesized intervention logic model. This study aims to fill these evidence gaps.

Methods

Study Design and Objectives

The objective of this study is to evaluate the impact of having access to the Purrble intervention, compared with an active control in the form of a noninteractive plush toy, on child daily

ER (primary outcome) as well as a range of secondary outcomes over 1 month.

The study is a 2-arm, exploratory randomized controlled trial comparing an intervention group (Purrble) with an active control group (noninteractive plush toy). The deployment period will be 4 weeks and will include daily parent self-report measures via ecological momentary assessment (EMA), as well as weekly validated surveys with a 1-month and 6-month follow-up (see Figure 1). The intervention period will start immediately after children receive their arm-appropriate toys. Participants in both the intervention and active control groups (Figure 2) will be able to keep the toys after the deployment period ends. Active control group participants will not be offered Purrble units postdeployment, as this would unblind the conditions before follow-up data collection.

Figure 1. Assessment design. EMA: ecological momentary assessment; ERC: Emotion Regulation Checklist; SDQ: Strengths and Difficulties Questionnaire; TWEETS: Twente Engagement With eHealth Technologies Scale.

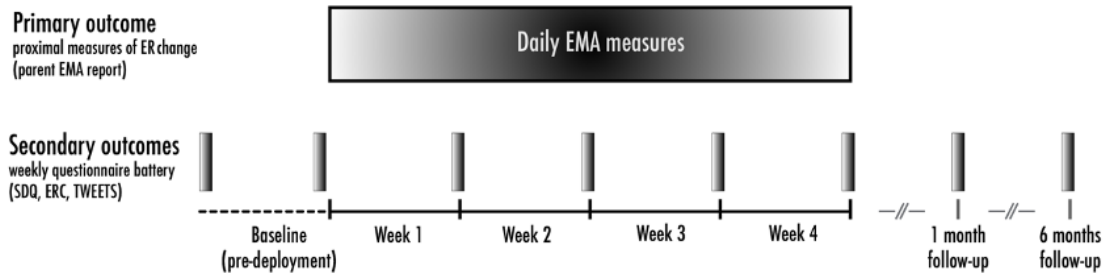
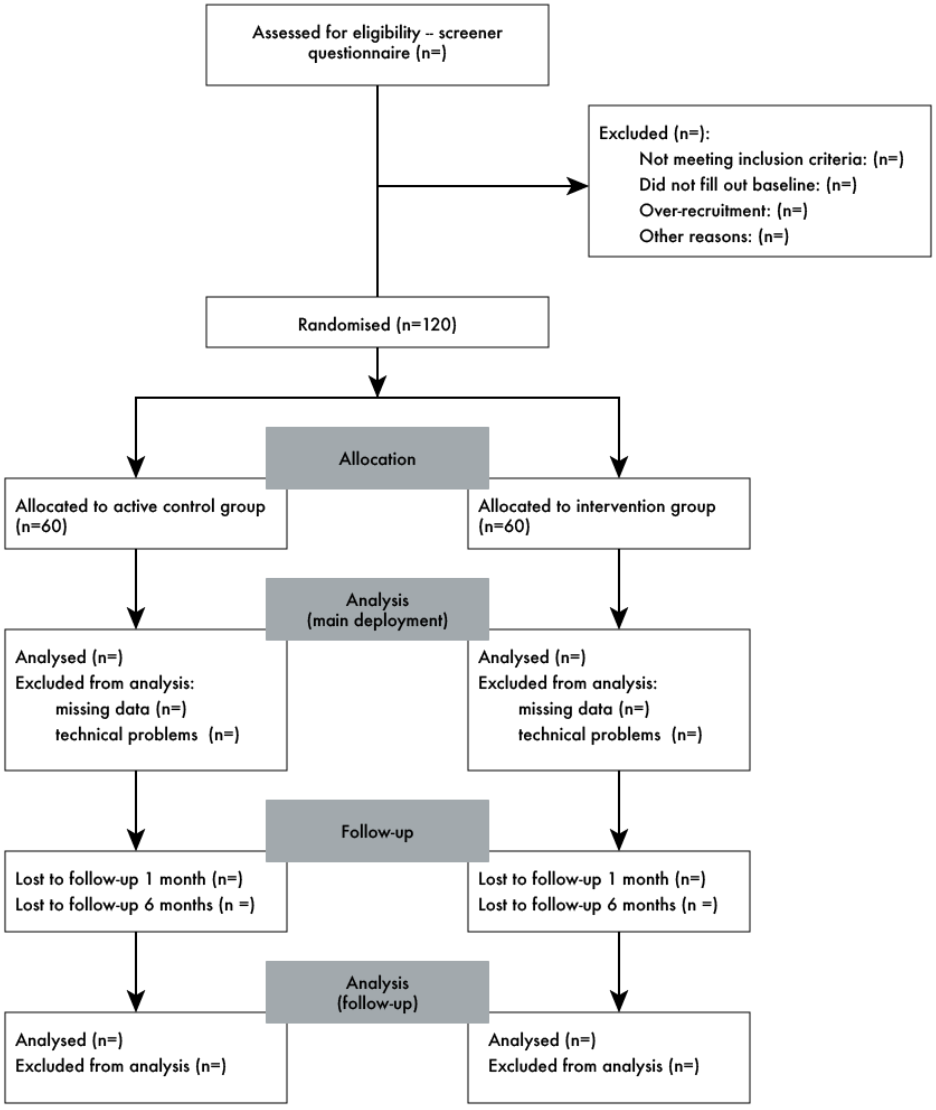


Figure 2. Participant selection flowchart.



Intervention

We hypothesize that engagement with an in situ, *bottom-up* ER intervention that enables in-the-moment soothing for children will lead to measurable changes in child self-regulatory behaviors over time.

Purrble—Intervention Design and Logic Model

The intervention takes the form of an interactive plush toy (Figure 3), which was designed to be handed over to the child and support in-the-moment soothing (see Theofanopoulou et al [31] and Slovak et al [32] for the design and data from previous deployments).

Figure 3. Purrble plush toy.

The toy is introduced to the child as an anxious creature that needs attention from humans, such as soft stroking and hugging. Embedded electronics enable the toy to produce vibration patterns that simulate a heartbeat (ranging from frantic to slow and steady). When picked up, the toy emits a frantic heartbeat that slows down if the child uses calm stroking movements, as registered by the embedded sensors. If the toy is soothed for long enough, the prototype transitions into a purring vibration indicating a calm, contented state. The minimum time for this transition is less than 1 minute, but the transition can take longer depending on the child-specific interactions with the prototype.

The logic model underlying the intervention is assumed to operate on 3 levels building on each other—see the study by Theofanopoulou et al [31] for more details:

- Level 1 pertains to *directly providing in-the-moment soothing support to children in naturally occurring emotional moments* when they would attempt to calm down. The toy's physical and interaction design was aimed at tapping into various known regulatory factors, grounded theoretically in the Gross extended process model of ER [35]. Specifically, we designed the prototype interaction with the aim to impact 2 separate stages of the ER process: the *attentional deployment stage* [36-39], by shifting children's attention from the emotion-eliciting situation toward interacting with the toy, and the *response modulation stage*, by facilitating down-regulation through pleasant tactile interaction analogously to the mechanisms presumed to underpin emotion regulatory effects of human-animal interaction [40-45].
- Level 2 is concerned with mechanisms that *facilitate children's long-term engagement* with the intervention, building on the positive subjective experience of in-the-moment soothing. The framing of the toy as an *anxious creature in need of assistance* is the hypothesized key driver; we assume that this will not only frame the interactions regarding helping regulate others' emotions (extrinsic ER; [41,46,47]) but also facilitate the creation of a sense of relationship and responsibility for the well-being of the creature, similar to the long-term engagement seen with child-orientated robots [48] or products such as Tamagotchi [49-51].
- Finally, level 3 is assumed to emerge from repeated experiences of soothing interactions over time, leading to a *shift in children's ER practices and implicit beliefs about emotion* (ie, the individual's beliefs about whether emotions can be regulated; see study by Ford and Gross [52] for details). Specifically, we hypothesize that repeated interactions with the toy will result in a shift in children's implicit beliefs about the controllability of emotion [52,53], a well-known target for intervention [54-58], as well as help reduce maladaptive ER patterns such as rumination or suppression [59].

Deployments with the research prototypes underpinning the current Purrble [31,32] show that, across all 25 families, children reported that the smart toy was incorporated into the children's ER practices and engaged with naturally in moments the children wanted to relax or calm down. Specifically, the data from [31] shows that the children interacted with the toy throughout the week-long deployment (eg, average active use for 74.9, SD 64.1 minutes per day; median 60.5), they found the experience enjoyable, and all children requested to keep the toy longer. Children's emotional connection to the toy appears to have driven this strong engagement. Parents reported satisfaction with and acceptability of the toy. No quantitative data on

changes in ER were collected in previous studies because of the small sample size and the focus on feasibility and understanding of appropriation within families.

Active Control Group

When compared with a traditional noninteractive plush toy, the intervention model underpinning Purrble includes 2 possible pathways through which the effects should occur:

- The first is the in-the-moment soothing support (level 1 in the logic model) that we hypothesize is driven by the interactivity of the toy. The lack of such situated down-regulation support should thus be the key difference between the intervention and an active control, that is, a noninteractive stuffed toy, leading to lower engagement over time (level 2) and a lack of impact on child ER practice (level 3).
- However, an alternative pathway is the ER routines (levels 2 and 3 in the logic model) that could, in principle, emerge around the intervention narrative of a physical object to use for calming down, even without the toy being interactive. In other words, if it was simply the narrative of an anxious creature in need of care (rather than the combination of the narrative together with the interactivity) that drives long-term engagement and changes in behavior, a noninteractive stuffed toy could still lead to the development of the same routines. We see this as an unlikely scenario, for example, given the prevalence of plush toys in most, if not all, households—but one that should be addressed in the study design.

For these reasons, we argue that a comparison with a nonactive control—such as waiting list or treatment-as-usual (ie, nothing)—would not allow us to distinguish the hypothesized impact on in-the-moment soothing of interactivity versus the emergence of new family routines and would also be open to unequal social desirability bias. However, from the perspective of the hypothesized logic model, it is not necessary for the active control to have exactly the same form factor as the active toy, as long as it is comparable in size, shape, and appeal. In fact, we have explicitly decided not to use deactivated Purrble units as active controls because of the increased risk of unblinding, whereby the participants search for or come across Purrble on the web (or notice the plastic enclosure with electronics inside the toy) and assume that their unit is malfunctioning.

Selection and Validation of Active Control Units

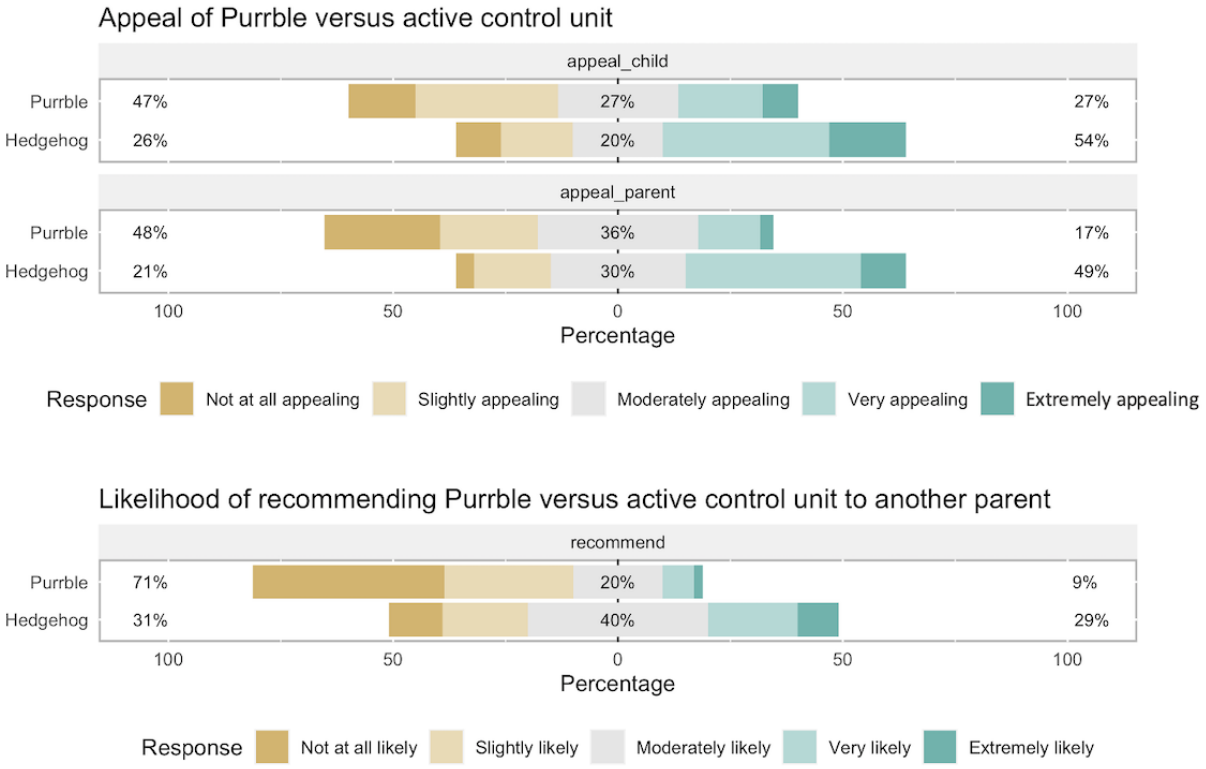
The selected active control toy is the *Wild Republic 8″ Hedgehog animal*. The selection process was guided by the following requirements: the plush toy needed to have analogous size, weight, and quality of materials, and at least similar (if not higher) visual appeal. We also made sure to include the design characteristics that our previous work suggested were important for the narrative around the toy [31,32]. These included selecting a similarly stylized animal (to enable emotion projection and feelings of care), as well as no visible mouth on the toy (to prevent setting an expectation about the toy's emotional state as a mouth would imply an emotional expression). In addition, we have adapted the one-page parent-facing descriptions of the narrative that come with Purrble also for the active control unit; as such, the active control families will receive the same general narrative—including that the creature is anxious and needs human care, but without the explicit mentions of the toy interactivity—and the same suggested activities for parents.

To validate that the active control is at least as visually appealing as the intervention, we ran a web-based experiment in which participants were randomly assigned to rate either the Hedgehog or the Purrble images. In both cases, the prompts were professional photos from the front and side on a white background, presented at equal size (Figure 4). The experiment was powered to detect a medium-sized effect (d=0.4) at 80% power for a comparison on a single measure, resulting in a sample size of 200 (1:1 allocation ratio). Participants were recruited through the web-based research platform Prolific, with the survey hosted by Qualtrics (including blocked randomization). Inclusion criteria for parents were the eldest child born in 2010-2013 (approximately aged 8-10 years), country of residence in the United Kingdom or the United States, and above 95% acceptance of tasks on Prolific. The participants were prompted to imagine that their oldest child had received the plush toy pictured above as a present. We then asked 3 questions, with the first question—appeal—preselected as the primary measure: (1) How appealing do you yourself find the toy? (2) How appealing do you think your child would find the toy? and (3) How likely would you be to recommend this toy to another parent?

Figure 4. On the left, an image of the Hedgehog toy for the active control group. On the right, an image of Purrble for the intervention.

The results show that the hedgehog was consistently rated higher than Purrble on all 3 questions (Figure 5). This suggests that, if anything, the active control should be more appealing to our study participants than the intervention units: it is a particularly stringent control condition to test the effect of a visually appealing, but noninteractive, plush toy. In other words, if it was purely the visual appeal of the units that would drive child or parent engagement and the resulting ER effects (as opposed to the interactivity of the intervention units), we would expect the active control to show at least as good if not better engagement and reports of changes in child ER from the families.

Figure 5. Rating of the questions regarding the appeal of Purrble versus the active control unit, and the likelihood of recommending Purrble versus the active control unit to another parent.



Participant Eligibility Criteria

Given Purrble's intended use as a targeted prevention intervention, we will recruit an *enriched* population of neurotypical children, aged 8-10 years, from families in the United States. The enrichment consists of recruiting families where the child is seen as struggling with some level of ER difficulty (as reported by their parent) but is not undergoing clinical treatment.

The specific inclusion criteria were a child aged 8-10 years, parent-reported score of ≥10 for the total difficulties score on the Strength and Difficulties Questionnaire (SDQ). The exclusion criteria for the child were current participation in another mental health intervention. In addition, an exclusion criterion for the parent and/or the child is not being fluent in English (as all measurement scales are in English).

The target child age range has been selected as collecting self-report measures from young children is a well-known challenge, especially when inquiring about complex cognitive concepts such as those involved in ER [60,61], and our pilot work in families and schools suggests that acceptability for the toy is high with children of this age, with children aged 8-10 years still using the toy as intended.

Recruitment, Randomization, and Blinding

Parents will be recruited by sending the study invitation to a mailing list of approximately 10,000 parents or guardians, whose children are receiving Committee for Children programs in school, and who have signed up to receive information from the Committee for Children.

Once eligibility is proven and parents fill out the baseline questionnaires, families will be randomly assigned to the intervention or active control group. Families will be randomized using a computerized algorithm and randomly permuted block sizes. The allocation schedule is generated by a Committee for Children researcher not directly involved in the data collection (and not aware of participants' details apart from their address) and is unknown to the investigator and the participants. The principal investigators will not be aware of the allocation until data collection is complete.

Blinding is present: the families will not be aware of the existence of another condition throughout the study, requiring the participation cap on students from any single class.

Outcome Measures

The primary outcome will be a daily EMA measure of child emotion regulation capability (as reported by parents) over a

period of 4 weeks. Exploratory analyses will investigate the intervention impact on secondary outcomes of child emotion regulation, collected weekly over the same 4-week period, with follow-ups at 1 month and 6 months postdeployment. See Table 1 for a summary of the outcome measures and assessment times.

Table 1. Summary of the outcome measures and assessment times.

Outcome measure	Baseline	Deployment				Follow-up			
		Week 1	Week 2	Week 3	Week 4	1 week	2 weeks	1 month	6 months
Perceived child ER ability		Collected daily	Collected daily	Collected daily	Collected daily				
Daily parent report ecological momentary assessment (modified differential emotions scale)		Collected daily	Collected daily	Collected daily	Collected daily				
Daily parent report ecological momentary assessment (engagement)		Collected daily	Collected daily	Collected daily	Collected daily				
Daily parent report ecological momentary assessment (reaction to triggers)		Collected daily	Collected daily	Collected daily	Collected daily				
Weekly parent questionnaire (Strength and Difficulties Questionnaire)	✓	✓	✓	✓	✓			✓	✓
Weekly parent questionnaire (ER Checklist)	✓	✓	✓	✓	✓			✓	✓
Weekly parent questionnaire (Twente Engagement With eHealth Technologies Scale)		✓	✓	✓	✓			✓	✓
Weekly children questionnaire (Difficulties in ER Scale)	✓	✓	✓	✓	✓			✓	✓
Weekly children questionnaire (emotion regulation-beliefs)	✓	✓	✓	✓	✓			✓	✓
Interviews with families						✓	✓		

Primary Outcome Measure

The primary outcome measure will consist of a composite end-of-day 4-item parent report measure of the *perceived child ER* ability throughout the day. The specific items are listed below, all measured as a visual analog scale [62,63] with *not at all* and *very much so* as the anchors. The composite score for each day will be computed as the mean value across the 4 items:

1. Today, to what extent was your child able to take difficult things in a stride?
2. Today, to what extent did your child get easily triggered or upset? (reverse-scored)
3. Today, to what extent was your child able to calm down easily if upset?
4. Today, to what extent did your child get very emotional even after the littlest things? (reverse-scored)

Specifically, this EMA item composite aims to indirectly tap into day-to-day changes in a child's ability to downregulate their emotions after (and thus cope with) triggering situations they routinely experience in their daily life. Our expectation is that contact with the Purrble will lead to the following:

1. Lower intensity negative emotions after facing everyday stressors (eg, by being able to downregulate before emotional response escalate—cf, level 1 in the theory of change).
2. Briefer duration of negative emotions after facing everyday stressors (eg, being able to downregulate emotions faster with Purrble—cf, levels 1 and 3 in the theory of change).

By being measured repeatedly over time and within subjects, the items capture the changes in emotional outcomes that would indicate changes in the child's ER ability, assuming that the trait-based reactivity to daily stressors remains stable. The items were thus selected to tap into the proximal outcomes of ER behavior that (1) would be affected if the intervention is effective, (2) is directly observable by parents, (3) is state-based (rather than trait-based) to enable daily measurement, and (4) is connected to the intervention theory of change.

The item selection drew on a range of established measures of emotion dysregulation (Strengths and Difficulties Questionnaire, SDQ [64], Emotion Regulation Checklist, ERC [65], Difficulties in Emotion Regulation Scale (DERS) [66], and Children's Emotional Management Scales [67]), as well as qualitative data from previous deployments [31,32] with parental reports of increased emotion regulation after potentially triggering events being the common theme.

Secondary Outcome Measures

Daily Parent Report EMA

In addition to the primary EMA outcome, we will collect several other daily EMA parent reports. The psychological constructs targeted are the *child*'s *general mood* and *daily engagement with the toy.*

The *child's daily mood* is measured by selected Modified Differential Emotions Scale (mDES) [68] emotion triplets, balancing 2 negative and 2 positive sets, while being informed by previous qualitative studies. The items are listed as follows, all measured on a visual analog scale [62,63], with *not at all* and *extremely* as the anchors:

1. How stressed, nervous, or oevrwhelmed did your child feel today?
2. How joyful, glad, or happy did your child feel today?
3. How angry, irritated, or annoyed did your child feel today?
4. How proud, confident, or self-assured did your child feel today?

The *daily engagement item* asks about the general perception of engagement with the toy (*How much did your child play with the toy today?*), measured on a visual analog scale [62,63], with *not even once* and *they were inseparable* as the anchors.

Finally, we will include a *series of explorative items that examine the child's reaction after potentially triggering events*. We will first ask the parents *Did anything happen today that would typically upset your child?* If yes, the protocol follows with several questions collecting qualitative and quantitative information regarding the number of such situations, the intensity and length of subsequent children's negative reactions, how many of these situations the child used the toy, who initiated the use, how helpful or unhelpful it was, and an opportunity to share open-ended comments or observations. The purpose of these items is to gain a qualitative understanding of the toys' use in challenging situations and to guide post deployment interviews.

Weekly Parent Reports

We will also collect *secondary distal outcomes* for both the intervention and active control groups, with 5 data points collected during the 4-week main deployment period: at baseline (just before intervention or control toys are delivered), and then weekly for a period of 1 month (end of week 1, week 2, week 3, and week 4), and then at 1-month and 6-month follow-up. The measures include parent reports on distal outcomes of child emotion regulation (SDQ and ERC) and engagement (adapted Twente Engagement With eHealth Technologies Scale [TWEETS]), as well as child reports on their emotion regulation strategies (DERS) and emotion regulation beliefs (ER mindset).

Weekly Questionnaires—Parents

Parent-reported emotional and behavioral difficulties of the child will be measured using the 25-item SDQ [64]. This well-established measure has shown satisfactory reliability and validity [64,69] and is commonly used to measure the impact of child-orientated interventions [46,47].

Parent-reported ER lability and competence will be measured using the 24-item Emotion Regulation Checklist [65] questionnaire. The ERC measures children's general emotion regulation capacities and consists of 23 questions divided into 2 subscales, which we will consider separately: the Lability or Negativity subscale measures inflexibility, liability, and dysregulation, whereas the Emotion Regulation subscale measures positive emotion regulation behavior and capacities, appropriate emotional expression, empathy, and emotional self-awareness. ERC is one of the most commonly used measures of emotion regulation in children [5].

The *parent-reported behavioral, cognitive, and affective engagement* with the intervention will be measured using an adapted version of the Twente Engagement with E-health Technologies Scale (TWEETS) [70] questionnaire. TWEETS is a new, promising instrument specifically designed to measure engagement with digital mental health interventions, with good reliability in previous studies [70]. The adaptation here is necessary to track parents' perceptions of child engagement, rather than the original self-report version. See Multimedia Appendix 1 for the fully adapted instrument.

Weekly Questionnaires—Children

Child-reported emotion dysregulation will be measured by a shortened version of the brief DERS [71], following previous work with children of similar ages (8-9 years [72]). DERS has been developed to measure clinically relevant difficulties in ER across 6-factor analytically derived subscales (awareness of emotion, clarity about own emotions, nonacceptance of emotion, lack of effective emotion regulatory strategies, lack of ability to engage in goal-directed activities, and lack of ability to manage impulses). The DERS [71,73] has been used extensively to facilitate understanding of how emotion dysregulation is associated with psychiatric symptoms and to measure treatment progress. See Multimedia Appendix 1 for the full adapted instrument.

Child-reported *beliefs about ER* beliefs questionnaire [54] have been adapted to child populations. The questionnaire measures child *entity beliefs* about their emotions [52,55,74], that is, whether children believe their emotions to be controllable. To simplify the required cognitive load, the adapted measure asks children to pick 1 out of 4 statements (eg, *I cannot control my feelings at all, I can control my feelings a little, I can control my feelings a lot,* and *I can control my feelings all the time*) rather than using the original Likert scale statements asking about agreement (eg, *The truth is, I have very little control over my emotions*). Our preliminary validation (221 children, aged 6-10 years, US sample) showed good reliability (0.844) (internal pilot study), compared with the adult version [54]. See Multimedia Appendix 1 for the full adapted instrument.

Postdeployment Interviews (Process Analysis)

We will collect semistructured interview data with parents of up to 40% of the experimental group sample (20-25 families), and approximately 25% of the control group (15 families). The interviews will be conducted within 2 weeks following the primary data collection period. We will specifically aim to recruit families who show the highest or lowest change in the

outcome data over the primary period to qualitatively understand the potential moderators of intervention responses for future research.

Following previous work [31], the semistructured interview guide will explore the engagement with the toy, any qualitative changes in child or family behavioral patterns that parents notice, appropriation (ie, how the intervention ended up being used by different participants), and use trajectory over time. In addition, we draw on the data from daily questionnaires as part of the interviews, such as discussing the trajectories of daily parental reports on child ER with the parent (eg, asking about specific instances where there is a spike or as a way of referring to particular times in the deployment).

Hypotheses

Primary Hypothesis

Across the trial, we hypothesize that access to the Purrble intervention (as opposed to the active control) will lead to an *increase in parent-reported daily child ER ability*, as measured by the primary outcome.

Secondary Hypotheses

Intervention effects will be moderated by daily engagement with toy and weekly data from the TWEETS questionnaire. In addition, we expect to see between-group differences in favor of Purrble for the secondary daily EMA parental-report outcomes: *an increase* in the *positive mDES items* and a *decrease* in the *negative mDES items*.

Finally, as exploratory analyses, we will investigate the following hypotheses for weekly outcome measures:

1. The decrease in *parent-reported emotional and behavioral difficulties* (as measured by the SDQ) will be greater in the intervention group (smart toy) than in the active control group (noninteractive toy).
2. *The decrease in ER lability* and *increase in emotion regulation competence* (as measured by the Lability or Negativity subscale and Emotion Regulation subscale questionnaires respectively) will be greater in the intervention group than in the active control group (noninteractive toy).
3. *Behavioral, cognitive, and affective engagement* with the intervention, as measured by the adapted *TWEETS questionnaire for parents*, will be higher for the intervention than the control group.
4. The decrease in *child-reported emotion dysregulation* (as measured by the DERS) will be greater in the intervention group than in the active control group (noninteractive toy).
5. The decrease in *child-reported entity beliefs of emotion regulation* (as measured by the ER mindset questionnaire) will be greater in the intervention group than in the active control group (noninteractive toy).

Adherence Protocol

We will use the following protocol to encourage participants' adherence to the data collection schedule. All decision points are based solely on data collection, rather than any indication of the intervention use or nonuse. The protocols for daily and weekly data collection were independently run.

The daily measures adherence protocol will be as follows: when a participant misses their end-of-day questionnaire, the system automatically generates a reminder next morning. If a participant has already received 2 automated reminders in a row and again misses daily measures, a research assistant will call the participant (in addition to an automated reminder) on the next workday, following a predetermined call script. If the participant does not respond, they will receive one more reminder the next day, and a second call on the following workday. If no data are received, the participant will be marked as dropped out as they will have missed at least 6 subsequent daily measures (ie, more than 20% of the overall data points). The protocol resets when the participant submits a daily questionnaire. In summary, the daily adherence protocol was as follows: 2× reminder, 1× call+reminder, 1× reminder, and 1× call+reminder, dropped from the study.

The *weekly measures adherence protocol* will be as follows: the survey links will be sent on Saturday midday, with an automated email reminder on Sunday morning. If data are missing by the end of Sunday, a research assistant will call the participant on Monday, following a predetermined call script. The participants will be sent a new link to the survey, with the possibility of submitting their response for the week by the end of Monday. We will not use adherence to weekly surveys as a decision to drop participants from the study, as weekly surveys do not collect the primary outcome.

All calls and other communications with participants will be logged by the research assistant on the web. Although the research assistant will be able to unblind the participants' condition if necessary, we do not expect this will be needed in most of the calls.

Data Analyses

All analyses of daily EMA outcomes (the primary outcome of daily ER and secondary outcomes of engagement with the toy and mood), as well as the analyses of the weekly outcomes, will be conducted using random-effect models for longitudinal regression. These models consider the nested nature of repeated-measures data and are robust to data missingness and violations of the normality assumption. The regression models will examine the difference in the outcome as a function of the assigned condition (Purrble vs active control). The models will adjust for the baseline levels of the score on the total difficulty scale in the SDQ to decrease noise. To account for participant-to-participant variability in EMA scoring as well as in trajectories of change in EMA scores over time, we will include a random intercept and random slope for time. All analyses will be conducted on an intent-to-treat basis and will use data from all randomized participants regardless of their level of participation.

A separate model will be fitted to each outcome. Given that this is an exploratory trial, we will not formally adjust for multiple comparisons. However, we will be cautious in our conclusions about any significant findings and will interpret all results in light of all performed analyses.

To examine the link between engagement with the intervention and ER outcomes, we will conduct 3 types of exploratory

analyses: first, given that we hypothesize that Purrble will be more engaging than the control-condition stuffed animal, we will examine whether intervention engagement is influenced by the treatment condition. To do so, we will regress our daily measure of engagement on the treatment condition, controlling for the previous day's engagement to reduce noise. Similarly, we will regress the weekly TWEETS scores on the treatment condition, controlling for the previous week's engagement. Second, we will examine whether engagement moderates the intervention impact on both our primary outcome, the daily measure of emotional regulation, and the weekly ERC and SDQ measurements. For the daily model, we will use our primary measure, the EMA assessment of ER, as the dependent variable, and will include, as regressors, treatment indicators and the EMA measure of engagement, as well as a term for their interaction. To decrease noise, the model will also include as a covariate the previous day's score on the ER measure. Similarly, for weekly models, we will regress the weekly ERC and SDQ scores on terms for the treatment indicator, TWEETS score, and their interaction. As in the daily model, we will also include a term for the ERC or SDQ score of the previous week to reduce noise. As an alternative approach, we will consider using the weekly average of the daily EMA engagement scores rather than TWEETS for the weekly analyses of the moderating influence of engagement, as these 2 scales tap into different aspects of the engagement experience.

Finally, as our logic model postulates that engagement may also mediate the impact of intervention, we will also conduct an analysis of the mediating role of engagement. Given the ambiguities of mediation analyses in longitudinal settings and the lack of consensus on best practices, for this analysis, we will follow the original Baron and Kenny approach to establishing mediation [75]. To do so, we will use, as our outcome variables, the change scores for the emotion-regulation measures (ERC and SDQ) from baseline to the end of study (end of week 4). To measure engagement, we will use the average of the weekly TWEETS assessments over the course of the study. To examine the mediating role of engagement, we will conduct 3 sets of analyses: first, we will estimate the impact of the treatment condition on the change in ER by regressing the emotion-regulation change score on the indicator of the treatment condition. Second, to examine whether treatment had an impact on engagement, we will regress the average of the weekly TWEETS assessments on the indicator for the treatment condition. Finally, we will estimate a model that regresses the ER change score on both the treatment indicator and engagement. To assess preliminary evidence on the mediating role of engagement, we will examine the magnitudes of effect coefficients in all models, as well as statistical significance, to determine whether the inclusion of engagement in the model has reduced the impact of the treatment condition. Given that the ERC and SDQ tap into different aspects of emotion regulation, we will conduct these analyses for both ERC and SDQ change scores.

Sample Size and Power

We calculated the sample size requirements to be able to detect a difference between the two arms on our primary outcome measure: the daily parent report of the child's ER throughout the day. On the basis of the data from our preliminary studies, we expect to see a medium effect size for this measure; therefore, to be conservative, we used a Cohen *d* of 0.3 in our sample size calculation. With this assumption, we calculated the sample size to be able to detect the main effect of the condition (Purrble vs active control) with 90% power and an α level of .05. Under the conservative assumption that the correlation between repeated measures will be 0.75, the required sample size is 92 participants. We inflated this number by 10% to help power the exploratory analyses of the secondary outcomes. Assuming a 20% dropout rate, our final sample size is 120 families.

Ethical Criteria and Ethics Committee

The study will be conducted according to local regulations and the Declaration of Helsinki. The Pearl institutional review board approved the study (#18-CFC-101). Written informed consent will be obtained from all parents, and written assent will be obtained from all children. The trial is registered with ClinicalTrials.gov (NCT04810455).

Results

This study is funded by the UKRI Future Leaders Fellowship (MR/T041897/1) and the Committee for Children. The ethical approval was received, and the study is preregistered with ClinicalTrials.gov. The recruitment procedures started in early March 2021. The data collection started in mid-April 2021, with the primary data collection period finished by the mid-May 2021.

Discussion

Principal Findings

This study aims to evaluate the benefits of access to a socially assistive robot on children's ER ability in situ, without the need for training for the child or parents. If successful, the study will provide a proof-of-concept example of a *bottom-up* ER intervention, enabling a new approach to developing child ER competency through technology-enabled ongoing support in everyday emotional situations. As such, this work complements the currently predominant *top-down* approaches, where ER strategies are taught in training contexts, and then the children are expected to transfer these strategies into daily life, often with no or limited in situ support. If shown effective, these in situ interventions can inspire a new approach in how ER interventions can be conceptualized, designed, and delivered.

More generally, ER in childhood is a prime target for a range of prevention and clinical interventions. In this regard, the existing Purrble toys can be seen as a potentially highly modular and extendable platform, where additions or minor changes to the core interaction paradigm can be used to target a range of participants (different ages, verbal acuity, etc), and a variety of different contexts (clinical and nonclinical settings). For example, our pilot data with clinicians and psychotherapists suggest potential benefits in the context of eating disorders and self-harm interventions for adolescents, as well as complementing therapeutic support for fostered or looked-after

children. Rigorous empirical data supporting the efficacy of the current intervention are crucial for such research.

Limitations

The following limitations of this study need to be considered. First, this study is designed as an exploratory RCT to account for the uncertainty about the effect sizes that should be expected given the novelty of the intervention delivery mechanism and proposed theory of change. The range of selected secondary measures (and the substantial qualitative process analysis) reflects this focus on hypothesis generation rather than aiming to design a definitive trial.

Second, a related limitation concerns the choice of primary measure. The bespoke 4-item composite measure of the parent-reported *child emotion regulation* ability throughout the day reflects the uncertainty about the impact of the intervention on distal ER outcomes, aiming to measure time-sensitive proximal aspects of the expected changes in child emotion regulatory ability that are also directly observable by the parent. Future work should target more established measures such as those targeted by the secondary outcome in this study (SDQ, ERC, DERS, and ER beliefs). We expect that the necessary sample size estimation for such studies will be guided by the empirical data collected in this study.

Third, the current commercial Purrble toys lack the capability to track in-the-moment interactions over time or gather any other data on daily use, as do the noninteractive active control units. As such, the study lacks objective measures of daily engagement and needs to rely on observer-report measures (parents), who are unlikely to fully account for the child's independent use of the toy. In addition, the lack of in-the-moment tracking also limits the methods available to verify level 1 (in-the-moment soothing) and level 2 mechanisms (child-initiated repeated interaction) from the theory of change. If the data from this study show the impact of the Purrble intervention on child ER in situ, future mechanistic or optimization studies should specifically focus on testing the pressumed level 1 and 2 processes.

Finally, the study design relies predominantly on end-of-day parent reports of child ER under naturally occurring daily stressors. This is in line with other studies on similarly aged child samples, and the ecological validity of the findings is a strength of the study design. However, further work could extend these methods with more controlled measures, such as in-laboratory experimental measures, as another triangulation of the meaningful impact of the intervention on child ER.

Conclusions

The proposed study is an explorative RCT that assessed for the first time the efficacy of a novel intervention model for child-led ER, delivered in situ through an interactive socially assistive robot. The strength of the approach lies in the ecologically valid deployment, with a strong active control condition that limits the effects of social desirability bias. If successful, the robotic platform can serve as a proof-of-concept example for a new approach to ER interventions, shifting the learning support directly into the daily moments when ER competencies need to be applied. Such a *situated* intervention model can be a good complement to the current therapy or workshop-based interventions.

Acknowledgments

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Conflicts of Interest

PS is one of the designers of the Purrble intervention, in a research consultancy agreement with the Committee for Children (Seattle, WA).

Multimedia Appendix 1
Adapted instruments.
[DOCX File , 868 KB - resprot_v10i11e28914_app1.docx]

References

1. Greenberg L. Emotion-Focused Therapy: Coaching Clients to Work Through Their Feelings. Washington: American Psychological Association; 2002:1-360.
2. Kring AM, Bachorowski J. Emotions and psychopathology. Cogn Emot 1999 Sep;13(5):575-599. [doi: 10.1080/026999399379195]
3. Mennin D, Farach F. Emotion and evolving treatments for adult psychopathology. Clin Psychol Sci Pract 2007 Dec;14(4):329-352. [doi: 10.1111/j.1468-2850.2007.00094.x]
4. Berenbaum H, Raghavan C, Le H, Vernon LL, Gomez JJ. A taxonomy of emotional disturbances. Clin Psychol Sci Pract 2003;10(2):206-226. [doi: 10.1093/clipsy.bpg011]
5. Compas BE, Jaser SS, Bettis AH, Watson KH, Gruhn MA, Dunbar JP, et al. Coping, emotion regulation, and psychopathology in childhood and adolescence: a meta-analysis and narrative review. Psychol Bull 2017 Sep;143(9):939-991 [FREE Full text] [doi: 10.1037/bul0000110] [Medline: 28616996]
6. Gross JJ, Muñoz RF. Emotion regulation and mental health. Clin Psychol Sci Pract 1995;2(2):151-164. [doi: 10.1111/j.1468-2850.1995.tb00036.x]

7. Troy A, Mauss I. Resilience in the face of stress: emotion regulation as a protective factor. In: Resilience and Mental Health: Challenges Across the Lifespan. Cambridge: Cambridge University Press; 2011:30-44.
8. Gross JJ. Emotion regulation: taking stock and moving forward. Emotion 2013 Jun;13(3):359-365. [doi: 10.1037/a0032135] [Medline: 23527510]
9. Gross JJ. Emotion regulation: affective, cognitive, and social consequences. Psychophysiology 2002 May;39(3):281-291. [doi: 10.1017/s0048577201393198] [Medline: 12212647]
10. John O, Gross J. Healthy and unhealthy emotion regulation: personality processes, individual differences, and life span development. J Pers 2004 Dec;72(6):1301-1333. [doi: 10.1111/j.1467-6494.2004.00298.x] [Medline: 15509284]
11. Chu B, Temkin A, Toffey K. Transdiagnostic mechanisms and treatment for children and adolescents: an emerging field. In: Oxford Handbooks Online. Oxford, United Kingdom: Oxford University Press; 2016.
12. Sloan E, Hall K, Moulding R, Bryce S, Mildred H, Staiger PK. Emotion regulation as a transdiagnostic treatment construct across anxiety, depression, substance, eating and borderline personality disorders: a systematic review. Clin Psychol Rev 2017 Nov;57:141-163. [doi: 10.1016/j.cpr.2017.09.002] [Medline: 28941927]
13. Aldao A, Mennin D. Emotion regulation. In: The Wiley Handbook of Anxiety Disorders. Hoboken, New Jersey, United States: John Wiley & Sons Inc; 2014:191-200.
14. Sakiris N, Berle D. A systematic review and meta-analysis of the Unified Protocol as a transdiagnostic emotion regulation based intervention. Clin Psychol Rev 2019 Aug;72:101751. [doi: 10.1016/j.cpr.2019.101751] [Medline: 31271848]
15. Ellard K, Fairholme C, Boisseau C, Farchione T, Barlow D. Unified Protocol for the transdiagnostic treatment of emotional disorders: protocol development and initial outcome data. Cogn Behav Pract 2010 Feb;17(1):88-101 [FREE Full text] [doi: 10.1016/j.cbpra.2009.06.002] [Medline: 33762811]
16. Webster-Stratton C, Taylor T. Nipping early risk factors in the bud: preventing substance abuse, delinquency, and violence in adolescence through interventions targeted at young children (0-8 years). Prev Sci 2001 Sep;2(3):165-192. [doi: 10.1023/a:1011510923900] [Medline: 11678292]
17. Kazdin AE. Developing treatments for antisocial behavior among children: controlled trials and uncontrolled tribulations. Perspect Psychol Sci 2018 Sep 29;13(5):634-650. [doi: 10.1177/1745691618767880] [Medline: 29958060]
18. Webster-Stratton C, Hammond M. Treating children with early-onset conduct problems: a comparison of child and parent training interventions. J Consult Clin Psychol 1997 Feb;65(1):93-109. [doi: 10.1037//0022-006x.65.1.93] [Medline: 9103739]
19. Dunn J, Brown J, Beardsall L. Family talk about feeling states and children's later understanding of others' emotions. Develop Psychol 1991;27(3):448-455. [doi: 10.1037/0012-1649.27.3.448]
20. Dunn J, Brown J, Slomkowski C, Tesla C, Youngblade L. Young children's understanding of other people's feelings and beliefs: individual differences and their antecedents. Child Develop 1991 Dec;62(6):1352-1366. [doi: 10.1111/j.1467-8624.1991.tb01610.x]
21. Denham S, Renwick-DeBardi S, Hewes S. Emotional communication between mothers and preschoolers: relations with emotional competence. Merrill-Palmer Q 1994;40(4):488-508 [FREE Full text]
22. Gottman JM, Katz LF, Hooven C. Parental meta-emotion philosophy and the emotional life of families: theoretical models and preliminary data. J Fam Psychol 1996;10(3):243-268. [doi: 10.1037/0893-3200.10.3.243]
23. Gilliom M, Shaw D, Beck J, Schonberg M, Lukon J. Anger regulation in disadvantaged preschool boys: strategies, antecedents, and the development of self-control. Develop Psychol 2002;38(2):222-235. [doi: 10.1037/0012-1649.38.2.222]
24. Eisenberg N, Fabes RA, Murphy BC. Parents' reactions to children's negative emotions: relations to children's social competence and comforting behavior. Child Dev 1996 Oct;67(5):2227-2247. [Medline: 9022240]
25. Ramsden S, Hubbard J. Family expressiveness and parental emotion coaching : their role in children's emotion regulation and aggression. J Abnorm Child Psychol 2002;30(6):657-667. [doi: 10.1023/A:1020819915881]
26. Katz LF, Hunter EC. Maternal meta-emotion philosophy and adolescent depressive symptomatology. Soc Develop 2007 May;16(2):343-360. [doi: 10.1111/j.1467-9507.2007.00388.x]
27. Lunkenheimer ES, Shields AM, Cortina KS. Parental emotion coaching and dismissing in family interaction. Soc Develop 2007 May;16(2):232-248. [doi: 10.1111/j.1467-9507.2007.00382.x]
28. Wyman PA, Cross W, Brown CH, Yu Q, Tu X, Eberly S. Intervention to strengthen emotional self-regulation in children with emerging mental health problems: proximal impact on school behavior. J Abnorm Child Psychol 2010 Jul;38(5):707-720 [FREE Full text] [doi: 10.1007/s10802-010-9398-x] [Medline: 20180009]
29. Buckner JC, Mezzacappa E, Beardslee WR. Characteristics of resilient youths living in poverty: the role of self-regulatory processes. Dev Psychopathol 2003;15(1):139-162. [doi: 10.1017/s0954579403000087] [Medline: 12848439]
30. O'Shaughnessy TE, Lane KL, Gresham FM, Beebe-Frankenberger ME. Children placed at risk for learning and behavioral difficulties. Remed Spec Edu 2016 Aug 19;24(1):27-35. [doi: 10.1177/074193250302400103]
31. Theofanopoulou N, Isbister K, Edbrooke-Childs J, Slovák P. A smart toy intervention to promote emotion regulation in middle childhood: feasibility study. JMIR Ment Health 2019 Aug 05;6(8):e14029 [FREE Full text] [doi: 10.2196/14029] [Medline: 31381502]
32. Slovák P, Theofanopoulou N, Cecchet A, Cottrell P, Bertran F, Dagan E, et al. "I just let him cry...: Designing socio-technical interventions in families to prevent mental health disorders. Proc ACM Hum-Comput Interact 2018 Nov 07;2(CSCW):1-34 [FREE Full text] [doi: 10.1145/3274429]

33. Sproutel. URL: http://www.sproutel.com [accessed 2020-12-29]
34. Purrble. URL: http://www.purrble.com [accessed 2020-12-29]
35. Gross JJ. Emotion regulation: current status and future prospects. Psychol Inq 2015 Mar 09;26(1):1-26. [doi: 10.1080/1047840X.2014.940781]
36. Aldao A, Sheppes G, Gross JJ. Emotion regulation flexibility. Cogn Ther Res 2015 Jan 1;39(3):263-278. [doi: 10.1007/s10608-014-9662-4]
37. Sheppes G, Gross JJ. Emotion regulation effectiveness: what works. CiteSeerX. 2012. URL: https://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.688.784&rep=rep1&type=pdf [accessed 2021-11-03]
38. Sheppes G, Scheibe S, Suri G, Radu P, Blechert J, Gross JJ. Emotion regulation choice: a conceptual framework and supporting evidence. J Exp Psychol Gen 2014 Feb;143(1):163-181. [doi: 10.1037/a0030831] [Medline: 23163767]
39. Farb NA, Anderson AK, Irving JA, Segal ZV. Mindfulness interventions and emotion regulation. In: Gross JJ, Albert D, Anderson AK, Appleton A, Ayduk O, editors. Handbook of Emotion Regulation. New York: The Guilford Press; 2014:548-567.
40. Beetz A, Uvnäs-Moberg K, Julius H, Kotrschal K. Psychosocial and psychophysiological effects of human-animal interactions: the possible role of oxytocin. Front Psychol 2012;3:234 [FREE Full text] [doi: 10.3389/fpsyg.2012.00234] [Medline: 22866043]
41. Doré BP, Morris RR, Burr DA, Picard RW, Ochsner KN. Helping others regulate emotion predicts increased regulation of one's own emotions and decreased symptoms of depression. Pers Soc Psychol Bull 2017 May;43(5):729-739. [doi: 10.1177/0146167217695558] [Medline: 28903637]
42. Reeck C, Ames DR, Ochsner KN. The social regulation of emotion: an integrative, cross-disciplinary model. Trends Cogn Sci 2016 Jan;20(1):47-63 [FREE Full text] [doi: 10.1016/j.tics.2015.09.003] [Medline: 26564248]
43. Coan JA, Schaefer HS, Davidson RJ. Lending a hand: social regulation of the neural response to threat. Psychol Sci 2006 Dec;17(12):1032-1039. [doi: 10.1111/j.1467-9280.2006.01832.x] [Medline: 17201784]
44. Crossman MK, Kazdin AE, Kitt ER. The influence of a socially assistive robot on mood, anxiety, and arousal in children. Prof Psychol Res Pract 2018 Feb;49(1):48-56. [doi: 10.1037/pro0000177]
45. Rabbitt SM, Kazdin AE, Scassellati B. Integrating socially assistive robotics into mental healthcare interventions: applications and recommendations for expanded use. Clin Psychol Rev 2015 Feb;35:35-46. [doi: 10.1016/j.cpr.2014.07.001] [Medline: 25462112]
46. Cosley BJ, McCoy SK, Saslow LR, Epel ES. Is compassion for others stress buffering? Consequences of compassion and social support for physiological reactivity to stress. J Experiment Soc Psychol 2010 Sep;46(5):816-823. [doi: 10.1016/j.jesp.2010.04.008]
47. Taylor SE. Social support: a review. In: Friedman HS, editor. The Oxford Handbook of Health Psychology. New York: Oxford University Press; 2011.
48. Turkle S. Authenticity in the age of digital companions. Interact Stud 2007 Oct 16;8(3):501-517. [doi: 10.1075/is.8.3.11tur]
49. Hayashi R, Kato S. Psychological effects of physical embodiment in artificial pet therapy. Artif Life Robotics 2016 Sep 15;22(1):58-63. [doi: 10.1007/s10015-016-0320-7]
50. Donath J. Artificial pets: simple behaviors elicit complex attachments. In: Bekoff M, editor. The Encyclopedia of Animal Behavior. Westport, CT: Greenwood Press; 2004.
51. Lee HR, Panont WR, Plattenburg B, de la Croix JP, Patharachalam D, Abowd G. Asthmon: empowering asthmatic children's self-management with a virtual pet. In: Proeedings of the CHI'10 Extended Abstracts on Human Factors in Computing Systems. 2010 Presented at: CHI '10: CHI Conference on Human Factors in Computing Systems; April 10 - 15, 2010; Atlanta Georgia USA p. 3583-3588. [doi: 10.1145/1753846.1754022]
52. Ford BQ, Gross JJ. Why beliefs about emotion matter: an emotion-regulation perspective. Curr Dir Psychol Sci 2018 Dec 10;28(1):74-81 [FREE Full text] [doi: 10.1177/0963721418806697]
53. Schleider JL, Weisz JR. Implicit theories relate to youth psychopathology, but how? A longitudinal test of two predictive models. Child Psychiatry Hum Dev 2016 Aug;47(4):603-617. [doi: 10.1007/s10578-015-0595-2] [Medline: 26443503]
54. Ford BQ, Lwi SJ, Gentzler AL, Hankin B, Mauss IB. The cost of believing emotions are uncontrollable: youths' beliefs about emotion predict emotion regulation and depressive symptoms. J Exp Psychol Gen 2018 Aug;147(8):1170-1190 [FREE Full text] [doi: 10.1037/xge0000396] [Medline: 29620380]
55. Tamir M, John OP, Srivastava S, Gross JJ. Implicit theories of emotion: affective and social outcomes across a major life transition. J Pers Soc Psychol 2007 Apr;92(4):731-744. [doi: 10.1037/0022-3514.92.4.731] [Medline: 17469955]
56. Molden DC, Dweck CS. Finding "meaning" in psychology: a lay theories approach to self-regulation, social perception, and social development. Am Psychol 2006 Apr;61(3):192-203. [doi: 10.1037/0003-066X.61.3.192] [Medline: 16594836]
57. Kneeland ET, Dovidio JF, Joormann J, Clark MS. Emotion malleability beliefs, emotion regulation, and psychopathology: integrating affective and clinical science. Clin Psychol Rev 2016 Apr;45:81-88. [doi: 10.1016/j.cpr.2016.03.008] [Medline: 27086086]
58. Halberstadt AG, Dunsmore JC, Bryant A, Parker AE, Beale KS, Thompson JA. Development and validation of the parents' beliefs about Children's Emotions Questionnaire. Psychol Assess 2013 Dec;25(4):1195-1210 [FREE Full text] [doi: 10.1037/a0033695] [Medline: 23914957]

59. Aldao A, Nolen-Hoeksema S, Schweizer S. Emotion-regulation strategies across psychopathology: a meta-analytic review. Clin Psychol Rev 2010 Mar;30(2):217-237. [doi: 10.1016/j.cpr.2009.11.004] [Medline: 20015584]
60. Mellor D, Moore KA. The use of Likert scales with children. J Pediatr Psychol 2014 Apr;39(3):369-379. [doi: 10.1093/jpepsy/jst079] [Medline: 24163438]
61. Adrian M, Zeman J, Veits G. Methodological implications of the affect revolution: a 35-year review of emotion regulation assessment in children. J Exp Child Psychol 2011 Oct;110(2):171-197. [doi: 10.1016/j.jecp.2011.03.009] [Medline: 21514596]
62. Voutilainen A, Pitkäaho T, Kvist T, Vehviläinen-Julkunen K. How to ask about patient satisfaction? The visual analogue scale is less vulnerable to confounding factors and ceiling effect than a symmetric Likert scale. J Adv Nurs 2016 Apr;72(4):946-957. [doi: 10.1111/jan.12875] [Medline: 26689434]
63. Huskisson EC. Measurement of pain. Lancet 1974 Nov 09;2(7889):1127-1131. [doi: 10.1016/s0140-6736(74)90884-8] [Medline: 4139420]
64. Goodman R. Psychometric properties of the strengths and difficulties questionnaire. J Am Acad Child Adolesc Psychiatry 2001 Nov;40(11):1337-1345. [doi: 10.1097/00004583-200111000-00015] [Medline: 11699809]
65. Shields A, Cicchetti D. Emotion regulation among school-age children: the development and validation of a new criterion Q-sort scale. Dev Psychol 1997 Nov;33(6):906-916. [doi: 10.1037//0012-1649.33.6.906] [Medline: 9383613]
66. Gratz K, Roemer L. Multidimensional assessment of emotion regulation and dysregulation: development, factor structure, and initial validation of the difficulties in emotion regulation scale. J Psychopathol Behav Assess 2004 Mar 17;26(1):41-54. [doi: 10.1023/B:JOBA.0000007455.08539.94]
67. Zeman JL, Cassano M, Suveg C, Shipman K. Initial validation of the children's worry management scale. J Child Fam Stud 2009 Sep 2;19(4):381-392. [doi: 10.1007/s10826-009-9308-4]
68. Fredrickson BL, Tugade MM, Waugh CE, Larkin GR. What good are positive emotions in crises? A prospective study of resilience and emotions following the terrorist attacks on the United States on September 11th, 2001. J Pers Soc Psychol 2003 Feb;84(2):365-376 [FREE Full text] [doi: 10.1037//0022-3514.84.2.365] [Medline: 12585810]
69. Goodman R, Ford T, Simmons H, Gatward R, Meltzer H. Using the Strengths and Difficulties Questionnaire (SDQ) to screen for child psychiatric disorders in a community sample. Br J Psychiatry 2000 Dec;177:534-539. [doi: 10.1192/bjp.177.6.534] [Medline: 11102329]
70. Kelders SM, Kip H, Greeff J. Psychometric evaluation of the TWente Engagement with Ehealth Technologies Scale (TWEETS): evaluation study. J Med Internet Res 2020 Oct 09;22(10):e17757 [FREE Full text] [doi: 10.2196/17757] [Medline: 33021487]
71. Victor SE, Klonsky ED. Validation of a brief version of the Difficulties in Emotion Regulation Scale (DERS-18) in five samples. J Psychopathol Behav Assess 2016 May 13;38(4):582-589. [doi: 10.1007/s10862-016-9547-9]
72. Schneider R, Long E, Arch J, Hankin B. The relationship between stressful events, emotion dysregulation, and anxiety symptoms among youth: longitudinal support for stress causation but not stress generation. Anxiety Stress Coping 2021 Mar;34(2):157-172. [doi: 10.1080/10615806.2020.1839730] [Medline: 33156724]
73. Gratz K, Roemer L. Multidimensional assessment of emotion regulation and dysregulation: development, factor structure, and initial validation of the difficulties in emotion regulation scale. J Psychopathol Behav Assess 2008 Oct 17;30(4):315 [FREE Full text] [doi: 10.1007/s10862-008-9102-4]
74. De Castella K, Platow M, Tamir M, Gross J. Beliefs about emotion: implications for avoidance-based emotion regulation and psychological health. Cogn Emot 2018 Jun;32(4):773-795. [doi: 10.1080/02699931.2017.1353485] [Medline: 28737108]
75. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986 Dec;51(6):1173-1182. [doi: 10.1037//0022-3514.51.6.1173] [Medline: 3806354]

Abbreviations

CEMS: Children's Emotional Management Scales
DERS: Difficulties in Emotion Regulation Scale
EMA: ecological momentary assessment
ERC: Emotion Regulation Checklist
ER: emotion regulation
mDES: Modified Differential Emotions Scale
SDQ: Strengths and Difficulties Questionnaire
TWEETS: Twente Engagement With eHealth Technologies Scale

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Protocol

Using Information and Communication Technologies to Engage Citizens in Health System Governance in Burkina Faso: Protocol for Action Research

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Abstract

Background: Health systems are complex systems involving a vast range of actors. In West Africa, they are often not accessible or responsive. Burkina Faso has widely expressed, in its public health policy, the need to improve both access to quality care and health system responsiveness. There is also a strong wish to give more voice to citizens. To support Burkinabè institutions in achieving these goals, we have developed an action research (AR) protocol.

Objective: This paper presents the protocol that will address citizens' participation in health policies and their empowerment through the expression of opinions, for accountability, as well as the strengthening of the health system using information and communication technologies (ICTs).

Methods: Our approach will consist of (1) enabling people to express their opinions on the health system by means of a toll-free (TF) service coupled with an interactive voice server (IVS); (2) building an information base with anonymous and reliable data; and (3) conducting information awareness-raising activities, including knowledge transfer (KT) and advocacy, social integration activities, development of OpenData platforms, and the capitalization and media coverage of governance issues. For this purpose, the AR project will be implemented in Burkina Faso. The design uses a concurrent mixed-methods approach. This AR project will evaluate the acceptability, process, effectiveness, and economic costs of the device's implementation. We will also analyze the potential for the data collected by the device to be used to improve practices.

Results: Data collection is in progress; the TF number was officially launched on July 1, 2020, and data collection is planned to continue throughout 2021. By using mixed methods, our AR will be approached from a variety of perspectives. Mixed methods will support us in combining the partial insights into sophisticated realities from qualitative inquiries with the data analyses produced by quantitative research.

Conclusions: This AR is expected to add knowledge on how to increase the empowerment of the population, especially the most vulnerable, to participate in democratic processes and enjoy and exercise their human rights. This protocol recommends implementing a low-cost, contextually adapted technology, associated with an evidence-based approach and carried out on a significant scale. The originality of this approach lies in the fact that it introduces a real AR dimension with local communities and nongovernmental organizations (NGOs), combined with an integrated strategy of KT and application throughout the project for all stakeholders.

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KEYWORDS

health governance; ICTs; citizen participation; responsiveness; social responsibility; Burkina Faso; technology platforms; democracy; health systems; equity; West Africa; public health; participation; health policy

Introduction

Health is at the heart of the Sustainable Development Goals (SDGs). Indeed, a healthy society is essential for economic development, and in turn, economic development is essential to improve population health. To achieve economic development and a healthy society, health systems must be more responsive to people's needs, as proposed by the World Health Organization (WHO) in 2000 [1,2]. WHO presents two main subdivisions of responsiveness: (1) respect for the person (dignity, confidentiality, autonomy of individuals and families regarding decisions related to their health) and (2) dignity for the patient (timeliness of care, access to social support networks during care, good quality of environment, choice of providers). For Mirzoev and Kane [3], this concept of responsiveness is complex and still underexplored [4,5]: "This perhaps explains [the] lack of comprehensive frameworks that go beyond the normative characteristics of responsiveness of health services and also justifies the examination of responsiveness as a distinct phenomenon" [3]. Successful responsiveness would be based on first clarifying people's expectations with a view to supporting health system actors' ability to respond appropriately to these expectations. This is an essential objective to achieve universal health coverage (UHC). Good governance with health system accountability is a critical component in UHC and quality of care [6]. Health system governance is a relatively modern concept that is not yet well assessed by research [4]. As a result, there is a lack of evidence on governance at the sub- and national levels. Nevertheless, by improving their governance, several low- and middle-income countries (LMICs) have made significant advances in ensuring access to quality health care compared to other states with similar wealth levels [7]. Despite the diversity of definitions of this concept, they all emphasize the importance of community participation and accountability [4,8]. Several studies have shown the important contribution of community participation to the success and sustainability of health programs and interventions [9,10]. It is considered an integral part of democracy and, as such, is recognized as an essential tool for health system governance [9]. However, beyond being a simple tool to improve governance, citizen participation is a fundamental right and an important objective to be pursued [11]. Unfortunately, in several sub-Saharan African countries, health systems are struggling to exploit the full potential of community participation [12], while community participation and accountability can be improved by providing effective channels for citizens to participate in decision making [13]. Indeed, putting in place institutional procedures for receiving complaints from users and health workers and disseminating basic knowledge about patients' rights are two ways to improve governance and strengthen the health system [14].

Giving users a voice would promote health workers' accountability to patients in order to positively influence their behavior and thereby improve care quality [15,16]. However, health workers' voices must also be included because of their involvement in the system [17,18]. Their job satisfaction is an essential parameter that influences productivity as well as the quality of work [19,20]. Job satisfaction has a significant impact on quality, efficiency, and commitment to work [21] and, at the same time, on health care costs [22]. It is crucial that workers' voices be heard, both to gain a deeper understanding of the health care system's dysfunctions and to better assess the potential impact on patient satisfaction [23].

Various methods exist for collecting complaints, each with its own limitations: suggestion boxes, which require knowing how to write; satisfaction surveys, which are sporadic and not proactive; recourse to justice, which is too often administratively cumbersome and costly; or complaint services, which raise issues of discretion with users and health workers [24]. Too many people are afraid of speaking up or complaining or are deterred by the lack of reaction to problems on the part of the system actors and the government [6].

Information and communication technologies (ICTs), such as mobile phones, offer new opportunities in the health field. In fact, recent years have seen a drive among international and local agencies, governments, and institutions to develop projects using ICTs. Access to mobile technology has become more democratic [25], such that the population can now become actors in information production [26]. Mobile health (mHealth) has the potential to support health systems [27] and help fill persistent gaps by facilitating communication and information exchange [28]. In Africa, there are many such interventions because of the approach's many advantages (access in hostile areas, high mobile phone penetration rate, lower costs, ease of use, etc) [29,30]. Many interventions involve using the short message service (SMS) [31,32] or voice messages via toll-free (TF) numbers [33,34] for purposes of information sharing or prevention.

In Burkina Faso, in 2014 and 2015, a pilot action research (AR) project to evaluate the technical, social, and instrumental relevance of a TF call service with an interactive voice server (IVS) was tested in 11 sectors in Ouagadougou to give the population and health workers a voice to express their opinions on their health system (Multimedia Appendix 1). That AR project showed that a TF number coupled with an IVS is a solution suited to the Burkinabè context for the free expression of views on the health system [35]. Our aim now is to scale up this AR project over a wider region than the pilot project, particularly in rural, semiurban, and urban areas. This will make it possible to compare results according to residential environment and sociological conditions (cultural differences between regions).

The AR protocol for setting up a TF-IVS presented here proposes to deploy a technological platform and strengthen the capacities of local implementing partners in Burkina Faso to improve citizen engagement and make health systems more responsive to their needs.

Methods

AR Approach

We have chosen an AR approach. The researchers involved have perfect mastery of this concept, which is adapted to both the country's context and the problem [36]. The AR approach will make it possible to continuously adapt the project and ensure maximum effectiveness for better citizen participation and consideration of users' needs in health decision making. AR is "a participatory democratic process that involves the development of practical knowledge of interest to the population, rooted in a participatory worldview that emerges at this particular historical period" [37].

Using an AR approach, which enables rapid learning, this project (named TechnOlogie PartIcipation Citoyenne en santé [TOPICs]) will study the acceptability, process, effectiveness, and financial cost of the digital device for citizen participation in health in urban and rural areas. It will also analyze the potential for using the evidence produced—in other words, the potential of the data collected by the device (TF-IVS) to improve practices. Finally, this research will draw lessons from the AR implementation to facilitate a possible national scale-up in the event of a successful outcome.

General Objectives and Research Questions

The objective of this project is to evaluate, in Burkina Faso, the large-scale implementation and acceptability of a technological system for collecting people's opinions on the health system, with a view to improving health governance and informing citizens about their health-related rights and duties.

The research questions (RQs) are as follows:

RQ1. What are the challenges involved in setting up, operating on a large scale, and using the digital device to gather the opinions of users and health workers about the Burkinabè health system?

RQ2. What factors internal or external to the AR project influence acceptance of the digital device to gather the opinions of users and health workers about the Burkinabè health system?

RQ3. What factors internal or external to the AR project influence the decision making of the actors or decision-making bodies based on the results of the digital device?

RQ4. How effective is the digital device in gathering the opinions of users and health workers about the Burkinabè health system?

RQ5. What are the economic costs of setting up and operating a system to collect the opinions of users and health workers on the Burkinabè health system?

RQ6. What are the effects of the knowledge transfer (KT) strategy and process on decision making?

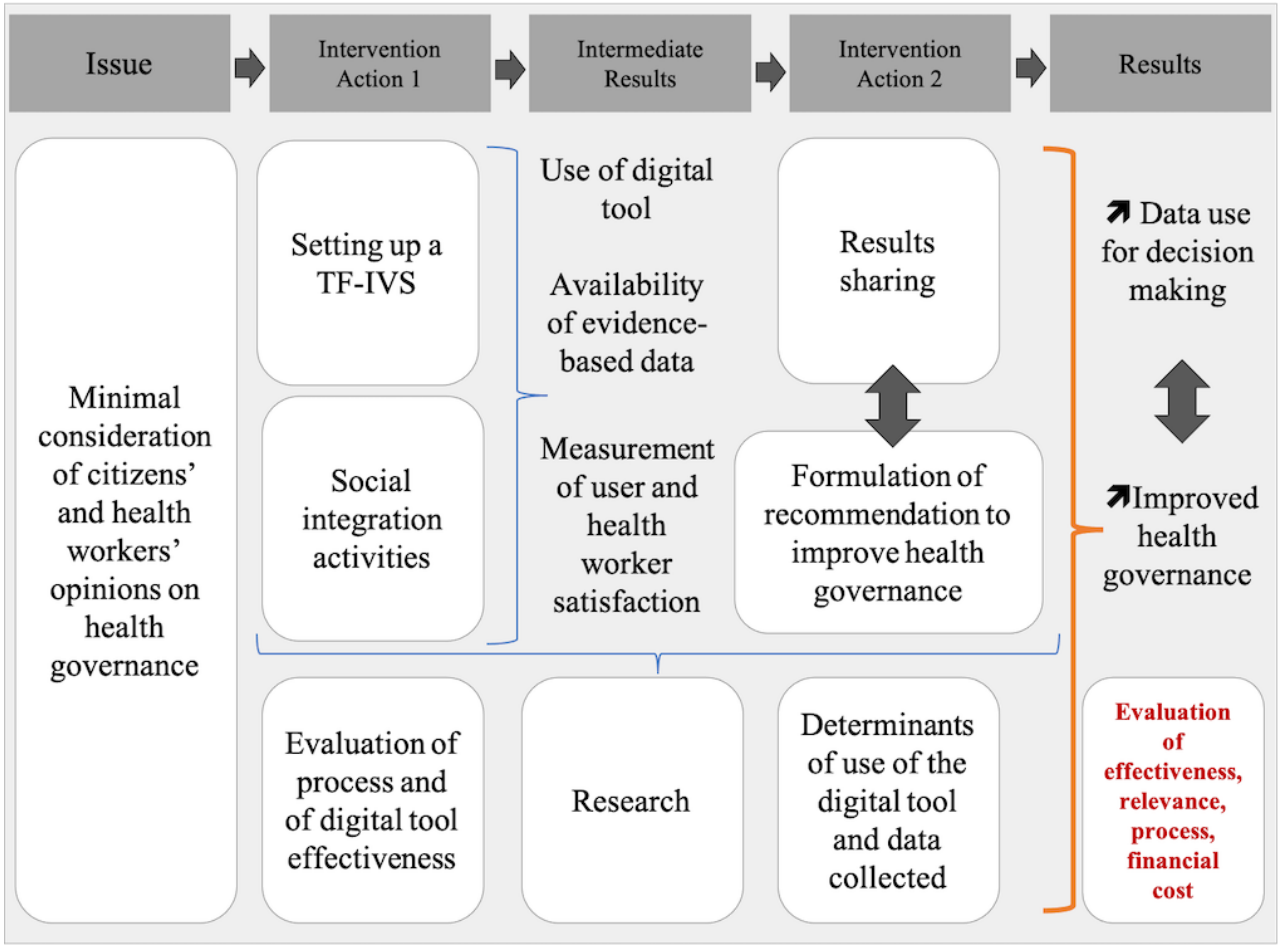
Evaluability Assessment

We first focused on defining needs and challenges, as well as on discussions with structures already carrying out similar experiences (to avoid duplication and ensure our process would be complementary to theirs).

We met with authorities and stakeholders from the central government, the region, and localities in the targeted areas. Then we collected information and made an inventory of the existing situation. This was followed by a process of validating our information and strategies. This work with stakeholders established the beginning of project ownership, a shared understanding of the implementation strategies, and mutual agreement on expected responsibilities and results.

Finally, we defined the geographic area to be covered by the AR project based on the possibility of applying our AR project both in urban areas (more suited to ICT implementation) and in rural areas in order to verify its feasibility. The issues related to project implementation in both rural and urban areas were among the main challenges considered in this preparation phase. Figure 1 presents the theory of change for the AR project.

Figure 1. Theory of change. TF-IVS: toll-free service coupled with an interactive voice server.



Types of Evaluation

Different types of evaluations will be carried out:

- Assessment of the relevance (instrumental, technical, contextual; RQ1, RQ2, and RQ4) of the digital device for expressing the opinions of the population and health workers about the Burkinabè health system
- Process evaluation to assess the factors (related to technology, context, support tools such as communication or training, etc) influencing the digital device's implementation (RQ1-RQ3 and RQ6)
- Prospective cost analysis (RQ1-RQ5) to estimate the full economic costs associated with the AR project
- Evaluation of the digital device's effectiveness for producing simple and evidence-based results to influence decision making needed to adapt the health system to the needs of the population and of health workers (RQ1-RQ6)

This AR project is based on evidence gathered through both a rigorous literature search and a previous pilot experiment that identified various subjects on which health center users and health professionals wanted to give their opinions on the health system [35].

Furthermore, because health interventions are strongly influenced by their context, this intervention was carefully conceptualized in relation to the Burkinabè situation [38]. As indicated by Craig et al [38], the following dimensions were taken into account: (1) the contexts in which the AR is intended to be applied, (2) the ways in which causal mechanisms and modes of delivery are context dependent, and (3) the dimensions of the context and how they are defined. As such, the Template for Intervention Description and Replication (TIDieR) for population health and policy (PHP) interventions will be helpful to report our AR project [39].

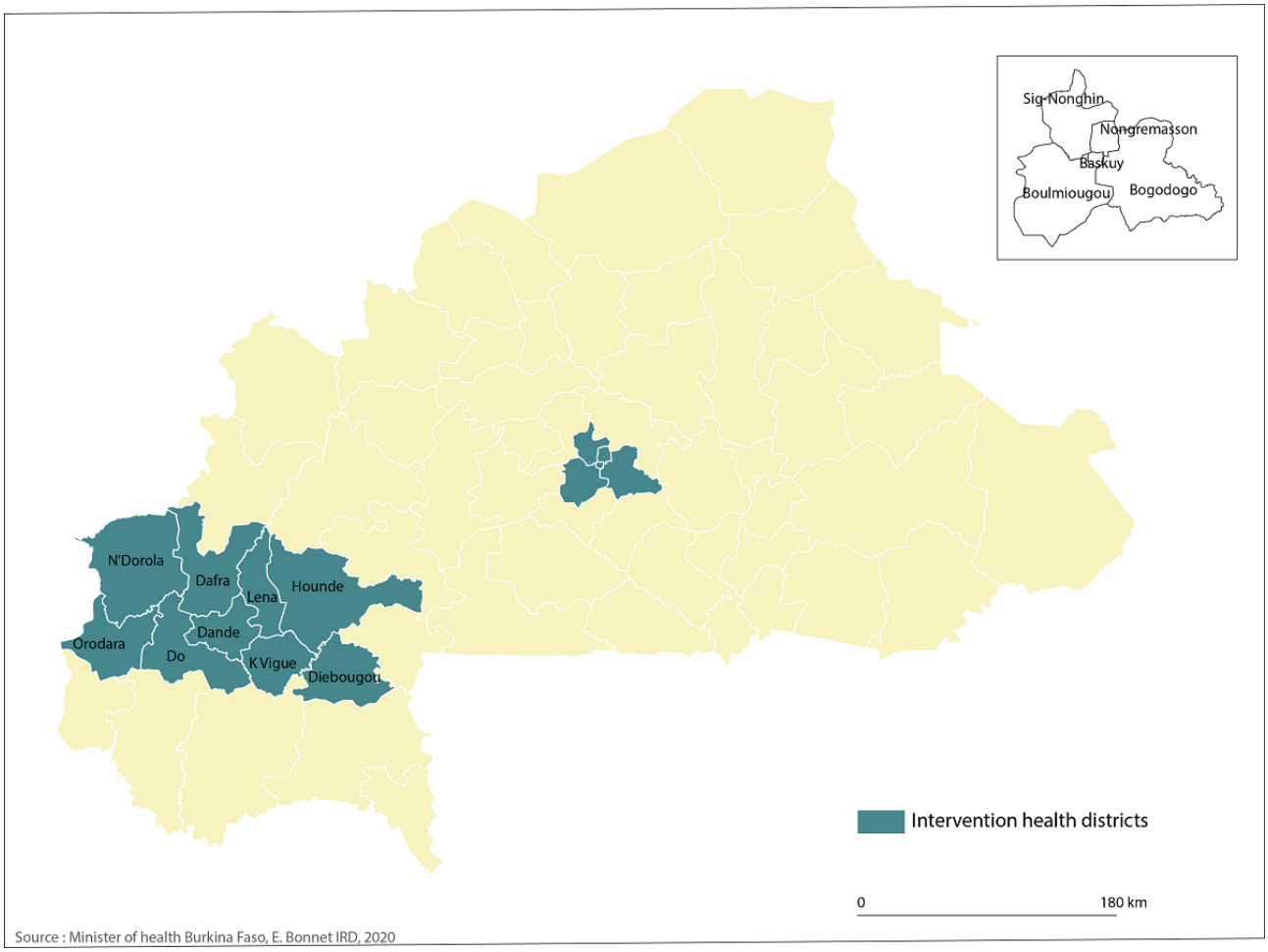
A group of four partners will implement this AR project: the International Health Unit (USI) of the University of Montreal, Canada; the Institut de recherche pour le développement (IRD), France; Heidelberg University, Germany; and the nongovernmental organization (NGO) Action-Gouvernance-Interaction-Renforcement, groupe de Santé en Développement (AGIR-SD), Burkina Faso. The AGIR-SD will conduct activities with the assistance of the IRD and University of Montreal researchers and the USI. The AGIR-SD is also involved in a teamwork process with a civil society organization (CSO) to raise public awareness and to organize information activities on the existence of the TF-IVS. Collaboration will be established between the German NGO Hilfe zur Selbsthilfe (HELP) and the AGIR-SD for coverage of the AR zones.

Site Selection

The TF-IVS will be implemented on a larger scale than the pilot project developed in Burkina Faso in 2014 [35], particularly in rural, semiurban, and urban areas, in order to be able to compare results according to place of residence and contextual realities, while taking into account the project's resources.

Of the three regions targeted by the AR project, two include the country's two largest cities (Ouagadougou and Bobo Dioulasso); these have a predominantly urban population. Diébougou is a rural area, which represents a challenge to test technological AR. The TF-IVS project will cover 14 health districts located in 3 regions (see Figure 2). It should be noted that in rural areas, just over half of the population (55.8%) owns a mobile phone, whereas in urban areas, almost 9 of 10 people (87.0%) own a mobile phone [40].

Figure 2. Health districts. IRD: Institut de recherche pour le développement.



Study Participants

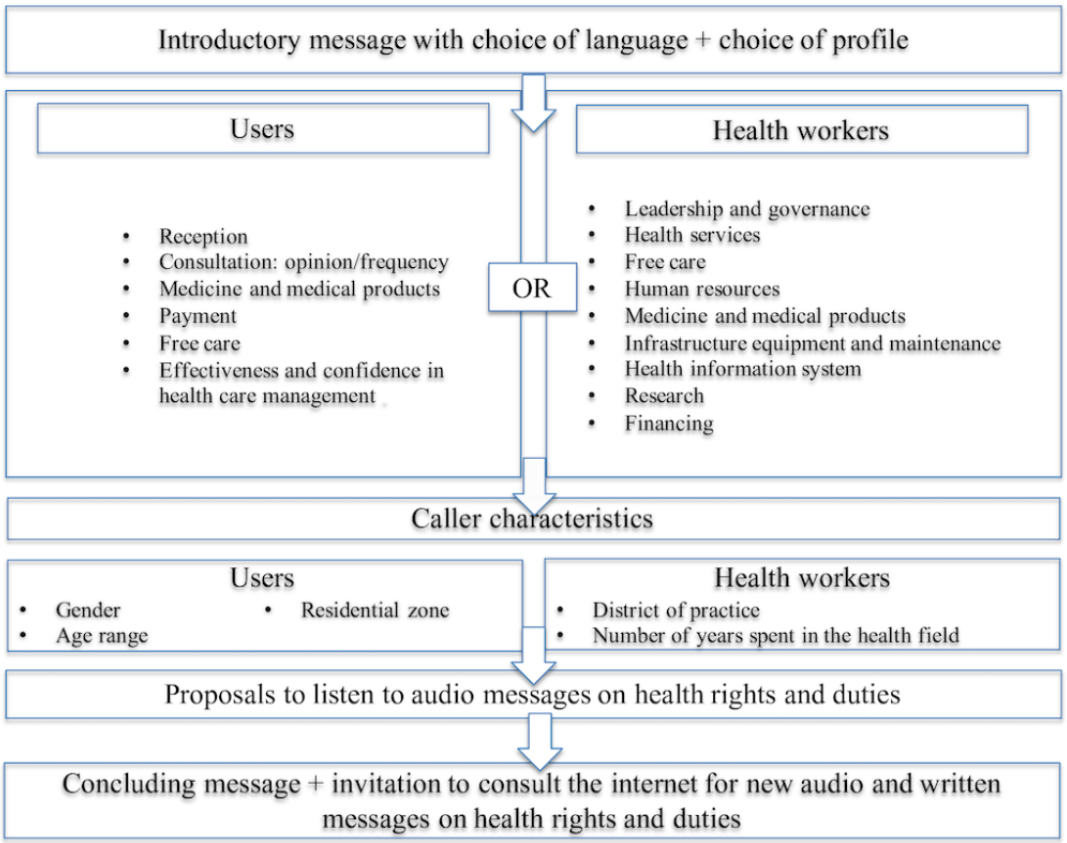
The direct beneficiaries are the users of health services in the health regions of the Center, the Hauts bassins, and the province of Bougouriba and, more particularly, women, girls, and the poor, as well as health workers and community relays. Secondary beneficiaries are the entire population; health system managers; decision makers; and political, administrative, customary, religious, and CSOs.

Study Setting and Population

In Burkina Faso, three operators share the mobile telephony market: Onatel, Telecel, and Orange. The mobile phone penetration rate was 95.95% in 2019 (Regulatory Authority for Electronic Communications and Posts [RAECP]) [41]. Mobile phone ownership rates are 79.4% for men and 51.7% for women. Almost two-thirds (64.3%) of Burkinabè aged 15 years or over owned a mobile phone in 2014. It is also known that half of the poorest 20% of individuals have a functional mobile phone, as do 82.3% of the richest 20% of individuals [40]. At the national level, 87.4% of individuals who did not own a phone but had used one in the past 30 days used the phone of a household member, and 12.4% used the phone of a non-household member. This access to phones is an opportunity for the initiative to succeed.

This health AR project will develop a TF number, free of charge, reachable from any landline or mobile phone, anonymous and available 24 hours a day, 7 days a week, in any of the 9 main languages spoken in the areas targeted by the project. Phone users will use their phone keypad to respond to questions. Service users and health workers will answer two different questionnaires designed for their group. Figure 3 outlines the various phases of the call and the separate themes covered for service users and health workers.

Figure 3. Diagram of surveys used.



While maintaining anonymity for ethical reasons, the system will request elements characterizing the caller, such as the city in which the health center is located, the health district in which the health worker is practicing, the sex of the caller, and their age group. The data collected will be stored on a local server secure and replicated in Burkina Faso. The data will be instantly transferred to the database accessible via the internet for collection.

Thus, persons calling the TF number will be able to answer the IVS questionnaire (Figure 3) and then will get an opportunity, at the end of the satisfaction measurement questionnaire, to receive information about their health-related rights and duties. The information about health rights that will be disseminated will have been validated by the project's technical committee.

A technological platform will be developed and managed by AfricaSys, which supported the pilot TF number project tested in 2015 [35] by the NGO AGIR-SD. The technological platform (Figure 4) will consist of a combination of the TF number, the IVS, the database, a computer, and a website (where the database is located). Figure 5 summarizes the design, process, and targets of the AR project.

The required infrastructure is based on continuous electrical, telephone, and internet access. A power generator is installed in Ouagadougou, in a facility belonging to the Institut de recherche au développement, to cope with frequent power and internet interruptions.

Support activities will be carried out. Communication activities will focus mainly on media and nonmedia communication campaigns in French and local languages. These will be implemented throughout the project to make known the device being made available to the population and health workers to express their opinions. Different communication channels will be used to enable the project to effectively achieve its communication objectives. This media campaign will be reinforced by social integration activities in the form of information and awareness-raising sessions in the community (talk-debate, discussion groups, sketches, etc). These will be aimed at encouraging people to use the digital devices available. Through a participatory approach, the project will involve several stakeholders and implement four packages of community activities:

- Contact with local, religious, and customary authorities for the project presentation and the negotiation of their adoption
- Meetings with different associations with common characteristics (people with disabilities, older and young people, women, craftspersons)
- Public awareness sessions for the general public
- Interactive radio broadcasts on topics related to rights and duties to health with the testimony of the population and based on data collected on satisfaction by the TF-IVS

Figure 4. TF-IVS technological platform. ActiveMQ is free software implementing the JMS specification. C++ is a computer programming language. MariaDB is free relational database management software. ReactJS is a computer programming language of the graphical user interface (web). SpringBoot is a set of libraries for the Java computer programming language. JMS: Java Message Service; JSON: (IT) format for structured data exchange; KPI: key performance indicator; REST API: Representational State Transfer Application Programming Interface; TF-IVS: toll-free service coupled with an interactive voice server.

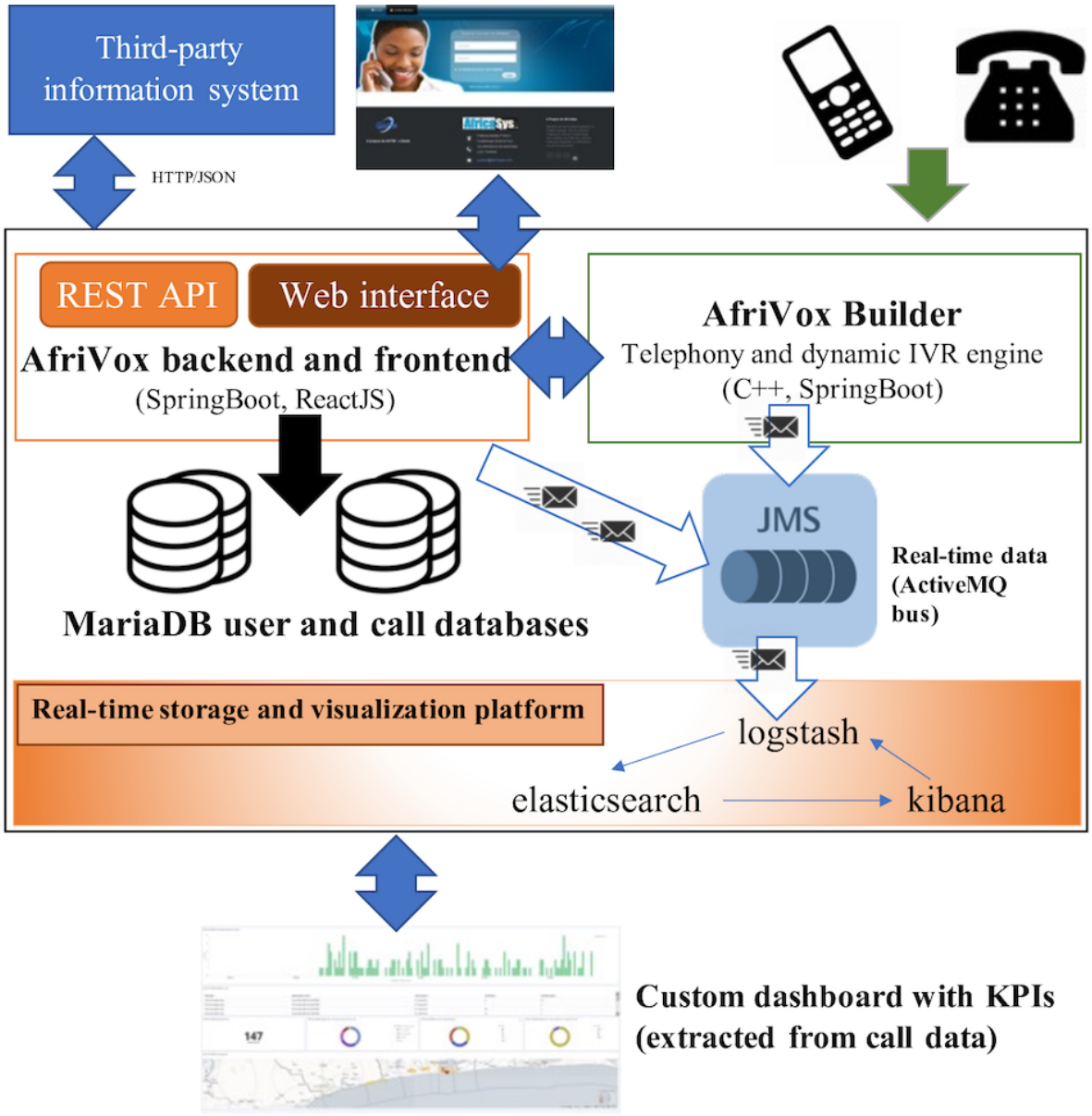
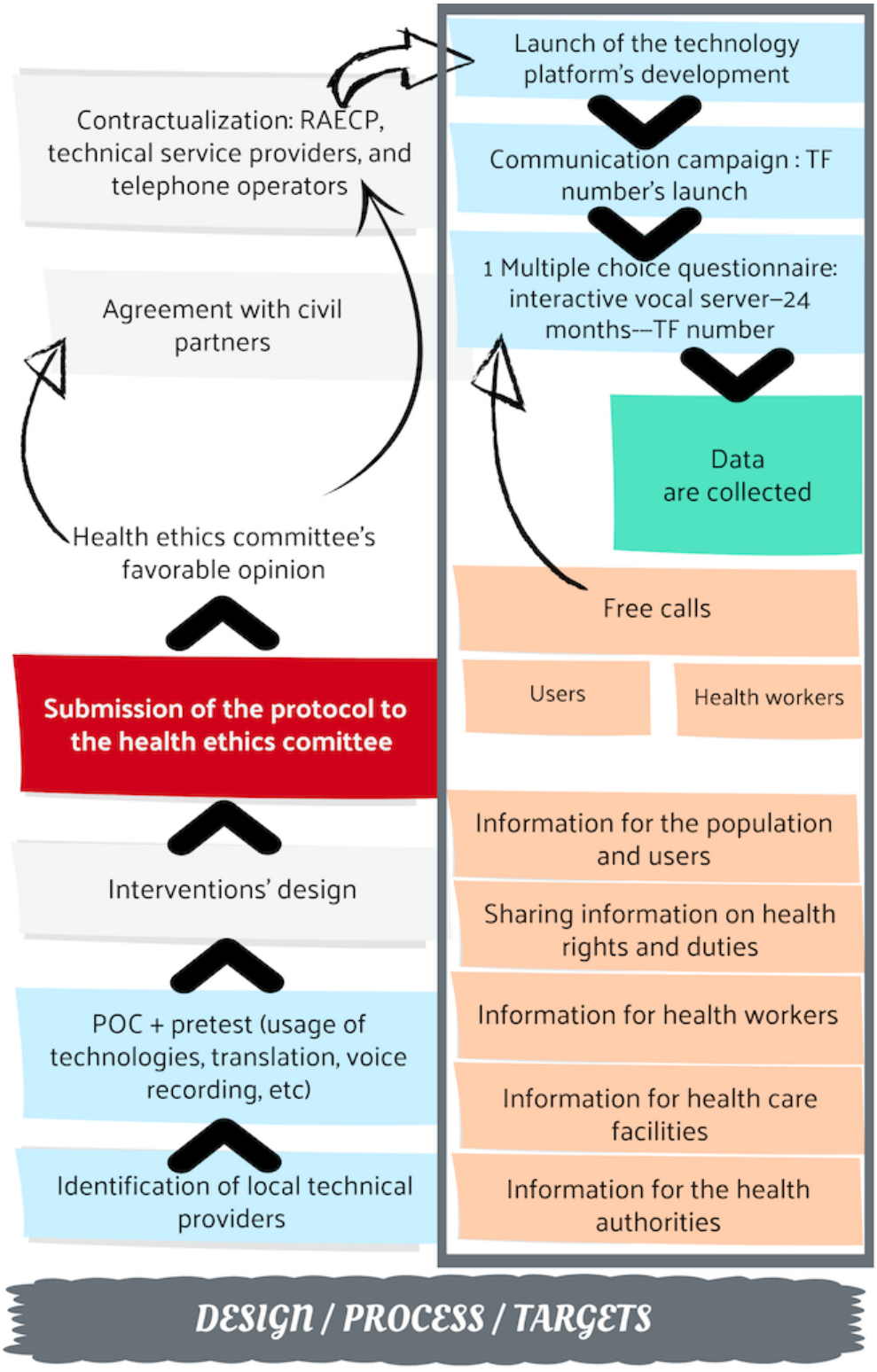


Figure 5. Design process and targets of the AR project. AR: action research; POC: proof of concept; RAECP: Regulatory Authority for Electronic Communications and Posts; TF: toll free.



Target Size

The AR project will consider the population of the three areas targeted as well as the associated health workers. The total population covered in the 14 health districts covered by the TF-IVS is presented in Table 1 [42].

Table 2 presents the situation (in 2018) of the public and private health infrastructures and the health worker population in the TF-IVS coverage areas [43]. The following are considered health workers: specialist physicians, general physicians, pharmacists, dental surgeons, specialized nurses, biology laboratory technicians, state-registered nurses, registered nurses, state midwives, and state medical officers [44].

Table 1. Population covered by the AR[a].

Location of the regional health department	Women (n)	Men (n)	Total (n)
Center	1,476,075	1,490,232	2,966,307
Hauts bassins	1,126,020	1,101,257	2,227,277
Diébougou	77,048	71,222	148,270
Total	2,679,143	2,662,711	5,341,854

[a]AR: action research.

Table 2. Public and private health infrastructure and health worker population in the AR[a] areas in 2018.

Location of the regional health department	Public health infrastructure (n)	Private health infrastructure (n)	Health worker population (n)
Center	162	135	3515
Hauts bassins	208	24	1847
Diébougou	25	0	159

[a]AR: action research.

Data Collection and Analysis

To carry out the different types of evaluations proposed before, we will adopt both a mixed-methods [45] and a multimethod approach.

Evaluation of the Implementation, Operation, Use, Acceptance, and Efficiency of the Digital Device (RQ1-RQ4)

We will approach these different evaluations from diverse angles, each of which is explained next, first from a quantitative and then from a qualitative standpoint. This subsection will address RQ1-RQ4 cited before.

A *quantitative approach* will be adopted to assess the device's use and establish a typology of users. This will make it possible to analyze the evolution of the device's use and the progression of user satisfaction (RQ1, RQ2, and RQ4).

Study Population and Sampling

The study population consists of all users of the digital device implemented. The data collected over the course of the AR project through the digital device will constitute data sources for quantitative analysis (usage evaluation, effectiveness evaluation, number of calls, number of responses from the digital device after each communication, etc). Thus, we will look at the data in the IVS dashboard. Spatial analyses will complement this quantitative component to assess whether there are geographical inequalities in the satisfaction with and use of the digital device. These analyses will also make it possible to evaluate the use of the TF number by location (geographical zone or health district). All the data will be organized in a geographic information system (GIS) using the QGIS software (Open Source Geospatial Foundation) program.

Collection Instruments

The quantitative data will be derived from the satisfaction questionnaire administered to people calling the IVS through the digital device set up by the AR project (see before). The questionnaire (Multimedia Appendix 2) has been constructed based on a review of the scientific literature and survey tools deployed to measure health system quality, services and care, perceived health status, and care seeking (use of and access to services). Several steps regarding the validation of the testing instrument were necessary. They include (1) validation of the questionnaires and messages on health rights and duties by the project team, the steering committee, and the communication unit of the Ministry of Health; (2) translation of the questionnaires and messages and validation of the translations (in terms of form and content); (3) validation of the tools by the ethics committee included in the research protocol; and (4) digitization of the tools in the IVS and testing the tool's functionality (verification of the coherence between the questions and the question jumps, and the data's synchronization) by the project team and the technical partner AfricaSys.

Data Analysis

Quantitative data will be subject to automated descriptive analysis and disaggregated by sociodemographic characteristics (gender, age groups, place of residence) and types of health facilities involved. The variables of interest will be those asking for the user's opinion on the user's care. We will conduct a descriptive evaluation to identify trends in caller characteristics. For all analyses, we plan to use R (Lucent Technologies) [46], an open source software package for computing and statistical graphs.

All data will be mapped at either the provincial level (health service users) or the health district level (health personnel). This will make it possible to identify possible territorial inequalities. Spatiotemporal statistics will be produced (Kulldorff spatial scan method [47,48]) to assess potential geographical fluctuations in time and territory (12 months) of calls and satisfaction variables.

Likewise, an analogous analysis will be carried out to identify associations between the use of digital devices by the population and actions to encourage their use. Indeed, we plan to document all communication and outreach activities daily throughout the implementation. This information will be used to measure the relationship between the number of communication campaigns,

their intensity, their type, and the number of calls. The idea is also to measure the duration of the effect of the campaigns on the number of calls, that is, we will calculate how long after the last campaign the number of calls drops.

This analysis will be further developed through the qualitative component.

Demographic data (age group, gender, municipalities, type of health facility concerned) will provide details on the characteristics of individuals who have used the digital device. Comparing these data with those of the general population census of municipalities covered by the AR will provide an indication of profiles of users of the digital device. The numbers of proper completions of the questionnaire via the TF-IVS will be interpreted as an indicator to measure the ease of use of these digital devices. Nevertheless, selection biases may persist despite the cultural consideration and adaptation of the communication strategy in the field and will be considered in the data analysis.

A *qualitative approach* will also be adopted to determine the conditions for success or failure of the AR project as a whole and of the digital device and the various support activities specifically [49]. In particular, we will seek to identify factors related to the use of the digital device by the population, on the one hand, and those associated with the use of the project results by social and health authorities, on the other (RQ2 and RQ3). This will provide an understanding of the technical challenges of operating and using the digital device and using the results produced (RQ1). Similarly, we will conduct an evaluation of the project's effectiveness as perceived by the various stakeholders (RQ4).

Acceptability Evaluation (RQ1-RQ3)

The success of an AR project's implementation depends on its acceptability, both for the implementing actors (patients, researchers, health professionals) and for the beneficiaries (patients or health professionals) [50]. Although acceptability is a necessary but not sufficient condition for the effectiveness of an AR project [51], we believe it is crucial to study it, given the exploratory nature of the research and the technological innovation of this AR project. We have adapted the conceptual framework proposed by Sekhon et al [52], which characterizes acceptability as a multidimensional construct that illustrates the degree to which people who give or obtain a health care intervention consider it suitable, based on planned or experienced psychological and emotional responses to the intervention. The seven dimensions of acceptability proposed in this framework will be measured. These are (1) the emotional attitude of the targets (users and health workers) toward the AR, (2) the coherence/understanding of the AR, (3) the opportunity cost of participating in the AR, (4) the perceived effectiveness of the AR, (5) self-efficacy, (6) the perceived amount of effort required to take part in the AR, and (7) the degree to which the AR is a good fit with an individual's value system.

The implementation study will be based on the Consolidated Framework for Implementation Research (CFIR; RQ1-RQ4) [53]. This conceptual framework recommends basing the study of factors influencing the implementation on five main dimensions: (1) the characteristics of the AR, (2) the external context of the health facilities, (3) the internal structure of the health facilities, (4) the characteristics of individuals, and (5) the process of implementing the AR project. Each of these dimensions includes useful constructs, chosen based on about 20 other frameworks. Given the exploratory nature of the AR project, we will not limit ourselves to these constructs during data collection and will endeavor to capture all additional information that may be useful to understand its implementation.

Sampling Population and Collection Instruments

Concerning RQ1-RQ4, three main targets will be of interest. These are:

- Target 1: project team members (04)—implementers and monitoring staff
- Target 2: Sociohealth authorities (regional health directorate [RHD], district executive team [DET], management committees, local elected officials)—key informants with relevant ministries' representatives
- Target 3: community members (CSOs, health committees, health service users, health workers, etc)

We will make a purposive selection of the various targets likely to provide the best information about the AR project, implementation challenges, acceptability, use of devices, and application of results. Purposive sampling is used to select units that can provide the most insight into the issues that are important for the evaluation [54]. This type of sampling enables analytic generalizations (predictions of the probable portability of results grounded in a theoretical investigation of the effect of context and the factors that produce the direct effects). Criteria used for sampling will incorporate criteria for *inclusion* in a specific category as cited before, as opposed to cases that are *external* to a particular criterion [55]. In this way, we will ensure maximum variation within the targets (selection according to age, gender, participation or not in the AR, beneficiaries or not of KT training, etc). Particular attention will be paid to collecting the needs of specific populations, such as women, adolescents, and vulnerable persons.

The objective of theoretical saturation is to provide maximum detail about the AR project. It is thus a matter of selecting individuals who will ensure that all aspects of the AR project are included in the review to the point where no further substantive new knowledge is collected [56].

Private face-to-face interviews will be used to collect data. These will be conducted in French using the interview guide (Multimedia Appendix 3) developed based on the various conceptual frameworks cited before.

Data Analysis

We will use the procedure for analyzing qualitative data in health research developed by Gale et al [57]. Thus, all interviews will be recorded after obtaining the interviewees' consent and then fully transcribed. The transcribed data will be coded using NVivo 12 software (QSR International) and then analyzed. Through content analysis, we will seek to understand general trends and particularities as well as recurrences and discrepancies by focusing on comparisons between stakeholder groups.

We will also undertake reflective analysis of the AR project to document successful practices and key implementation steps. This will take the form of workshops with the stakeholders to ask about their practices and the adaptations that enabled them to optimize the project implementation.

Economic Analysis (RQ5)

We will conduct a prospective cost analysis to assess the full economic costs associated with the AR project, collecting information as the project is being rolled out. Our aim will be to capture the full value of all resources used by any of the parties involved in the design and implementation of a given activity related to the AR. We will adopt a health system perspective, accounting for all costs incurred, whether for equipment, personnel mobilized, or activities.

Sampling and Collection Instruments

To trace all costs pertaining to the design and implementation of the AR project, we will adopt an activity-based costing (ABC) approach. Accordingly, we will start by mapping all microlevel activities related to the design and implementation of the initiative and then trace all resources consumed by these activities. We will supplement these first two steps by reviewing the complete documentation of the AR project and engaging in repeated exchanges with key stakeholders.

To attribute a value to either single resources (when possible) or complete activities (should the former not be possible), we will extract relevant cost information from the financial statements of the implementing partners. To estimate resource consumption for activities that cannot be traced in financial statements, we will conduct key informant interviews with implementation partners. We will obtain unit costs for valuation from existing costing sources in Burkina and, when necessary, complement that information with other information reported by key informants during interviews.

Data Analysis

To estimate the full economic cost of the AR project, we will multiply the resources consumed by the related unit costs and aggregate cost information across sources. In addition, to produce an accurate estimate of which activities and cost categories absorb the highest proportion of costs, we will disaggregate the analysis into both activity (eg, training, supervision) and cost categories (eg, mobile phone charges, personnel, transport). Our analysis will differentiate start-up costs from implementation costs.

KT Analysis (RQ6)

We will apply an integrated KT and knowledge translation strategy throughout the AR project. To measure the effects and processes of the KT approach to decision making, a mixed-methods approach (quantitative and qualitative) will also be used.

As a first step, to measure the overall satisfaction of participants in training and deliberative workshops, their appreciation of the content, and their suggestions for improvement [58] and to evaluate their intention to use the knowledge, we will undertake a *quantitative analysis*.

Study Population and Sampling

For the KT evaluation, the study population will comprise participants both in KT training sessions, including project team members (implementers and monitoring staff), and in deliberative workshops (sociohealth authorities—RHD, DET, management committees, local elected officials) and key informants from relevant ministries.

Collection Instruments

Data will be collected at the end of each training session and workshop and again 3 months later. Because of the difficulty of obtaining objective measures of change through observable behaviors, we will use indirect measures based on social cognition theories. The theory of planned behavior (TPB) measures the intention to use the information to change practices [59-61]. More specifically, the TPB states that the intention to engage in new behavior is predicted by the attitude toward the behavior to be adopted, the subjective social norm surrounding this behavior change, and the perceived control over the change to be made [62]. A reliable, innovative tool (α from 0.69 to 0.89 and G from 0.5 to 0.9) with 15 questions will be adapted to measure the participants' intention to use the content presented [63]. It should be noted that this is essentially the same tool that will be used to evaluate training and deliberative workshops (see Multimedia Appendix 4).

Data Analysis

Data from the intent survey will be treated as continuous variables, and changes between different measurement times will be examined using a repeated-measures analysis of variance at the time variable. We will use the process tracing method [64] to explore information from the analysis of the quantitative questionnaires used to develop an initial portrait of potential users' attitudes toward the research and their intention to use the items discussed in a deliberative workshop. This method will allow us to combine quantitative results with qualitative data from the interviews.

In addition to these data to be collected, it is essential to assess the use of knowledge for behavior change (activities carried out, decisions taken and implemented; RQ6); for this purpose, we will also perform a *qualitative analysis*.

Sampling Population and Collection Instruments

The KT assessment will also be based on qualitative interviews (see the interview guide in Multimedia Appendix 5). Three months after the activities, a semistructured interview grid will cover the important points for the evaluation, while leaving the necessary scope for further study of relevant elements that arise during the interviews [54]. The dimensions addressed in these interviews will allow us to complete and understand in greater depth the information collected using quantitative tools (reactions, attitudes, and intention to use). Results of the qualitative and quantitative analyses will be triangulated using a triangulation-convergence approach [45], in which the quantitative and qualitative components identify the same object in parallel, before being combined at the time of interpretation to increase the richness of the conclusions and contrast the information from complementary analytical angles.

In addition to formal interviews, we will also use qualitative data from informal interviews with different stakeholders, participant observations during the workshops, and activity reports (technical committee meetings, steering committee meetings, KT workshops, etc). These additional data will be used mainly to assess the impact of the KT strategy and data-sharing activities on the use of results for decision making by health and social authorities.

Qualitative Data Analysis

The qualitative material will be subjected to an iterative [56,65] thematic examination. The frequency of use and the nature of the knowledge used will be studied applying descriptive analyses, and analyses of variance will be used for comparative investigation of research use by demographic variables (user type, workplace, etc). Exploratory factor analysis will identify the internal structure of factors and their equivalence for respondents in various categories. The predictive power of these factors in knowledge use will then be examined by multiple regression.

Communication Campaigns to Publicize the TF Number's Evaluation

Study Population and Sampling

For the campaign's evaluation, the study population will be composed of sociohealth authorities (RHD, DET, management committees, local elected officials—critical informants with relevant ministries' representatives) and community members (CSOs, health committees, health service users, health workers, etc).

Collection Instruments

Data will be collected at the end of each restitution session, which will be organized. The quantitative data will be derived from a questionnaire. The survey will measure the dimensions of interest, originality, visual appeal, instructive, and memorability of the campaigns.

Data Analysis

Quantitative data will be subject to automated descriptive analysis and disaggregated by sociodemographic characteristics (gender, groups, place of residence) and types of stakeholders involved (policymakers/CSO members/health center users). The variables of interest will be those asking for the stakeholders' opinions on the effectiveness of the communication campaign to publicize the TF number. For all analyses, we plan to use R or computing and statistical graphs.

An even more in-depth evaluation of the effect of the communication campaigns on the use of the TF number (also through community work to raise awareness about health rights and duties) could be carried out by the project's donor, World Affairs Canada, during its final evaluation.

Patient and Public Involvement

This study protocol emerged during a series of meetings with authorities and stakeholders from the central government, the region, and areas in the targeted areas regarding their health and health care needs. This project is aimed at the population and health workers; they were indirectly involved in this study's design. This project is based on evidence gathered through both a rigorous literature search and a previous pilot experiment in Burkina Faso that identified various subjects on which health center users and health professionals wanted to give their opinions on the health system. For the evaluation of the implementation, operation, use, acceptance, and efficiency of the digital device, the persons involved will mainly be the project team members, the sociohealth authorities, and community members. Finally, to maximize collaboration and to ensure that knowledge users are invested in using the study findings, a KT approach will be embedded throughout this project. Those who will benefit will be participants both in KT training sessions, including project team members, and in deliberative workshops and key informants from relevant ministries.

Results

Data collection is in progress, the TF number was officially launched on July 1, 2020, and data collection is planned to continue throughout 2021. By using mixed methods, our AR will be approached from a variety of perspectives. Mixed methods will support us in combining the partial insights into sophisticated realities from qualitative inquiries with the data analyses produced by quantitative research.

Data Dissemination

The data collected through the TF-IVS will be analyzed regularly, and the results will be disseminated on an ongoing basis to provide users of the health system and health authorities at all levels of the system with evidence to improve decision making. This sharing of results will be done through regular feedback to administrative personnel, health authorities, and CSOs. In addition to the activities planned in the KT strategy (as described in the Data Collection and Analysis section), the data-sharing strategy is defined as follows:

- An open data platform will be developed. It will be interoperable with the District Health Information System 2 (DHIS-2) of the National Health Information System (NHIS) to integrate the essential indicators. Presently, there are no secure servers in Burkina Faso capable of hosting 24 hours a day, 7 days a week, with optimal reliability the data that will be generated. Thus, initially, the data will be sent to France (OVH Roubaix), but a replication of the database will be set up in Burkina Faso. However, Burkina Faso's health ministry and its health information systems services are currently building a data center to host all the country's health data. Once the health ministry's data center is accessible, the project's data hosting will be migrated to the ministry's system. An automated information-sharing module will reinforce this approach for members of the project's technical and steering committees and other key stakeholders. The results will also be posted to the TOPICs project web portal, at which time they will be viewable by anyone in the population.
- A documentary film will be produced at the end of the project on the issues of governance and access to quality care for the most vulnerable. This film will be shared with

the population, public decision makers, and other stakeholders.
- Reports on results, collection strategies, and means of expression will be prepared based on each of the technology assessments deployed. A capitalization report based on the evaluation reports will be prepared for the dissemination and popularization of the project results. This report will be made available to international, national, regional, and local institutions (policymakers, decision makers, CSOs, NGOs, associations, researchers, ICT/equality between women and men [EWM] experts).

Ethical Considerations

Ethical approval was obtained from the Institutional Health Research Ethics Committee (IRSS) on September 24, 2019. The protocol research project registration number is 23–2019/CEIRES.

The use of the TF number will be free and voluntary. No personal information will be compiled from it. In this way, the data collected will be anonymous and kept confidential. The telephone operators who route the calls to the platform have contractually agreed to respect the confidentiality of the data and metadata of the calls. The software publisher has also contractually committed not to monitor or use identification data. Number capture, even if partial, was activated to identify the source telephone operators and quantify the share of each in terms of call flow (an important metric for the project). Finally, the software publisher has implemented additional security mechanisms for accessing and using the data with (1) secure individual access via a virtual private network (VPN), (2) a connection via a login and password to access the data, and (3) the implementation of a mechanism that allows, via pseudo-anonymization based on the SHA-256 hash algorithm, to transform each actual telephone number into a unique and irreversible digital fingerprint. A correspondence table has been set up in a different database, always with secure access.

All individual interviews will be conducted after the free and informed consent of the people interviewed. There is no risk associated with participating in this research project. The people who will be met will not receive any financial reward for their participation.

However, AR has policy and ethical implications that go well beyond the pure concerns of the free and informed consent of human subjects encountered in traditional research. Access to data; information use during and after investigation; the intellectual property of publishable materials resulting from the process; decision making throughout the study; and the impact of change on the individuals, organizations, and interest groups involved are essential issues that will inevitably confront the researchers.

Discussion

Importance of Principal Findings

mHealth technologies should contribute to improving the conditions of access to and provision of health care, while supplying a means to support public health policies [27]. Given human resource shortages and a lack of material and infrastructural support, the mobile device consequently would appear to reduce financial costs [66], be time effective, and overcome distances. Thus, mHealth constitutes a useful tool for reducing the technical and human burden of setting up surveys, making it possible to develop multiple data sources that are easily accessible and transferable between actors. Many such interventions [67] in sub-Saharan Africa offer information or prevention services [29] or give patients an opportunity to call a TF number and talk with a contact person. However, the use of SMS has shown its limitations [68], especially when addressing a rural population. In the literature, there are few interventions using ICTs associated with the IVS to improve health services access and health system governance at the same time.

Strengths

Our protocol is innovative for several reasons: On the one hand, it proposes a technology associated with an evidence-based approach, adapted to the context, performed on a large scale, equitably and presumably at low cost; on the other hand, this approach is original in its AR dimension with communities and local NGOs, which includes a real KT component and spatial analysis of data, while using mixed methods of AR evaluation.

The IVS will be used to administer a survey to patients and health workers in the areas targeted by the project. This questionnaire was constructed through a rigorous scoping review that referenced the content offered to patients to measure satisfaction with the quality of and access to health care in West Africa [69-72]. It incorporates topics chosen by callers during the first phase of the TF-IVS pilot project [35] in connection with health system reforms, particularly in terms of the introduction of certain free services [73].

This AR project is to be carried out on a large territorial scale, integrating urban, rural, and periurban territories. The three zones combined cover 25% of the national population and are therefore intended to be reasonably representative of national opinion.

This questionnaire has been designed to be anonymous, adaptable, accessible, equitable, user friendly, and understandable (with clear instructions) to a heterogeneous population. For this purpose, a faithful translation into eight languages will make it possible to offer this service to the entire community of the targeted localities. This service will be available for all, everywhere and anytime, allowing people to give their opinion openly and anonymously.

The choice was made to conduct an audio survey rather than using SMS, because the former does not require any writing or reading skills and can thus be accessible to everyone. The necessary device is easy to use (the service is intuitive and easy to handle) and does not require a smartphone, just a touch phone.

Sustainability is an essential consideration when implementing an AR project [74]. Here, sustainability is supported on two fronts: (1) the call is free for the target populations and the user's device is widely available (can be purchased or borrowed) and (2) costs are low, in terms of human and financial resources, for the organization that finances the project.

Moreover, touch-key technology enables additionally detailed, rigorous, and objective analysis, while being more efficient in terms of resources and time. It facilitates data management, in that data can be processed automatically online. Analyses will be executed over time and geographically. These spatiotemporal data represent a relevant added value for the evaluation of the project because they will measure spatial disparities in health care quality satisfaction. In addition, these types of mapping results are data that can be easily explained to decision makers and the public [75].

The uniqueness of this AR project lies, in particular, in the importance of making results available in several ways to different actors and in as many geographical areas as possible (at the regional and health district levels). This can be done by implementing an elaborate KT strategy based on the evidence regarding KT effectiveness [76]. The strategy will consist of (1) training [77] all implementing partners in techniques for making research results accessible to and usable by decision makers and the public from the start of the project and (2) presenting these results (problems identified by the AR and recommendations and proposals for action plans) at deliberative workshops, at the middle and end of the project, in the form of policy briefs [78] to complement the evidence produced by the project with other data from local expertise so that the resulting AR can be piloted in a feasible, applicable, and research-informed manner. The results of this work will be disseminated and shared through various information and awareness-raising strategies to encourage their adoption by health actors [79], and in particular by making data available on the platform to decision makers and other stakeholders in the health system.

However, for this KT strategy to be successful, it will be necessary to carry out in parallel the essential activity of making people aware of their health-related rights and duties, while informing them about the existence and the importance of using the TF number. Indeed, significant efforts will be made to create an enabling environment for people to understand and accept the system and be able to use it [80]. For that purpose, the AR project envisions involving local radio stations, communities, spiritual groups, trade unions, and local, religious, customary authorities.

The last main strength of this project is the evaluation approach, which is suited to complex problems. It will be subtle, in that it will be designed according to mixed methods, where each method will be applied rigorously in relation to the criteria set out before in the methodology. A convergent sort mode will be used to connect the data from a quantitative phase with the collection and analysis of data from another qualitative phase in order to be able to produce an assessment as relevant as possible throughout the AR project.

Conclusions

To have a healthy society, everyone must be able to benefit from UHC, which implies an approach centered on the right to health. Achieving this goal requires not only strong political will but also the participation of all stakeholders. It is in this perspective that our AR project will take place. To improve health governance, we propose to exploit the technological potential of mobile telephony by offering a free service aimed at legitimately highlighting poor practices to serve as a basis to improve their management with the support of public opinion and health workers. In this way, the AR project would empower people to participate in democratic processes and to enjoy and exercise their human rights. Special attention will be paid to evaluating the project. By measuring its effectiveness, or lack thereof, we will be able to understand why, how, and under what conditions it can be most successful, based on the evidence produced. This approach could be relevant for supporting governments in their quest to improve population health.

Acknowledgments

This work is supported by Global Affairs Canada (grant no. D003027/P01475) and stems from the call for proposals “Technological Platforms for Strengthening Public Sector Accountability and Citizen Engagement.” The project was selected by Global Affairs Canada through a competitive process. Ethical approval was obtained by the Institutional Health Research Ethics Committee (IRSS) through its ethics committee, the Institutional Ethics Board for Health Sciences Research (IEBHSR), on September 24, 2019. The action research (AR) protocol has the research project registration no. 23–2019/CEIRES. All of the AR data will be deposited into a dataverse on https://data.ird.fr and will be accessible for consultation.

Authors' Contributions

SB wrote the first draft of the paper with the support of VR, EB, MDA, and CD. All coauthors revised the manuscript as well as read and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Summary of the AR pilot project implemented in Burkina Faso in 2014 and 2015. AR: action research.
[PNG File , 714 KB - resprot_v10i11e28780_app1.png]

Multimedia Appendix 2

Interview guides.
[DOCX File , 27 KB - resprot_v10i11e28780_app2.docx]

Multimedia Appendix 3
TF-IVS questionnaire. TF-IVS: toll-free service coupled with an interactive voice server.
[DOCX File , 55 KB - resprot_v10i11e28780_app3.docx]

Multimedia Appendix 4
Interview guide for evaluation of the deliberative workshop.
[DOCX File , 19 KB - resprot_v10i11e28780_app4.docx]

Multimedia Appendix 5
Workshop evaluation questionnaire.
[DOCX File , 36 KB - resprot_v10i11e28780_app5.docx]

References

1. DeSilva A, Valentine N, World Health Organization. Global Programme on Evidence for Health Policy. (2000) . Measuring responsiveness: results of a key informants survey in 35 countries. 2000. URL: https://apps.who.int/iris/handle/10665/67781 [accessed 2020-02-26]
2. Murray CJL, Evans DB, World Health Organization. Global Programme on Evidence for Health Policy. (2003) . Health systems performance assessment : debates, methods and empiricism. 2003. URL: https://apps.who.int/iris/handle/10665/42735 [accessed 2020-06-16]
3. Mirzoev T, Kane S. What is health systems responsiveness? Review of existing knowledge and proposed conceptual framework. BMJ Glob Health 2017;2(4):e000486 [FREE Full text] [doi: 10.1136/bmjgh-2017-000486] [Medline: 29225953]
4. Siddiqi S, Masud TI, Nishtar S, Peters DH, Sabri B, Bile KM, et al. Framework for assessing governance of the health system in developing countries: gateway to good governance. Health Policy 2009;90(1):13-25. [doi: 10.1016/j.healthpol.2008.08.005] [Medline: 18838188]
5. Gilson L, Palmer N, Schneider H. Trust and health worker performance: exploring a conceptual framework using South African evidence. Soc Sci Med 2005;61(7):1418-1429. [doi: 10.1016/j.socscimed.2004.11.062] [Medline: 16005777]
6. Van Belle S, Mayhew SH. What can we learn on public accountability from non-health disciplines: a meta-narrative review. BMJ Open 2016;6(7):e010425 [FREE Full text] [doi: 10.1136/bmjopen-2015-010425] [Medline: 27388347]
7. Yuan B, Jian W, He L, Wang B, Balabanova D. The role of health system governance in strengthening the rural health insurance system in China. Int J Equity Health 2017;16(1):44 [FREE Full text] [doi: 10.1186/s12939-017-0542-x] [Medline: 28532418]
8. World Health Organization. Health Systems Governance for Universal Health Coverage, Action Plan. 2014. URL: http://www.who.int/universal_health_coverage/plan_action-hsgov_uhc/en/ [accessed 2019-11-15]
9. Langseth P. Civil service reform: a general view. In: Villadsen S, Lubanga F, editors. Democratic Decentralization in Uganda: A New Approach to Local Governance. Kampala: Fountain Publishers; 1996:1-35.
10. Sinha D. Empowering communities to make pregnancy safer: an intervention in rural Andhra Pradesh. In: Health and Population Innovation Fellowship Programme Working Paper no. 5. New Delhi: Population Council; 2008:1-36.
11. Rifkin SB. Community participation in maternal and child health/family planning programmes : an analysis based on case study materials. In: WHO IRIS. Geneva: World Health Organization; 1990.
12. Standing H. Understanding the 'demand side' in service delivery : definitions, frameworks and tools from the health sector. London: DFID Health Systems Resource Centre; 2004. URL: http://www.heart-resources.org/wp-content/uploads/2012/10/Understanding-the-demand-side-in-service-delivery.pdf [accessed 2020-06-15]
13. McGee R, Pettit J, editors. Power, Empowerment and Social Change. New York: Routledge; 2019.
14. World Health Organization. People-Centred and Integrated Health Services: An Overview of the Evidence. 2015. URL: https://www.who.int/servicedeliverysafety/areas/people-centred-care/evidence-overview/en/ [accessed 2019-11-29]
15. Boydell V, McMullen H, Cordero J, Steyn P, Kiare J. Studying social accountability in the context of health system strengthening: innovations and considerations for future work. Health Res Policy Syst 2019;17(1):34-36 [FREE Full text] [doi: 10.1186/s12961-019-0438-x] [Medline: 30925889]
16. Sebert Kuhlmann KA, Gullo S, Galavotti C, Grant C, Cavatore M, Posnock S. Women's and health workers' voices in open, inclusive communities and effective spaces (voices): measuring governance outcomes in reproductive and maternal health programmes. Dev Policy Rev 2017;35(2):289-311. [doi: 10.1111/dpr.12209]
17. Mbwele B, Ide N, Mrema J, Ward Sarah A, Melnick J, Manongi R. Learning from health care workers' opinions for improving quality of neonatal health care in kilimanjaro region, northeast Tanzania. Ann Med Health Sci Res 2014;4(1):105-114 [FREE Full text] [doi: 10.4103/2141-9248.126614] [Medline: 24669341]

18. Janicijevic I, Seke K, Djokovic A, Filipovic T. Healthcare workers satisfaction and patient satisfaction: where is the linkage? Hippokratia 2013;17(2):157-162 [FREE Full text] [Medline: 24376323]
19. Nikic D, Arandjelovic M, Nikolic M, Stankovic A. Job satisfaction in health care workers. Acta Medica Medianae 2008;47:9-12.
20. Bovier PA, Perneger TV. Predictors of work satisfaction among physicians. Eur J Public Health 2003;13(4):299-305. [doi: 10.1093/eurpub/13.4.299] [Medline: 14703315]
21. Lohmann J, Souares A, Tiendrebéogo J, Houlfort N, Robyn PJ, Somda SMA, et al. Measuring health workers' motivation composition: validation of a scale based on Self-Determination Theory in Burkina Faso. Hum Resour Health 2017;15(1):33 [FREE Full text] [doi: 10.1186/s12960-017-0208-1] [Medline: 28532426]
22. Fillol A, Lohmann J, Turcotte-Tremblay A, Somé PA, Ridde V. The importance of leadership and organizational capacity in shaping health workers' motivational reactions to performance-based financing: a multiple case study in Burkina Faso. Int J Health Policy Manag 2019;8(5):272-279 [FREE Full text] [doi: 10.15171/ijhpm.2018.133] [Medline: 31204443]
23. Haas JS, Cook EF, Puopolo AL, Burstin HR, Cleary PD, Brennan TA. Is the professional satisfaction of general internists associated with patient satisfaction? J Gen Intern Med 2000;15(2):122-128 [FREE Full text] [doi: 10.1046/j.1525-1497.2000.02219.x] [Medline: 10672116]
24. Chang E, Cohen J, Koethe B, Smith K, Bir A. Measuring job satisfaction among healthcare staff in the United States: a confirmatory factor analysis of the Satisfaction of Employees in Health Care (SEHC) survey. Int J Qual Health Care 2017;29(2):262-268. [doi: 10.1093/intqhc/mzx012] [Medline: 28339641]
25. Oyeyemi SO, Wynn R. The use of cell phones and radio communication systems to reduce delays in getting help for pregnant women in low- and middle-income countries: a scoping review. Glob Health Action 2015;8(1):28887 [FREE Full text] [doi: 10.3402/gha.v8.28887] [Medline: 26362421]
26. Mericskay B, Roche S. Cartographie 2.0: le grand public, producteur de contenus et de savoirs géographiques avec le web 2.0. Cybergeo: Eur J Geogr 2011:1-19 Science et Toile, document 552. [doi: 10.4000/cybergeo.24710]
27. Labrique AB, Vasudevan L, Kochi E, Fabricant R, Mehl G. mHealth innovations as health system strengthening tools: 12 common applications and a visual framework. Glob Health Sci Pract 2013;1(2):160-171 [FREE Full text] [doi: 10.9745/GHSP-D-13-00031] [Medline: 25276529]
28. Hampshire K, Porter G, Mariwah S, Munthali A, Robson E, Owusu SA, et al. Who bears the cost of 'informal mhealth'? Health-workers' mobile phone practices and associated political-moral economies of care in Ghana and Malawi. Health Policy Plan 2017;32(1):34-42 [FREE Full text] [doi: 10.1093/heapol/czw095] [Medline: 27476501]
29. Duclos V, Yé M, Moubassira K, Sanou H, Sawadogo NH, Bibeau G, et al. Situating mobile health: a qualitative study of mHealth expectations in the rural health district of Nouna, Burkina Faso. Health Res Policy Syst 2017;15(Suppl 1):47 [FREE Full text] [doi: 10.1186/s12961-017-0211-y] [Medline: 28722558]
30. Aranda-Jan CB, Mohutsiwa-Dibe N, Loukanova S. Systematic review on what works, what does not work and why of implementation of mobile health (mHealth) projects in Africa. BMC Public Health 2014;14(1):188 [FREE Full text] [doi: 10.1186/1471-2458-14-188] [Medline: 24555733]
31. Hazra A, Khan ME, Mondal SK. Mobile phone messaging to husbands to improve maternal and child health behavior in India. J Health Commun 2018;23(6):542-549. [doi: 10.1080/10810730.2018.1483444] [Medline: 29902122]
32. Huang S, Li M. Piloting a mHealth intervention to improve newborn care awareness among rural Cambodian mothers: a feasibility study. BMC Pregnancy Childbirth 2017;17(1):356 [FREE Full text] [doi: 10.1186/s12884-017-1541-z] [Medline: 29037179]
33. Huq NL, Azmi AJ, Quaiyum MA, Hossain S. Toll free mobile communication: overcoming barriers in maternal and neonatal emergencies in Rural Bangladesh. Reprod Health 2014;11:52 [FREE Full text] [doi: 10.1186/1742-4755-11-52] [Medline: 25015126]
34. Huda TM, Alam A, Tahsina T, Hasan MM, Khan J, Rahman MM, et al. Mobile-based nutrition counseling and unconditional cash transfers for improving maternal and child nutrition in Bangladesh: pilot study. JMIR Mhealth Uhealth 2018;6(7):e156 [FREE Full text] [doi: 10.2196/mhealth.8832] [Medline: 30021707]
35. Lechat L, Bonnet E, Queuille L, Traoré Z, Somé PA, Ridde V. Relevance of a toll-free call service using an interactive voice server to strengthen health system governance and responsiveness in Burkina Faso. Int J Health Policy Manag 2019;8(6):353-364 [FREE Full text] [doi: 10.15171/ijhpm.2019.13] [Medline: 31256567]
36. D'Ostie-Racinea L, Dagenais C, Ridde V. Examining conditions that influence evaluation use within a humanitarian non-governmental organization in Burkina Faso (West Africa). Syst Pract Action Res 2019;34(1):1-35. [doi: 10.1007/s11213-019-09504-w]
37. Reason P, Bradbury H, editors. The Sage Handbook of Action Research: Participative Inquiry and Practice, 2nd ed. London; Thousand Oaks, CA: SAGE Publications; 2008:1-720.
38. Craig P, DiRuggiero E, Frohlich K, Mykhalovskiy E, White M, on behalf of the Canadian Institutes of Health Research (CIHR)–National Institute for Health Research (NIHR) Context Guidance Authors Group (listed alphabetically): Campbell R, Cummins S, Edwards N, Hunt K, Kee F, Loppie C, Moore L, Ogilvie D, Petticrew M, Poland B, Ridde V, Shoveller J, Viehbeck S, Wight D. Taking Account of Context in Population Health Intervention Research: Guidance for Producers, Users and Funders of Research. Southampton: NIHR Evaluation, Trials and Studies Coordinating Centre; 2018.

39. Campbell M, Katikireddi SV, Hoffmann T, Armstrong R, Waters E, Craig P. TIDieR-PHP: a reporting guideline for population health and policy interventions. BMJ 2018;361:k1079 [FREE Full text] [doi: 10.1136/bmj.k1079] [Medline: 29769210]
40. Institut National de la Statistique et de la Démographie. Résultats de l'Enquête Multisectorielle Continue (EMC) - Phase1. URL: https://www.insd.bf/index.php/publications?id=151 [accessed 2019-11-25]
41. Autorité de Régulation des Communications Electroniques et des Postes (ARCEP). Market Observatory National Mobile Telephony Market Data 2nd Quarter 2019 Internet. URL: http://www.arcep.bf/le-mobile/ [accessed 2019-11-25]
42. National Institute of Statistics and Demography, Ministry of Economy and Finance. Demographic Projections from 2007 to 2020 by Region and Province. Burkina Faso: National Institute of Statistics and Demography; 2009:1-69.
43. Ministère de la santé. Annuaire Statistique 2018. avec l'apui de l'UNICEF. Burkina Faso: Direction générale des études et des statistiques sectorielles; 2019.
44. National Statistics Council. Annuaire Statistique 2017. 2017. URL: http://cns.bf/IMG/pdf/annuaire_ms_2017.pdf [accessed 2019-11-26]
45. Creswell J, Plano Clark VL. Designing and Conducting Mixed Methods Research, 2nd ed. Los Angeles, CA: SAGE Publications; 2011.
46. R Core Team. R: A Language and Environment for Statistical Computing. Vienna: R Foundation for Statistical Computing; 2018. URL: https://www.R-project.org [accessed 2020-01-31]
47. Kulldorff M, Nagarwalla N. Spatial disease clusters: detection and inference. Stat Med 1995;14(8):799-810. [doi: 10.1002/sim.4780140809] [Medline: 7644860]
48. Kulldorff M. A spatial scan statistic. Commun Stat Theory Methods 2007;26(6):1481-1496. [doi: 10.1080/03610929708831995]
49. Olivier de Sardan JP. La rigueur du qualitatif. Les contraintes empiriques de l'interprétation socio-anthropologique. Louvain-La-Neuve: Academia-Bruylant; 2009:368.
50. Stok FM, de Ridder DTD, de Vet E, Nureeva L, Luszczynska A, Wardle J, et al. Hungry for an intervention? Adolescents' ratings of acceptability of eating-related intervention strategies. BMC Public Health 2016;16(1):5 [FREE Full text] [doi: 10.1186/s12889-015-2665-6] [Medline: 26729328]
51. Diepeveen S, Ling T, Suhrcke M, Roland M, Marteau TM. Public acceptability of government intervention to change health-related behaviours: a systematic review and narrative synthesis. BMC Public Health 2013;13:756 [FREE Full text] [doi: 10.1186/1471-2458-13-756] [Medline: 23947336]
52. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. BMC Health Serv Res 2017;17(1):88 [FREE Full text] [doi: 10.1186/s12913-017-2031-8] [Medline: 28126032]
53. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implement Sci 2009;4:50 [FREE Full text] [doi: 10.1186/1748-5908-4-50] [Medline: 19664226]
54. Patton MQ. Qualitative evaluation and research methods. In: Designing Qualitative Studies, Qualitative Designs and Data Collection. Beverly Hills, CA: SAGE Publications; 1990:169-186.
55. Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K. Purposeful sampling for qualitative data collection and analysis in mixed method implementation research. Adm Policy Ment Health 2015;42(5):533-544 [FREE Full text] [doi: 10.1007/s10488-013-0528-y] [Medline: 24193818]
56. Miles M, Huberman AM. Qualitative Data Analysis: An Expanded Sourcebook, 2nd ed. Thousand Oaks, CA: Sage Publications; 1994.
57. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol 2013;13:117 [FREE Full text] [doi: 10.1186/1471-2288-13-117] [Medline: 24047204]
58. Dagenais C, Dargis-Damphousse L, Dutil J. The essential skills series in the essential skills series in evaluation: assessing the validity of the ES Participant Workshop Evaluation Questionnaire. Can J Program Eval 2011;26(2):89.
59. Armitage CJ, Conner M. Efficacy of the theory of planned behaviour: a meta-analytic review. Br J Soc Psychol 2001;40(Pt 4):471-499. [doi: 10.1348/014466601164939] [Medline: 11795063]
60. Godin G, Kok G. The theory of planned behavior: a review of its applications to health-related behaviors. Am J Health Promot 1996;11(2):87-98. [doi: 10.4278/0890-1171-11.2.87] [Medline: 10163601]
61. Foy R, Bamford C, Francis JJ, Johnston M, Lecouturier J, Eccles M, et al. Which factors explain variation in intention to disclose a diagnosis of dementia? A theory-based survey of mental health professionals. Implement Sci 2007;2(1):31 [FREE Full text] [doi: 10.1186/1748-5908-2-31] [Medline: 17894893]
62. Ajzen I. The theory of planned behavior. Organ Behav Hum Decis Process 1991;50(2):179-211. [doi: 10.1016/0749-5978(91)90020-t]
63. Boyko JA, Lavis JN, Dobbins M, Souza NM. Reliability of a tool for measuring theory of planned behaviour constructs for use in evaluating research use in policymaking. Health Res Policy Syst 2011;9(1):29 [FREE Full text] [doi: 10.1186/1478-4505-9-29] [Medline: 21702956]

64. Bennett A. Process tracing: a Bayesian perspective. In: Box-Steffensmeier JM, Brady HE, Collier D, editors. The Oxford Handbook of Political Methodology. Oxford: Oxford University Press; 2009.
65. Strauss A, Corbin J. Grounded theory methodology: an overview. In: Denzin NK, Lincoln YS, editors. Handbook of Qualitative Research. Thousand Oaks, CA: Sage Publications; 1994:273-285.
66. Larsen-Cooper E, Bancroft E, Rajagopal S, O'Toole M, Levin A. Scale matters: a cost-outcome analysis of an m-Health intervention in Malawi. Telemed J E Health 2016;22(4):317-324 [FREE Full text] [doi: 10.1089/tmj.2015.0060] [Medline: 26348994]
67. Schuster C, Perez Brito C. Cutting Costs, Boosting Quality and Collecting Data Real-Time: Lessons from a Cell Phone-Based Beneficiary Survey to Strengthen Guatemala's Conditional Cash Transfer Program.: World Bank; 2011. URL: https://tinyurl.com/zc5kscex [accessed 2019-11-18]
68. Chakraborty D, Gupta A, Seth A. Experiences from a mobile-based behaviour change campaign on maternal and child nutrition in rural India. : Association for Computing Machinery Press; 2019 Presented at: Proceedings of the Tenth International Conference on Information and Communication Technologies and Development (ICTD '19; January 2019; New York p. 1-11. [doi: 10.1145/3287098.3287110]
69. van Duong D, Binns CW, Lee AH, Hipgrave DB. Measuring client-perceived quality of maternity services in rural Vietnam. Int J Qual Health Care 2004;16(6):447-452. [doi: 10.1093/intqhc/mzh073] [Medline: 15557354]
70. Haddad S, Fournier P, Potvin L. Measuring lay people's perceptions of the quality of primary health care services in developing countries. Validation of a 20-item scale. Int J Qual Health Care 1998;10(2):93-104. [doi: 10.1093/intqhc/10.2.93] [Medline: 9690882]
71. Ramanah R, Dumont A, Schepens F, Traore M, Gaye A, Schaal JP, et al. Satisfaction with obstetrical care: development and validation of a scale on quality of care. Gynecol Obstet Fertil 2014;42(7-8):477-482 ISSN 1297-9589. [doi: 10.1016/j.gyobfe.2014.05.002] [Medline: 24951184]
72. Webster TR, Mantopoulos J, Jackson E, Cole-Lewis H, Kidane L, Kebede S, et al. A brief questionnaire for assessing patient healthcare experiences in low-income settings. Int J Qual Health Care 2011;23(3):258-268. [doi: 10.1093/intqhc/mzr019] [Medline: 21531989]
73. Ridde V, Yaméogo P. How Burkina Faso used evidence in deciding to launch its policy of free healthcare for children under five and women in 2016. Palgrave Commun 2018;4(1):119. [doi: 10.1057/s41599-018-0173-x]
74. Pluye P, Potvin L, Denis J, Pelletier J, Mannoni C. Program sustainability begins with the first events. Eval Program Plann 2005;28(2):123-137. [doi: 10.1016/j.evalprogplan.2004.10.003]
75. Boyko JA, Lavis JN, Abelson J, Dobbins M, Carter N. Deliberative dialogues as a mechanism for knowledge translation and exchange in health systems decision-making. Soc Sci Med 2012;75(11):1938-1945. [doi: 10.1016/j.socscimed.2012.06.016] [Medline: 22938912]
76. Dagenais C, Malo M, Robert, Ouimet M, Berthelette D, Ridde V. Knowledge transfer on complex social interventions in public health: a scoping study. PLoS One 2013;8(12):e80233 [FREE Full text] [doi: 10.1371/journal.pone.0080233] [Medline: 24324593]
77. Tchameni Ngamo S, Souffez K, Lord C, Dagenais C. Do knowledge translation (KT) plans help to structure KT practices? Health Res Policy Syst 2016;14(1):46 [FREE Full text] [doi: 10.1186/s12961-016-0118-z] [Medline: 27316972]
78. Manson H. Systematic reviews are not enough: policymakers need a greater variety of synthesized evidence. J Clin Epidemiol 2016;73:11-14 https://www.jclinepi.com/article/S0895-4356(16)00103-7/references#relatedArticles. [doi: 10.1016/j.jclinepi.2015.08.032] [Medline: 26912122]
79. Lavis J, Permanand G, Oxman AD, Lewin S, Fretheim A. SUPPORT tools for evidence-informed health policymaking (STP) 13: preparing and using policy briefs to support evidence-informed policymaking. Health Res Policy Sys 2009;7(S1):1-9 7(Suppl 1):S13. [doi: 10.1186/1478-4505-7-s1-s13]
80. Shohet L, Renaud L. Analyse critique des pratiques exemplaires sur la littératie en matière de santé. Can J Public Health 2006;97(S2):S10-S14. [doi: 10.1007/BF03405366]

Abbreviations

ABC: activity-based costing
AGIR-SD: Action-Gouvernance-Interaction-Renforcement, groupe de Santé en Développement
AR: action research
CFIR: Consolidated Framework for Implementation Research
CSO: civil society organization
DET: district executive team
DHIS2: District Health Information System 2
EWM: equality between women and men
GIS: geographic information system
HELP: Hilfe zur Selbsthilfe
ICT: information and communication technology

IEBHSR: Institutional Ethics Board for Health Sciences Research
IRD: Institut de recherche pour le développement
IRSS: Institutional Health Research Ethics Committee
JMS: Java Message Service
JSON: (IT) format for structured data exchange
KPI: key performance indicator
KT: knowledge transfer
LMIC: low- and middle-income country
mHealth: mobile health
NGO: nongovernmental organization
NHIS: National Health Information System
PHP: population health and policy
RAECP: Regulatory Authority for Electronic Communications and Posts
REST API: Representational State Transfer Application Programming Interface
RHD: regional health directorate
RQ: research question
SDG: Sustainable Development Goal
SMS: short message service
TF: toll free
TF-IVS: toll-free service coupled with an interactive voice server
TOPICs: TechnOlogie PartIcipation Citoyenne en santé
TIDieR: Template for Intervention Description and Replication
TPB: theory of planned behavior
UHC: universal health coverage
USI: International Health Unit
VPN: virtual private network
WHO: World Health Organization

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Protocol

A Web-Based Risk-Reframing Intervention to Influence Early Childhood Educators' Attitudes and Supportive Behaviors Toward Outdoor Play: Protocol for the OutsidePlay Study Randomized Controlled Trial

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Abstract

Background: Early learning and childcare centers (ELCCs) can offer young children critical opportunities for quality outdoor play. There are multiple actual and perceived barriers to outdoor play at ELCCs, ranging from safety fears and lack of familiarity with supporting play outdoors to challenges around diverse perspectives on outdoor play among early childhood educators (ECEs), administrators, licensing officers, and parents.

Objective: Our study objective is to develop and evaluate a web-based intervention that influences ECEs' and ELCC administrators' perceptions and practices in support of children's outdoor play at ELCCs.

Methods: The development of the fully automated, open-access, web-based intervention was guided by the intervention mapping process. We first completed a needs assessment through focus groups of ECEs, ELCC administrators, and licensing officers. We identified key issues, needs, and challenges; opportunities to influence behavior change; and intervention outcomes and objectives. This enabled us to develop design objectives and identify features of the OutsidePlay web-based intervention that are central to addressing the issues, needs, and challenges of ECEs and ELCC administrators. We used social cognitive theory and behavior change techniques to select methods, applications, and technology to deliver the intervention. We will use a two-parallel-group randomized controlled trial (RCT) design to evaluate the efficacy of the intervention. We will recruit 324 ECEs and ELCC administrators through a variety of web-based means, including Facebook advertisements and mass emails through our partner networks. The RCT study will be a purely web-based trial where outcomes will be self-assessed through questionnaires. The RCT participants will be randomized into the intervention group or the control group. The control group participants will read the Position Statement on Active Outdoor Play.

Results: The primary outcome is increased tolerance of risk in children's play, as measured by the Teacher Tolerance of Risk in Play Scale. The secondary outcome is self-reported attainment of a self-developed behavior change goal. We will use mixed effects models to test the hypothesis that there will be a difference between the intervention and control groups with respect to tolerance of risk in children's play. Differences in goal attainment will be tested using logistic regression analysis.

Conclusions: The OutsidePlay web-based intervention guides users through a personalized journey that is split into 3 chapters. An effective intervention that addresses the barriers to outdoor play in ELCC settings has the potential to improve children's access to outdoor play and support high-quality early childhood education.

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KEYWORDS

early years; risky play; teacher; childcare; early learning; risk perception; outdoor play

Introduction

Background

Outdoor play and its embedded risk-taking is crucial for children's physical, social, emotional, and intellectual development [1,2]. Playing outdoors can enhance children's self-confidence, social connectedness, physical activity, and risk management [1-3]. The United Nations Convention on the Rights of the Child codifies the importance of children's right to play and accessibility to adequate spaces for outdoor play [4]. Generational declines in outdoor play are trending internationally [5-8]. The consequent increases in sedentary behavior may be associated with negative health consequences such as declines in Canadian children's mental health [2] and an increase in obesity rates [9].

Declines in outdoor play are associated with a variety of societal factors such as changes in technology and increases in screen time; access to, and quality of, outdoor play spaces; parenting ideals that prioritize children's achievement; and surveillance [8]. A main barrier relates to caregivers' safety concerns and apprehensions of children's risk-taking in outdoor play, which negatively affects children's play opportunities and, subsequently, their development [2,5,6]. This includes limits in the home environment imposed by parents, restrictive policies that constrict play-space design and play behaviors in public spaces, and limitations on children's play time and opportunities at schools and early learning and childcare centers (ELCCs). These educational environments can be critical venues to increase outdoor play opportunities and support equitable access to high-quality play because they are spaces where children spend most of their waking hours.

The importance of outdoor play became acute during the COVID-19 pandemic and its associated restrictions. In many countries, including Canada, ELCCs were closed for several weeks before reopening with COVID-19 safety protocols in place. The closures and restrictions led to significant changes in daily life for children and families, including how Canadian children engage in play and recreation. During this time of physical distancing and behavior restrictions, there were significant declines in time spent outdoors and in outdoor play among children and youth in Canada [10]. This worrying trend can compromise children's mental health and disease resistance because play is a critical outlet for children's stress management, and time spent outdoors playing helps boost immunity through physical activity and access to vitamin D and also supports well-being [6,11]. Children with access to friends and play reported greater well-being during the pandemic [12].

ELCCs can be important allies in supporting early childhood development. Research clearly indicates that investments in early childhood education have significant and far-reaching impacts throughout the lifespan and, importantly, can help reduce inequality, mitigating the effects of early childhood disadvantage [13]. In Canada, as well as in many other Western countries, most parents rely on ELCCs for childcare. Almost half (46%) of Canadian parents reported using childcare in 2011, with up to 86% of these parents using childcare on a regular basis [11]. Children often spend >30 hours per week in childcare, and for some children, this might be their main opportunity for outdoor play [14]. However, ELCC pedagogies are not always explicit on the importance of outdoor play, and ELCCs vary widely on their provision and quality of outdoor play opportunities [15]. Early childhood educators (ECEs) report struggles in providing stimulating outdoor play. Actual and perceived barriers include ECEs' and administrators' safety fears, liability concerns, and limited knowledge on the importance of outdoor play [15,16], which can result in risk aversion, restrictive rules, and a lack of engaging play spaces [16-19]. The COVID-19 pandemic has heightened challenges as well as the importance of supporting children's outdoor time [10,20,21]. Guidelines in many jurisdictions encourage maximum outdoor time as an effective infection prevention strategy [22]. Many ELCCs are struggling with implementing these recommendations because pre-existing barriers such as parental safety concerns [23] have endured, if not intensified. The need to support a shift in ELCC practice to encourage outdoor play is clear, as is the need for an intervention that addresses the identified barriers and challenges.

Previously, we developed the OutsidePlay intervention to support parents of children aged 6-12 years to reframe their perceptions of the risks their children faced in outdoor play and to plan for a change in parenting behavior to support their children's outdoor play [24]. We developed 2 versions of the intervention: an in-person version and a web-based version. Both were underpinned by social cognitive theory (SCT), incorporating behavior change techniques (BCTs), and took users through a personalized journey whereby they proceeded through a series of self-reflection questions and choose-your-own-adventure video scenarios to ultimately develop a plan for change. We conducted a randomized controlled trial (RCT) with 451 mothers, examining the efficacy of both versions of the intervention. The results indicated that the OutsidePlay intervention was effective in increasing

mothers' tolerance of risk in children's play at 1 week and 3 months after the intervention, whereas an in-person workshop only indicated significant effects at 1 week [25]. The efficacy of the OutsidePlay web-based intervention for parents provided support for developing an intervention for ECEs to support outdoor play at ELCCs.

Objective

Our study objective is to develop and evaluate a web-based intervention to influence ECEs' and administrators' perceptions and practices in support of children's outdoor play within ELCCs. This paper outlines the intervention mapping (IM) process, a protocol that we followed to develop and test the intervention.

Methods

Study Design

IM guided the planning, development, and evaluation of the fully automated and open-access web-based intervention [26]. IM has proven effective for the development of many web-based interventions [27,28]. Furthermore, this strategy supports a theory-based approach that focuses on understanding and accommodating the needs and perspectives of the end users at all stages of the design. IM involves 6 steps, which are outlined in the context of this study in Textbox 1.

Textbox 1. Overview of intervention-mapping approach to developing the OutsidePlay web-based intervention for early learning and childcare centers.

The 6 steps involved in the intervention-mapping approach

- Step 1: Understanding the problem
  - Established key partnerships and worked with study partners. Our study partners included the coauthors, each of whom brought unique disciplinary and experiential perspectives, including early childhood education, child development, behavior change, and digital technology. We also worked with the University of British Columbia's Child Care Services and the City of Richmond to access childcare sites used as the backdrop for the videos in the intervention
  - Conducted a literature review on early childhood educator perceptions of outdoor play in the early learning and childcare center setting
  - Conducted a needs assessment of the target population through 5 focus groups with early childhood educators, administrators, and licensing officers to explore their perceived key issues, needs, and challenges that required intervention
  - Developed a logic model of the problem. The literature review and focus group data informed identification of the problem and determinants influencing the problem
  - Established intervention goals. The logic model helped identify the goals and targets for the intervention that related to determinants that were amenable to change
- Step 2: Intervention objectives and outcomes
  - Developed a logic model of change to identify what needs to change and for whom. This linked the behavioral and environmental change objectives to specific outcomes that helped meet the intervention objectives
- Step 3: Intervention design
  - Selected theory- and evidence-based behavior change methods. Social cognitive theory formed the theoretical basis for our choice of behavior change techniques
  - Selected optimal applications and technology to deliver the intervention. The OutsidePlay web-based intervention had proven effective in supporting parents' attitude and behavior changes [25]. The participants in the focus groups stressed the importance of easy access to any resource and that a web-based intervention can provide an efficient, convenient, and inexpensive means to support behavior change with broad reach [29]
  - Developed a mock-up of the intervention grounded in social cognitive theory
  - Tested the intervention through 12 cognitive interviews with early childhood educators to assess their perceptions of the intervention
- Step 4: Intervention production
  - Refined the intervention based on cognitive interview findings and partners' and collaborators' feedback
  - Engaged in full production and finalizing of the intervention
- Step 5: Intervention implementation plan
  - Developed the intervention implementation and mobilization plan. This sought to ensure that target audiences would be aware of, and motivated to engage with, the intervention
- Step 6: Intervention evaluation
  - Identified evaluation objectives and methods
  - Will conduct single-blind randomized controlled trial to test the efficacy of the intervention

We obtained ethics approval from the University of British Columbia and Children's and Women's Health Centre of British Columbia Research Ethics Board (H19-01230; H19-03644). The health risks of the intervention are negligible. The potential benefits are that participants learn more about the importance of children's outdoor play and engage in desirable changes in their practice that allow children more opportunities for high-quality outdoor play.

Participant Recruitment and Eligibility Criteria

The inclusion criteria for the focus groups and individual cognitive interview participants included the following:

1. Being aged ≥19 years.
2. Being an ECE, ELCC administrator, early childhood education faculty or student, or licensing officer in Metro Vancouver.
3. Being able to speak, read, and understand English.

We recruited participants through a variety of means that we have successfully used in past research. These included using

social media such as Facebook and Facebook advertisements, mass emails through our partner networks, and snowball methods.

The inclusion criteria for the RCT participants will include the following:

1. Being aged ≥19 years.
2. Currently working as an ECE or ELCC administrator in Canada.
3. Being able to speak, read, and understand English.

Given that the study will be conducted entirely on the web, computer and internet literacy is in fact an implicit eligibility criterion. Eligible participants will provide consent on the web by selecting checkboxes. Once done, a copy of the completed consent form will be made available for download. The enrolled participants will be invited to fill in the baseline measures in REDCap (Research Electronic Data Capture) and enter their email address to which a unique link to their intervention or control materials will be sent. We will use the participant email address only to administer web-based baseline and follow-up measures and will not share this information with the researchers who will be conducting the analysis. The participant email addresses will be also used to prevent multiple trial entries. The RCT study will be a purely web-based trial where outcomes will be self-assessed through questionnaires.

We will aim to recruit 324 ECEs and ELCC administrators through a variety of web-based means, including Facebook advertisements and mass emails through our partner networks. The institutional affiliations (ie, the University of British Columbia and the BC Children's Hospital Research Institute) will be displayed on the consent form and throughout the web-based RCT survey as well as in the OutsidePlay intervention. There will be no human involvement unless the participants have inquiries or report technical issues. RCT participants who have any questions or feedback to share can contact us by email or phone, details of which will be provided in the trial and the OutsidePlay intervention.

The participants will not need to pay to participate in the study; however, they will need to be working as ECEs as stated in the eligibility criteria. As for participant remuneration, a nominal honorarium of $50 was paid to each focus group interview participant; in addition, they received a professional development certificate for their attendance. The focus group interview participants were paid cash at the end of the focus group in which they participated. The individual cognitive interview participants also received US $40 each for their participation. The RCT participants will receive US $24 at baseline and US $20 at each of the 2 follow-ups, totaling US $64. The RCT participant honoraria will be processed through electronic transfer using participant email addresses. In addition, the RCT participants allocated to the intervention group who complete the OutsidePlay intervention will receive a professional development certificate for 100 minutes.

Trial Status

Participant recruitment began on December 1, 2020, and was completed by March 15, 2021. Follow-up data collection was ongoing through July 2021.

Results

IM Step 1: Understanding the Problem

Needs Assessment Focus Groups

A literature review examined current discourses on ECE perceptions of outdoor play at ELCCs, focused on identifying the perceived barriers and facilitators. This was performed to inform the intervention and draft the semistructured focus group interview questions for the needs assessment (Multimedia Appendix 1). The focus group interviews explored ECEs' and ELCC administrators' perceived key issues, needs, and challenges that required intervention (eg, what challenges do you encounter around supporting children's outdoor play? What would help support you in that role?).

We conducted 5 focus group interviews with 40 ECEs, ELCC administrators, ECE faculty and students, and licensing officers in the summer of 2019. Of the 40 participants, 40 (100%) were women, which clearly reflected the dominant proportion of women in the ECE-related field [30,31], and 33 (83%) were ECEs, although many held >one role. After obtaining the participants' consent and demographic information, a member of our research team (MB, FM, or MZ) facilitated the session, whereas 2 others (FM, MZ, or TC) took notes and sought clarifications when necessary. All research team members completed field notes to document their reflections after the focus group. Each focus group lasted between 60 and 90 minutes. The focus group interviews were transcribed verbatim and analyzed using thematic analysis methods [32].

Focus Group Results

A thematic analysis was conducted using a socioecological framework [33] to consider the identified needs and challenges at the individual, interpersonal, organizational, and policy levels and the interconnections and interactions among these levels. The complete focus group methods and findings have been submitted for publication elsewhere, and a brief summary of the findings is provided below.

At an individual level, all the participants agreed that outdoor play is an important part of childhood and that they could play an important role as facilitators. However, many acknowledged fear and anxiety regarding the potential for injury. The participants had a range of different beliefs about children's general competence to manage their own risks. They were also concerned about differing levels of risk tolerance among ECE colleagues, administrators, licensing officers, and parents, which made them apprehensive of their actions being criticized and viewed as negligent. These beliefs, which were often linked to their own childhood and their previous experiences as ECEs, either facilitated or impeded their support for children's outdoor play.

At an interpersonal level, many participants discussed the importance of building positive relationships with children, colleagues, parents, and licensing officers. Positive and continual communication was deemed fundamental to boosting ECEs' and ELCC administrators' self-confidence and agency in facilitating and promoting children's outdoor play. In particular,

the participants proposed that understanding and embracing their colleagues' differing levels of risk tolerance could create a comfortable and flexible space to foster children's outdoor play, as well as opportunities for ECEs to build their risk tolerance.

At an organizational level, the participants discussed the quality and availability of the outdoor space at their centers. Some ECEs were concerned that their outdoor play spaces were inadequate, which limited their use of these spaces. At the broader community and societal level, the participants discussed their views of existing licensing regulations. Some found them too vague, whereas others cautioned that more prescriptive guidelines would be excessively restrictive.

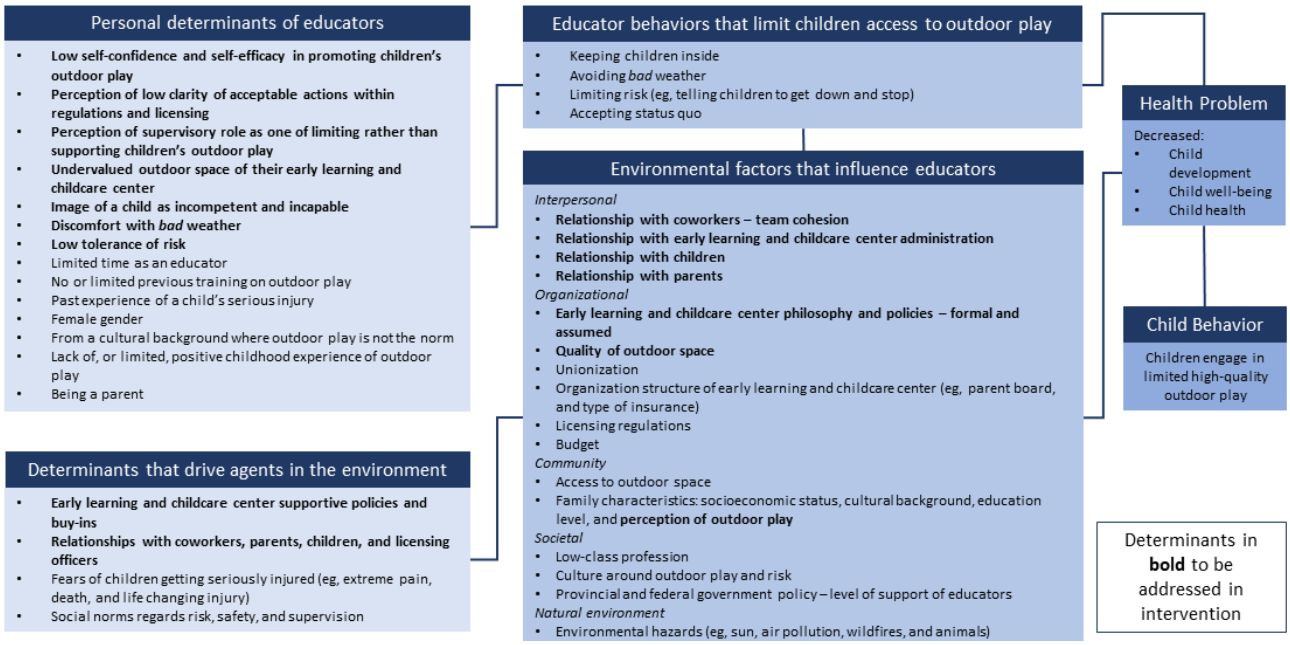
In response to questions regarding what the participants perceived would be helpful in supporting their role in facilitating children's outdoor play, all agreed that an intervention was needed that could educate ECEs and ELCC administrators about the importance of outdoor play and help them to manage their fears around the risk involved, as well as support children's risk taking.

However, the participants cautioned that the support would need to be flexible enough to suit ECEs and ELCC administrators with differing levels of knowledge, experience, and tolerance for children's outdoor play. A specific recommendation was to build the intervention so as to make it adaptable for users to use as little or as much of the intervention as they would like, enabling them to go at their own pace and return to the intervention as many times as they would like. The participants also suggested that it would be ideal to keep the duration of the intervention to up to an hour, include children of different age groups, and use relatable images (ie, nonideal conditions that included artificial surfaces, urban environments, and adverse weather conditions). The participants stressed the importance of packaging the intervention using plain language—suitable for newcomers to Canada—while acknowledging diverse cultural and demographical contexts, as well as a positive and encouraging ethos that recognizes the ECE as the expert and person best positioned to support quality outdoor play.

Logic Model of the Problem

The literature review and focus group findings were translated into a logic model of the problem for the intervention (Figure 1). It yielded a clear set of determinants that could be addressed (or not) in the intervention, focusing on personal determinants within the individual (behavior change) and interpersonal levels (environment change).

Figure 1. Logic model of the problem.



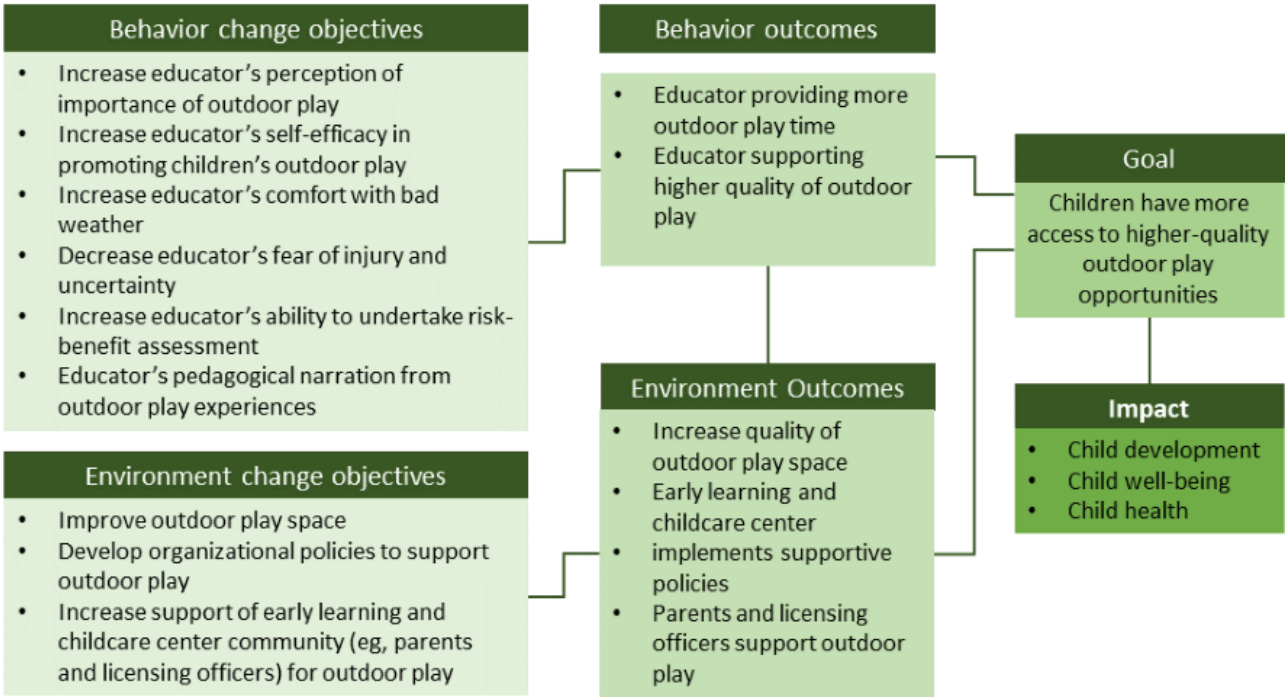
Intervention Goal

The intervention goal is to support ECEs and ELCC administrators to increase children's access to regular, sustained, and high-quality outdoor play at ELCCs.

IM Step 2: Intervention Outcomes and Objectives

The logic model of change identified behavior and environment change objectives and outcomes for the intervention (Figure 2).

Figure 2. Logic model of change.



IM Step 3: Intervention Design

Theoretical Underpinning

We used SCT [26] as a theoretical framework to guide the intervention design. SCT conceives that individuals are most motivated to act when they have high self-efficacy and dissatisfaction and believe that a change in behavior will lead to the desired outcome. More specifically, SCT includes elements such as self-efficacy ("I am capable of providing children at my center more opportunities for outdoor play"), outcome expectations ("Risky play will benefit children"), and self-evaluated dissatisfaction ("My fears are potentially harming children").

Underpinned by the notion that behavioral patterns are primarily determined by their social and cultural contexts, the taxonomy of BCT provides an array of strategies that help to change individuals' behavior [34]. To efficiently use this method in the OutsidePlay web-based intervention, each behavior and environment change objective was paired with a technique that can target the given determinant, which can be translated into a practical application in the target population's contexts [35]. The selected BCTs aligned with the behavior and environment objectives, providing a practical and specific evidence-based approach.

Intervention Content

A mock-up of the intervention was developed, consisting of the homepage and 3 chapters that guide users through a personalized journey: a brief introduction about children's outdoor play, self-reflection, interactive video scenarios, and goal setting. Table 1 summarizes the intervention content, the SCT constructs that were addressed, and the BCTs used for each element of the intervention. The interfaces of the intervention are available in Multimedia Appendix 2. The full intervention can be viewed on the OutsidePlay website [36].

Table 1. Intervention content, social cognitive theory constructs addressed, and behavior change techniques used.

Intervention	Description	Social cognitive theory construct	Behavior change technique[a]
Homepage: Introduction	• Introductory video on the benefits of outdoor play and introducing the intervention • Definition of outdoor and risky play and why it is important • Description of the intervention components • Logos of study partners	• Outcome expectations • Knowledge	• 5.1 Information about health consequences • 5.3 Information about social consequences • 5.6 Information about emotional consequences • 9.1 Credible source

Chapter 1: Reflection	• Introductory video to chapter 1
	• Self-reflection questions about the user's own childhood play experience:
	  • Who were you with?
	  • Where were you?
	  • What were you feeling?
	  • Imagine the sounds, sights, and smells you were experiencing
	  • Were you inside or outside?
	  • Were you taking risks?
	  • What was your favourite thing to do?
	  • What did you get out of it?
	  • How did this experience influence you?
	• Questions about the user's ELCCb
	  • How do children currently play at your center?
	  • How would you like children to be able to play at your center?
	• Finding the user's whys
	  • What is the one main reason why you want to support children's outdoor play opportunities?
	  • How do you support children's outdoor play at your center?
	  • What gets in your way the most in supporting children's outdoor play?
		• Outcome expectations
		• Knowledge
		• Barriers and opportunities
			• 6.2 Social comparison
			• 13.2 Framing or reframing
			• 13.3 Incompatible beliefs

Chapter 2: Six Interactive Video Scenarios	• Introductory video to chapter 2
	• Six interactive video scenarios
	  • Communicating with parents and caregivers
	  • Rough-and-tumble play
	  • Play at heights
	  • Conflict resolution
	  • Play with loose parts
	  • Play at speed
		• Outcome expectations
		• Knowledge
		• Observational learning
		• Barriers and opportunities
		• Self-efficacy
		• Behavioral skills
			• 1.2 Problem solving
			• 4.1 Instruction on how to perform the behavior
			• 5.1 Information about health consequences
			• 5.3 Information about social and environmental consequences
			• 5.6 Information about emotional consequences
			• 6.1 Demonstration of the behavior
			• 6.2 Social comparison
			• 9.1 Credible source
			• 9.3 Comparative imagining of future outcomes
			• 13.2 Framing or reframing

Chapter 3: Creating Your Plan	• Introductory video to chapter 3
	• Guide the user to establish a manageable goal to support children's outdoor play at their ELCC:
	  • What is one thing that you can do to support children's outdoor play?
	  • Invite the user to set a timeline for the goal
		• Outcome expectations
		• Self-efficacy
		• Behavioral skills
		• Intentions
			• 1.1 Goal setting (behavior)
			• 1.2 Problem solving
			• 1.3 Goal setting (outcome)
			• 1.4 Action planning

[a]The behavior change technique numbers in this column correspond to the numbering in the behavior change technique taxonomy described in the study by Michie et al [34].

[b]ELCC: early learning and childcare center.

The Homepage greets users with a video introducing the OutsidePlay web-based intervention. It then invites users to take part in a personalized journey to learn more about how to support outdoor play and set a plan to reach their goal. The Homepage then unpacks essential information about children's outdoor play. It covers what is outdoor play and why it is important for children, as well as the common challenges and barriers that ECEs and ELCC administrators encounter. The Homepage was built considering the BCTs of information about health, social, and emotional consequences and credible sources.

Chapter 1 is designed to guide users to find their reasons for why they want to promote children's outdoor play at their center. It invites users to think about their own childhood (where they played and whom they played with) and how they felt when they were playing outside and taking risks. This brings in users' private realms to have them more invested in the topic and equipped with perspectives other than those of ECEs or ELCC administrators. This exercise is to prepare users to compare and contrast their own outdoor play experiences with those of the children at their center. This affords an opportunity for users to critically assess why it is important for them to support children's outdoor play and reflect on their role. Users are then guided to consider the barriers and challenges they perceive in supporting outdoor play. In this chapter, the intervention uses BCTs of social comparison, framing or reframing, and incompatible beliefs.

Chapter 2 presents interactive video scenarios with animated characters in real-life ELCC outdoor space backgrounds. Initially, 8 scenarios were proposed: (1) communicating with parents and caregivers, (2) rough-and-tumble play, (3) play at heights, (4) conflict resolution, (5) play with loose parts, (6) play at speed, (7) play with a chance of getting lost, and (8) play near dangerous elements. These scenarios exhibit different situations that could happen in ELCC contexts based on the idea of outdoor risky play [37]. These scenarios are meant to address the barriers and challenges that users had identified in chapter 1 and offer ways to manage them. In this chapter, the OutsidePlay web-based intervention uses the BCTs of problem solving; instruction on how to perform the behavior; information about health, social, environmental, and emotional consequences; demonstration of the behavior; social comparison; credible source; comparative imagining of future outcomes; and framing or reframing to enhance their self-efficacy and outcome expectation.

Most of the scenarios embed the risk-benefit assessment process [38,39] to guide users' ways of thinking and decision-making. The general ethos is that children are competent and capable, and ECEs and ELCC administrators are best positioned to support children's outdoor play. This ethos underlines that children need to play freely and learn from their own efforts and mistakes, while taking responsibility for keeping themselves and others safe [38,39].

In each scenario, users are presented with a baseline story. For instance, the play-at-speed scenario begins with children playing tag on slippery ground (Figure 3). An ECE then appears and asks users what they should do and presents 2 possible choices based on the risk-benefit assessment process, for example, (1) "It's wet and muddy, let's play indoors" (active intervention) or (2) "Let the children keep playing" (open observation). The rest of the scenario plays out according to the choice users make, followed by a debrief video by an ECE summating the key takeaways and providing practical guidance for users. As the final step in chapter 2, users are invited to think about the most important message that they inferred from the given scenario.

Figure 3. Image of the baseline story of the Play at Speed scenario.

In chapter 3, with the learning imbibed from chapters 1 and 2, users are invited to think of a concrete and achievable goal and create a plan to accomplish it. It is a personalized journey, where they can carefully consider their barriers and challenges in providing children outdoor play at their center while focusing on their whys. They have the options to print out or email themselves their complete journey map, including their goal and the timeline. The OutsidePlay web-based intervention can take up to 100 minutes to complete, depending on participants' movements through each chapter.

Testing the Intervention With the Target Population

We conducted 12 individual cognitive interviews to test the intervention mock-up with the target audience. This involved observing the participants as they navigated the content and probing their thoughts and reactions. The individual cognitive interview participants were all women (12/12, 100%), many of whom held more than one role, including ECE (8/12, 67%), ELCC administrator (2/12, 17%), licensing officer (3/12, 25%), and ECE student (1/12, 8%), and had been working in the field for a mean of 17.9 (SD 9.23) years. After obtaining participant consent and demographic information, the full mock-up of the OutsidePlay web-based intervention was presented on PowerPoint (Microsoft Corporation) slides. As the primary purpose of the individual cognitive interview was to assess the resonance of the intervention with the target population, we focused on gathering practical feedback (eg, What do you think about the format of this intervention? Do you find this session engaging? What did you expect to find or learn before you started using the intervention? and Would you use it as a resource for children's outdoor play?). Each cognitive interview lasted 60-90 minutes.

Cognitive Interview Results

Of the 12 participants, 12 (100%) agreed that an intervention on children's outdoor play was timely, reflecting the recent growing interest in the topic of children's outdoor play. Their feedback helped ensure the use of appropriate language within the intervention that reflected the terminology used in the current early childhood education field. Originally, 8 interactive video scenarios were proposed to be included. On the basis of the individual cognitive interview participants' preferences, 2 were removed. The 6 scenarios that the participants found most resonant and applicable to their ELCC contexts were (1) communicating with parents and caregivers, (2) rough-and-tumble play, (3) play at heights, (4) conflict resolution, (5) play with loose parts, and (6) play at high speed. Play with a chance of getting lost and play near dangerous elements did not make the final list because most of the participants did not find them relevant to their practice. For example, most of them assessed that their ELCC's outdoor play space would not allow children to get lost (eg, fenced-in facilities or situated in a high-rise building), and losing a child on a field trip was perceived as very unlikely. As for play near dangerous elements, we proposed a scenario that involved children taking their boots off and playing in a mud puddle. Although we originally considered it a modest example of the dangerous natural element aspect of the scenario, the participants did not find this scenario relatable and, instead, suggested adding the muddy and slippery element into the play-at-high-speed scenario.

In addition, based on their feedback, we enhanced some of the answer options for the self-reflection questions in chapter 1 and used plain language as much as possible with an encouraging tone, acknowledging users with varying degrees of comfort and knowledge in outdoor play. For example, we made a series of short videos that premised each question and acknowledged the different positions and backgrounds that users might come from. The intention was to create a safe place for users to reflect on the question.

IM Step 6: Intervention Evaluation Plan

Hypotheses

We will assess the efficacy of the intervention to increase ECEs' and ELCC administrators' tolerance for children's outdoor play (primary outcome) and attain a behavior change goal related to providing outdoor play opportunities for children at their center (secondary outcome). We hypothesize as follows:

1. The participants completing the OutsidePlay web-based intervention will have a significantly greater increase of tolerance of risk in play than those in the control group.
2. A greater proportion of the participants completing the OutsidePlay web-based intervention will attain their behavior change goal than those in the control group.

RCT Design

The study will use a single-blind (researchers and outcome assessors), two-parallel-group RCT design to determine the superior efficacy of the intervention over the control group. The trial has been registered on ClinicalTrials.gov with the US National Institute of Health's Protocol Registration and Results System [40] (NCT04624932), which was released on April 26, 2021.

Information on the study will be available for the potential participants' review on the web. It will detail the entire study procedure, including the consenting, randomization, and follow-up process. When the eligible participants provide consent to participate, they will be invited to complete the baseline survey, including a demographic questionnaire and survey measurements. Next, each participant will be randomized to 1 of the 2 groups by the REDCap electronic data capture intervention [41] hosted at the BC Children's Hospital Research Institute. The randomization list will be generated beforehand by the Sealed Envelope service (Sealed Envelope Ltd) using randomized permuted blocks of sizes 4, 6, and 8. The list will then be transferred to REDCap. The groups include (1) the control and (2) the OutsidePlay web-based intervention. The participants may assume which intervention is the *intervention of interest* based on the details of the 2 groups involved in the RCT in the consent form: control (eg, generic information) and intervention (eg, web-based tool). The participants will have equal likelihood of assignment to each group using a basic (rather than stratified) randomization method. They will not be blinded to allocation because the nature of the intervention does not allow it. There will be no outcome assessors because it will

be exclusively on the web. Allocation will be concealed to the researchers at participant assignment.

We initially considered stratifying randomization by different characteristics. However, ELCCs in Canada are very diverse, and not all of them would necessarily influence access to higher-quality outdoor play. From the literature, key characteristics include the perceptions of the ECEs toward outdoor play as well as the quality of the available outdoor play environments. These can vary widely, regardless of the region, urban or rural location, or other site characteristics. Given that our intervention is designed to influence ECE perceptions, stratification according to this characteristic was not appropriate.

RCT Sample Size Consideration

The Teacher Tolerance of Risk in Play Scale (T-TRiPS) [42] will be our main study outcome. The T-TRiPS is a 25-item measure with dichotomous yes or no responses on items that reflect the 6 categories of risky play in the study by Sandseter [1] (great heights, high speed, dangerous tools, dangerous elements, rough-and-tumble, and disappear or get lost). Sample items include, "Would you let your students climb as high as they wanted in a tree or another surface?" and "Do you wait to see how well your students manage challenges before getting involved?" Possible scores range from –5 to 5, with higher scores reflecting more risk tolerance; in previous research, the scores ranged from –4.09 to 4.56 [42]. The T-TRiPS is a modified version of the TRiPS for parents [43] to measure teachers' perceptions of risk. The T-TRiPS has been psychometrically validated [42], and we will administer it strictly on the web through REDCap where participants will input their responses directly.

With a sample size of 206 ECEs in total, a linear mixed model examining the impact of intervention compared with control, including an interaction with time, will have 80% power at 0.05 level of significance to detect a difference of 0.75 between the intervention and control groups when the SD is 1.82 and the correlation value between repeated observations is 0.75. From our previous work [24,25], we anticipate requiring 324 complete baseline assessments among ECEs and ELCC administrators who will then be randomized into the 2 groups. Specifically, we are assuming a retention rate of 74.7% (242/324) at our first assessment and a retention rate of 85.1% (206/242) at our second assessment, which would result in a final sample of 206 ECEs, corresponding to 103 in each group.

Interventions

The participants in the control group will be provided with a PDF copy of the Position Statement on Active Outdoor Play, which includes information on research and recommendations for action regarding children's outdoor play [44,45]. This 4-page document was developed by a cross-sectoral consortium of researchers, practitioners, and stakeholders to provide recommendations for parents, educators, health professionals, administrators, and various levels of government to address the barriers to children's outdoor play. This PDF will be delivered on the web through REDCap. The participants in the web-based intervention group will be provided with a link to the intervention [36].

RCT Measurement Occasions and Follow-ups

The participants will complete a questionnaire package at 3 time points: baseline, before the intervention; 1 week after the intervention; and 3 months after the intervention. Long-term change is unlikely if participants do not make initial changes; thus, the 1-week postintervention follow-up was selected to assess short-term efficacy, while still providing participants sufficient time to make their initial planned changes. The 3-month postintervention follow-up will assess long-term efficacy once the participants have had 3 months to reflect on the intervention and implement change. Survey data will be collected and managed using REDCap [41]. Baseline data collected will include sociodemographic data: sex, age, language spoken most often at home, province of employment, role, and length of time in the early childhood education field. The participants will also complete measures to assess primary and secondary outcomes at each time point. We are anticipating completing the data collection by the end of summer 2021.

RCT Outcome Measures

The primary outcome measure is change in the participants' T-TRiPS score. We expect an increase. The secondary outcome measure is self-reported behavior change on attaining the goal that the participants set for themselves upon completion of the allocated intervention. At baseline, the participating ECEs will be invited to think about what they could do to give children at their center more opportunities for outdoor play and to set a specific and realistic goal for themselves. This goal will be used at the 2 follow-ups to assess their goal attainment. The participants will be asked to report if they have attained their goal (ie, yes or no) at 1 week and then 3 months after the intervention.

Adherence to Intervention

Adherence to the OutsidePlay web-based intervention will be measured and verified by an automated system that will archive complete participant journey maps (refer to step 3).

Data Management

Data will be entered by the participants directly into REDCap, which is hosted on a secure, firewall-protected server at the BC Children's Hospital Research Institute. The database is password protected and only accessible by responsible staff members. REDCap maintains an audit trail that captures all user activity, including data manipulation and export. Exported data will be stored on a secure, firewall-protected server at the BC Children's Hospital Research Institute in a password-protected file only accessible by responsible staff members.

The participants' confidentiality will be highly respected, and each participant will be assigned a unique study number in the trial. This number will not include any personal identifiable information. A contact (ie, the University of British Columbia Office of Research Ethics) to report concerns about the rights of the research participants will be provided. This is to ensure that the participants have access to support if the trial was harmful to them.

RCT Statistical Analyses

All participants allocated to 1 of the 2 groups will be included in the analyses, regardless of deviation from the protocol, missed follow-up observations, or withdrawal. All baseline characteristics will be summarized by means and SDs or frequencies and percentages as appropriate by intervention group. T-TRiPS data will be visualized in the form of box plots by intervention group and time. To test our hypothesis that the ECEs completing the intervention will have a significantly greater increase of tolerance of risk in play, linear mixed effects models will be built to assess the relationship between intervention group and T-TRiPS score. Time will be included in the model as a categorical variable, and the baseline T-TRiPS score as well as an interaction term between time and intervention will be included to explore the possibility that the impact of the intervention diminishes over time. Intent-to-treat analysis of T-TRiPS scores will use last observation carried forward as the method of imputation. To test our hypothesis that a greater proportion of the participants completing the intervention will attain their behavior change goal than those in the control group (secondary outcome measure), the 3-month postintervention behavior change goal outcome (yes or no) will be the primary outcome of interest, and we will use logistic regression analysis. Model diagnostics will be run to test modeling assumptions. We will not perform any additional analyses such as subgroup or adjusted analyses.

Quality Assurance and Monitoring

A written standard operating procedure and researcher protocol manual will be used for staff training for all study procedures to ensure data quality and consistent application of the study protocols. The state of recruitment, data completeness, control of correct randomization, and allocation of participants will be regularly verified. In all, 3 sets of automated reminders will be deployed to the participants' email addresses if the baseline survey is not completed within 24, 48, and 60 hours. The participants will also receive 3 sets of automated reminders (eg, 1 each day for 3 days) through email at the 1-week and 3-month postintervention follow-ups, provided that they have completed their baseline requirement. Any deviations from the expected standards will be reported to, and discussed with, the study manager. Any protocol modifications will be reported to the University of British Columbia and Children's and Women's Health Centre of British Columbia Research Ethics Board, as well as the US National Institute of Health's Protocol Registration and Results System.

IM Step 4: Intervention Production

After making modifications to the intervention based on the cognitive interview participants' feedback and expert advice from partners and collaborators, we finalized the mock-up and moved into full production, developing user interface, media, and subsequently assembling the platform in its entirety. A series of beta-testing sessions was conducted with 9 participants: 5 (56%) through individual cognitive interviews and 4 (44%) who tested the intervention at their own convenient time and shared feedback through email. The aim of beta testing was to finesse the OutsidePlay web-based intervention itself (eg, fix bugs and glitches) and to prepare for the RCT in step 6.

IM Step 5: Intervention Implementation Plan

Consistent with the BCT credible source [34], a partnership with trusted organizations within the ECE sector in Canada is critical to the implementation of the intervention once it has been evaluated. We have extensive relationships in the ECE sector in Canada and sought to increase the persuasiveness of the message in the OutsidePlay intervention by using our target audience's pre-existing and trusted communication channels. We identified >600 relevant childcare programs and centers, postsecondary institutions, childcare resources and referral centers, and government departments across Canadian provinces to assist with deployment of the intervention once it has been evaluated.

We developed marketing materials suitable for the organizations and target audience, including the introductory video on the OutsidePlay web-based intervention that could be posted separately from the platform. As described in Table 1, the introductory video addresses the SCT constructs of outcome expectations and knowledge through the BCTs information about consequences (health, social, and emotional) from a credible source (university and children's hospital). Furthermore, we developed 5 infographics depicting various key messages of the intervention that included a quick response code directing users to the intervention [36] (Multimedia Appendix 3).

Consistent with the BCT rewarding completion, we contacted ECE registries in Canadian provinces to register the intervention as a workshop, where applicable, to provide professional development certificates for users who completed the intervention. This option was available for ECEs for 6 of the 10 Canadian provinces. Furthermore, many registries agreed to assist with the RCT participant recruitment and promote the intervention to their members once the RCT results were finalized. The intervention was soft launched on December 1, 2020 [36]. It will be officially launched upon completion of the RCT analyses. The intervention content will be frozen during the RCT.

Discussion

Outdoor Play Within ELCCs

The importance of outdoor play to children's health development and outcomes is clear [1-3]; yet, there are many barriers to ensuring daily opportunities for high-quality outdoor play. ELCCs can be critical settings for outdoor play opportunities and can help reduce inequities in access to outdoor play. Many ELCCs struggle to provide regular and high-quality outdoor play opportunities, citing multiple perceived barriers [15,16]. In Canada, there are few interventions to increase outdoor play opportunities for children in ELCCs; most of the existing ones consist of professional development workshops of varying length and quality. To our knowledge, no interventions have been developed that are grounded in health behavior change theory and techniques and none that have been evaluated through an RCT. Influenced by our previous success in developing an effective intervention for parents [25], we designed the OutsidePlay intervention to shift ELCC stakeholders' perceptions and practices to support outdoor play within ELCCs.

Strengths and Limitations

Guided by the systematic IM process and using BCTs grounded in SCT, the OutsidePlay web-based intervention represents a novel, evidence-based, and rigorously designed tool to support change. The IM process enabled considering and addressing the target population's key issues, needs, and challenges in the context of providing children high-quality outdoor play in the ELCC setting. More specifically, the intervention design and development followed an organic process that involved collaboration among researchers, practitioners, and digital technology experts, with regular consultation with the target population. This inclusion of various stakeholders from the outset enabled the development of content that was relatable, acceptable, and engaging, using the preferred modality and user-friendly media.

Furthermore, the web-based format reduces barriers to uptake by allowing for widespread and free access. Web-based delivery also made it possible for users to use the intervention at their convenience and to return to the intervention, picking up from where they left off. The RCT will evaluate the efficacy of the intervention, providing necessary evidence to inform the mobilization of the intervention and widespread efforts to support children's outdoor play. We expect that a routine application setting will be slightly different than the protocol used in the trial because it will not involve reminders and payment upon completion of the intervention. However, users who use the intervention in a nontrial setting will still be able to receive a professional development certificate for 100 minutes.

The primary study limitation is that the accessibility of the intervention is not always guaranteed because of the system and bandwidth requirements of the content in the intervention (ie, high-resolution media). This issue was well known from our previous study, and we designed the intervention to adjust the quality of videos and images based on each user's internet bandwidth. However, this did not solve the problem caused by users accessing the intervention from old or incompatible devices. Likewise, although we attempted to ensure that the intervention was as user-friendly and easy to navigate as possible, a minimum level of computer literacy was necessary to use it. We recognize that internet access and computer literacy are issues with the potential to increase inequities and that they require further careful consideration.

Second, because of the nature of the intervention, the participants could not be blinded, which is a typical limitation in eHealth trials. During the consenting process, the participants will be informed that there will be 2 groups in the trial (ie, control and intervention). The participants may be able to determine the group they are assigned to based on the differences in time commitment.

Another limitation stems from the study samples included in step 1 (focus groups) and step 3 (cognitive interviews). Most of the interview participants resided in the Metro Vancouver area (urban or suburban) in British Columbia, Canada. Hence, key issues, needs, and challenges pertinent to other Canadian provinces, let alone other countries, may not be reflected in the intervention. For example, the Metro Vancouver area has a milder climate than many other parts of Canada. Therefore, specific cold weather–related issues (eg, snow and freezing rain) were not prominent in our interviews.

Conclusions

The OutsidePlay web-based intervention guides users through a personalized journey that is grounded in behavior change theory and techniques. If effective, this relatively low-cost, easily accessible intervention may have the potential to address ECEs' and ELCC administrators' perceived challenges and needs in promoting and accommodating children's outdoor play in ELCC settings, thereby supporting high-quality early childhood education.

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Authors' Contributions

MB conceived of the study. MB led development of the study design, with contribution from CSH, JJ, and EO. MB conducted the study analysis, with contribution from CSH, FM, MZ, TC, and EF. MB and CSH wrote the initial and subsequent drafts of this manuscript. AM advised on the statistical analytical plan. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Focus Group Interview Questions.

[PDF File (Adobe PDF File), 163 KB - resprot_v10i11e31041_app1.pdf]

Multimedia Appendix 2
Interfaces of OutsidePlay Intervention.
[PDF File (Adobe PDF File), 51324 KB - resprot_v10i11e31041_app2.pdf]

Multimedia Appendix 3
Infographics.
[PDF File (Adobe PDF File), 1188 KB - resprot_v10i11e31041_app3.pdf]

References

1. Sandseter EB. Characteristics of risky play. J Adventure Educ Outdoor Learn 2009 Jun 29;9(1):3-21 [FREE Full text] [doi: 10.1080/14729670802702762]
2. Brussoni M, Gibbons R, Gray C, Ishikawa T, Sandseter E, Bienenstock A, et al. What is the relationship between risky outdoor play and health in children? A systematic review. Int J Environ Res Public Health 2015 Jun 08;12(6):6423-6454 [FREE Full text] [doi: 10.3390/ijerph120606423] [Medline: 26062038]
3. Wray A, Martin G, Ostermeier E, Medeiros A, Little M, Reilly K, et al. Physical activity and social connectedness interventions in outdoor spaces among children and youth: a rapid review. Health Promot Chronic Dis Prev Can 2020 Apr;40(4):104-115 [FREE Full text] [doi: 10.24095/hpcdp.40.4.02] [Medline: 32270668]
4. Clark H, Coll-Seck AM, Banerjee A, Peterson S, Dalglish SL, Ameratunga S, et al. A future for the world's children? A WHO-UNICEF-Lancet Commission. Lancet 2020 Feb 22;395(10224):605-658. [doi: 10.1016/S0140-6736(19)32540-1] [Medline: 32085821]
5. Kyttä M, Hirvonen J, Rudner J, Pirjola I, Laatikainen T. The last free-range children? Children's independent mobility in finland in the 1990s and 2010s. J Transp Geogr 2015 Jul;47:1-12 [FREE Full text] [doi: 10.1016/j.jtrangeo.2015.07.004]
6. Bento G, Dias G. The importance of outdoor play for young children's healthy development. Porto Biomed J 2017;2(5):157-160 [FREE Full text] [doi: 10.1016/j.pbj.2017.03.003] [Medline: 32258612]
7. Gray P. The decline of play and the rise of psychopathology in children and adolescents. Am J Play 2011;3(4):443-463 [FREE Full text]
8. Holt NL, Neely KC, Spence JC, Carson V, Pynn SR, Boyd KA, et al. An intergenerational study of perceptions of changes in active free play among families from rural areas of Western Canada. BMC Public Health 2016 Aug 19;16(1):829 [FREE Full text] [doi: 10.1186/s12889-016-3490-2] [Medline: 27538781]
9. Bassett D, John D, Conger S, Fitzhugh E, Coe D. Trends in physical activity and sedentary behaviors of United States youth. J Phys Act Health 2015 Aug;12(8):1102-1111. [doi: 10.1123/jpah.2014-0050] [Medline: 25347913]
10. Moore SA, Faulkner G, Rhodes RE, Brussoni M, Chulak-Bozzer T, Ferguson LJ, et al. Impact of the COVID-19 virus outbreak on movement and play behaviours of Canadian children and youth: a national survey. Int J Behav Nutr Phys Act 2020 Jul 06;17(1):85 [FREE Full text] [doi: 10.1186/s12966-020-00987-8] [Medline: 32631350]
11. Shaw B, Bicket M, Elliott B, Fagan-Watson B, Mocca E, Hillman M. Children's independent mobility: an international comparison and recommendations for action. Policy Studies Institute. 2015 Jul. URL: https://www.nuffieldfoundation.org/sites/default/files/files/7350_PSI_Report_CIM_final.pdf [accessed 2021-09-23]
12. Mitra R, Waygood O, Fullan J. Subjective well-being of Canadian children and youth during the COVID-19 pandemic: the role of the social and physical environment and healthy movement behaviours. Prev Med Rep 2021 May 18;23:101404 [FREE Full text] [doi: 10.1016/j.pmedr.2021.101404] [Medline: 34189017]
13. Heckman J. The economics of inequality: the value of early childhood education. Am Educ 2011;35(1):31-35 [FREE Full text]
14. Child care in Canada. Statistics Canada, Government of Canada. 2015 Nov 30. URL: https://www150.statcan.gc.ca/n1/pub/89-652-x/89-652-x2014005-eng.htm#a2 [accessed 2021-09-20]
15. Copeland K, Khoury J, Kalkwarf H. Child care center characteristics associated with preschoolers' physical activity. Am J Prev Med 2016 Apr;50(4):470-479 [FREE Full text] [doi: 10.1016/j.amepre.2015.08.028] [Medline: 26585052]
16. Dietze B, Kashin D. Outdoor play - building capacity to support outdoor play in early childhood education. Encyclopedia on Early Childhood Development. 2019. URL: http://www.child-encyclopedia.com/outdoor-play/according-experts/building-capacity-support-outdoor-play-early-childhood-education [accessed 2021-09-23]
17. Alden C. Advancing outdoor play and early childhood education: a discussion paper. The Lawson Foundation. 2019. URL: https://lawson.ca/op-discussion-paper/ [accessed 2021-09-23]
18. Karsten L. It all used to be better? Different generations on continuity and change in urban children's daily use of space. Child Geogr 2005 Dec;3(3):275-290. [doi: 10.1080/14733280500352912]
19. Tandon PS, Saelens BE, Christakis DA. Active play opportunities at child care. Pediatrics 2015 Jun;135(6):1425-1431 [FREE Full text] [doi: 10.1542/peds.2014-2750] [Medline: 25986016]

20. de Lannoy L, Rhodes RE, Moore SA, Faulkner G, Tremblay MS. Regional differences in access to the outdoors and outdoor play of canadian children and youth during the COVID-19 outbreak. Can J Public Health 2020 Dec;111(6):988-994 [FREE Full text] [doi: 10.17269/s41997-020-00412-4] [Medline: 33057923]
21. Moore SA, Faulkner G, Rhodes RE, Vanderloo LM, Ferguson LJ, Guerrero M, et al. Few Canadian children and youth were meeting the 24-hour movement behaviour guidelines 6-months into the COVID-19 pandemic: follow-up from a national study. Appl Physiol Nutr Metab 2021 Aug 09:1-16 [FREE Full text] [doi: 10.1139/apnm-2021-0354] [Medline: 34370965]
22. Public health guidance for child care settings. BC Centre for Disease Control. 2021. URL: http://www.bccdc.ca/Health-Info-Site/Documents/COVID_public_guidance/Guidance_Child_Care.pdf [accessed 2021-09-23]
23. Riazi NA, Wunderlich K, Gierc M, Brussoni M, Moore SA, Tremblay MS, et al. "You can't go to the park, you can't go here, you can't go there": exploring parental experiences of COVID-19 and its impact on their children's movement behaviours. Children (Basel) 2021 Mar 12;8(3):219 [FREE Full text] [doi: 10.3390/children8030219] [Medline: 33809221]
24. Brussoni M, Ishikawa T, Han C, Pike I, Bundy A, Faulkner G, et al. Go play outside! Effects of a risk-reframing tool on mothers' tolerance for, and parenting practices associated with, children's risky play: study protocol for a randomized controlled trial. Trials 2018 Mar 07;19(1):173 [FREE Full text] [doi: 10.1186/s13063-018-2552-4] [Medline: 29514699]
25. Brussoni M, Han CS, Lin Y, Jacob J, Pike I, Bundy A, et al. A web-based and in-person risk reframing intervention to influence mothers' tolerance for, and parenting practices associated with, children's outdoor risky play: randomized controlled trial. J Med Internet Res 2021 Apr 27;23(4):e24861 [FREE Full text] [doi: 10.2196/24861] [Medline: 33904820]
26. Michie S, Johnston M, Francis J, Hardeman W, Eccles M. From theory to intervention: mapping theoretically derived behavioural determinants to behaviour change techniques. Appl Psychol 2008 Jul 08;57(4):660-680. [doi: 10.1111/j.1464-0597.2008.00341.x]
27. Wheeler A, Fowler J, Hattingh L. Using an intervention mapping framework to develop an online mental health continuing education program for pharmacy staff. J Contin Educ Health Prof 2013;33(4):258-266. [doi: 10.1002/chp.21198] [Medline: 24347104]
28. Li D, Moskowitz D, Macapagal K, Saber R, Mustanski B. Using intervention mapping to developmentally adapt an online HIV risk reduction program for adolescent men who have sex with men. Prev Sci 2020 Oct;21(7):885-897. [doi: 10.1007/s11121-020-01148-w] [Medline: 32761287]
29. Batterham P, Calear A. Preferences for internet-based mental health interventions in an adult online sample: findings from an online community survey. JMIR Ment Health 2017 Jun 30;4(2):e26 [FREE Full text] [doi: 10.2196/mental.7722] [Medline: 28666976]
30. Bulletin flash-info – travail et rémunération. Institut de la Statistique du Québec. URL: https://statistique.quebec.ca/fr/document/bulletin-flash-info-travail-et-remuneration [accessed 2021-09-23]
31. Highlights of women's earnings in 2015. U.S. Bureau of Labor Statistics. 2016 Nov. URL: https://www.bls.gov/opub/reports/womens-earnings/2015/pdf/home.pdf [accessed 2021-09-23]
32. Braun V, Clarke V, Hayfield N, Terry G. Thematic analysis. In: Handbook of Research Methods in Health Social Sciences. Singapore: Springer; 2019:843-860.
33. Bronfenbrenner U. Ecological models of human development. In: Postlethwaite TN, Husen T, editors. The International Encyclopedia of Education, 2nd Edition. Amsterdam: Elsevier; 1994:37-43.
34. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med 2013 Aug;46(1):81-95. [doi: 10.1007/s12160-013-9486-6] [Medline: 23512568]
35. Kok G, Gottlieb NH, Peters GY, Mullen PD, Parcel GS, Ruiter RA, et al. A taxonomy of behaviour change methods: an intervention mapping approach. Health Psychol Rev 2016 Sep;10(3):297-312 [FREE Full text] [doi: 10.1080/17437199.2015.1077155] [Medline: 26262912]
36. Brussoni M, Han C, Jacob J. What is outdoor play? OutsidePlay. URL: https://outsideplay.ca/ [accessed 2021-09-19]
37. Sandseter EB. Categorising risky play—how can we identify risk‐taking in children's play. Eur Early Child Educ Res J 2007 Jun 25;15(2):237-252. [doi: 10.1080/13502930701321733]
38. Gill T, Power M, Brussoni M. Risk benefit assessment for outdoor play: a Canadian toolkit. Outdoor Play Canada. 2019. URL: https://www.outdoorplaycanada.ca/portfolio_page/risk-benefit-assessment-for-outdoor-play-a-canadian-toolkit/ [accessed 2021-09-23]
39. Ball D, Gill T, Spiegal B. Managing risk in play provision: implementation guide. Play England. London: Department for Children, Schools & Families, 2008; 2012. URL: https://dera.ioe.ac.uk/8625/1/00942-2008DOM-EN.pdf [accessed 2021-09-23]
40. Clinical Trials. US National Library of Medicine. URL: https://clinicaltrials.gov/ [accessed 2021-09-23]
41. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)— a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 Apr;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
42. Ihrig K. Teacher tolerance of risk in play scale (T-TRiPS): evaluating the psychometric properties of a new measure. Colorado State University. 2020. URL: https://mountainscholar.org/handle/10217/232469 [accessed 2021-09-23]

43. Hill A, Bundy AC. Reliability and validity of a new instrument to measure tolerance of everyday risk for children. Child Care Health Dev 2014 Jan;40(1):68-76. [doi: 10.1111/j.1365-2214.2012.01414.x] [Medline: 22846064]
44. Tremblay M, Gray C, Babcock S, Barnes J, Bradstreet C, Carr D, et al. Position statement on active outdoor play. Int J Environ Res Public Health 2015 Jun 08;12(6):6475-6505 [FREE Full text] [doi: 10.3390/ijerph120606475] [Medline: 26062040]
45. The biggest risk is keeping kids indoors - The ParticipACTION report card on physical activity for children and youth. ParticipACTION. 2015. URL: https://participaction.cdn.prismic.io/participaction%2F61cf55e8-c1c0-42c7-ba6b-1480fd2c29b9_participaction-2015-report-card-full.pdf [accessed 2021-09-22]

Abbreviations

BCT: behavior change technique
ECE: early childhood educator
ELCC: early learning and childcare center
IM: intervention mapping
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SCT: social cognitive theory
T-TRiPS: Teacher Tolerance of Risk in Play Scale

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Protocol

Health Education Through a Campaign and mHealth to Enhance Knowledge and Quality of Life Among Patients With Chronic Kidney Disease in Bangladesh: Protocol for a Randomized Controlled Trial

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Abstract

Background: Despite the growing burden of chronic kidney disease (CKD), disease knowledge and understanding are still lacking, especially in Bangladesh.

Objective: The aim of this study was to evaluate the outcome of a health education intervention in order to enhance knowledge, health-related quality of life (QOL), and motivation regarding healthy lifestyles among rural and periurban adults suffering from CKD.

Methods: A parallel-group (1:1) randomized controlled trial is ongoing in the Mirzapur subdistrict, Bangladesh, where two groups of patients with CKD are being compared. Patients aged 18 years and over with CKD (stages 1-3) were enrolled in November 2020. Patients were randomly allocated into either the intervention group (n=63) or the control group (n=63). The control group received usual treatment, while the intervention group received health education through a CKD campaign facilitated by a nephrologist and via mHealth (ie, periodic mobile phone calls) from community health workers. Both groups were followed up for a period of 6 months. The primary endpoint is patients' increased knowledge measured using the Chronic Kidney Disease Knowledge Questionnaire. The secondary endpoints are improved QOL measured using the standardized EuroQol 5-Dimension 5-Level (EQ-5D-5L) questionnaire as well as improvements in the levels of blood pressure, BMI, serum creatinine, fasting blood sugar, hemoglobin, cholesterol, high-density lipoprotein cholesterol, triglyceride, serum uric acid, blood urea nitrogen, and albumin to creatinine ratio.

Results: Enrollment of participants began in November 2020; the intervention and follow-up were completed in May 2021. We enrolled 126 patients in the study. Patients' mean ages were 57.97 (SD 15.03) years in the control group and 57.32 (SD 14.37) years in the intervention group. There were 45 out of 63 (71%) females in the control group and 38 out of 63 (60%) females in the intervention group. In addition, there were 38 out of 63 (60%) literate patients in the control group and 33 out of 63 (52%) literate patients in the intervention group.

Conclusions: It is expected that a combined approach, incorporating both a CKD campaign and mHealth, for health education may be an effective tool for increasing knowledge and improving QOL among patients with CKD.

Trial Registration: ClinicalTrials.gov NCT04094831; https://clinicaltrials.gov/ct2/show/NCT04094831

International Registered Report Identifier (IRRID): DERR1-10.2196/30191

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KEYWORDS

chronic kidney disease; campaign; mHealth; knowledge; Bangladesh

Introduction

Background

Chronic kidney disease (CKD) is a public health concern worldwide [1] and directly affects the global burden of morbidity and mortality [2]. CKD is associated with substantial financial costs for both patients and health care systems, and low- and middle-income countries (LMIC) have a much higher economic burden of CKD than developed countries [3]. If the stage of CKD advances in patients, the cost of medical treatment increases [4]. In LMIC, most people with kidney failure have insufficient access to lifesaving renal replacement therapy [5]. Diabetes, hypertension, obesity, and aging are the leading associated factors for CKD throughout the world [6]. These comorbidities make patients with CKD more vulnerable to end-stage renal disease (ESRD) [7].

Knowledge and self-management behaviors must be learned and practiced in order to slow the progression of CKD [8]. Studies have documented that knowledge is essential for slowing kidney function advancement through behavior adjustments, such as physical exercise, dietary changes, patient monitoring (eg, blood pressure [BP] and blood glucose), and adherence to medication [9]. Patients with CKD may benefit from knowledge to change their behavior, improve their outcomes, and lower their mortality rates [10]. Considering the increasing prevalence of CKD, only 6% of the general population and 10% of those at high risk are aware of their CKD status in LMIC [11]. This low health literacy and unawareness in the early stage of the disease are ultimately responsible for CKD disease progression [12]. It has been noted, however, that proper CKD knowledge and management as well as mitigation of CKD-related risks may delay the progression to ESRD and other interrelated health consequences [10,13]. However, most of the patient education research regarding CKD has focused on patients with ESRD. A few studies on CKD have been conducted in Bangladesh, where most were prevalence studies based on a hospitalized urban population; however, there has been no such study in rural Bangladesh describing the knowledge of CKD and health-related quality of life (QOL).

In the field of nephrology, both developed and developing countries are still implementing mobile health (mHealth) [14,15]. However, mobile phone call–based health education has great potential to provide CKD knowledge and improve QOL because it relies on basic mobile technology and requires limited literacy or numeracy skills [16]. In countries with minimal or no national health insurance, such as Bangladesh, CKD education in the early stages of the disease could be an integral part of patient management and the reduction of its related risk factors to slow down its progression; the need is greater in rural and periurban areas. Community health workers (CHWs) have the potential to make a significant difference in the community's well-being as well as in the lives of people living with kidney disease [17]. A nephrologist-facilitated health campaign, on the other hand, has high potential for delivering CKD education. Thus, this study aimed to evaluate the outcome of a health education intervention in order to enhance knowledge, health-related QOL, and motivation about healthy lifestyle among rural and periurban adults suffering from CKD (stages 1-3).

Hypothesis

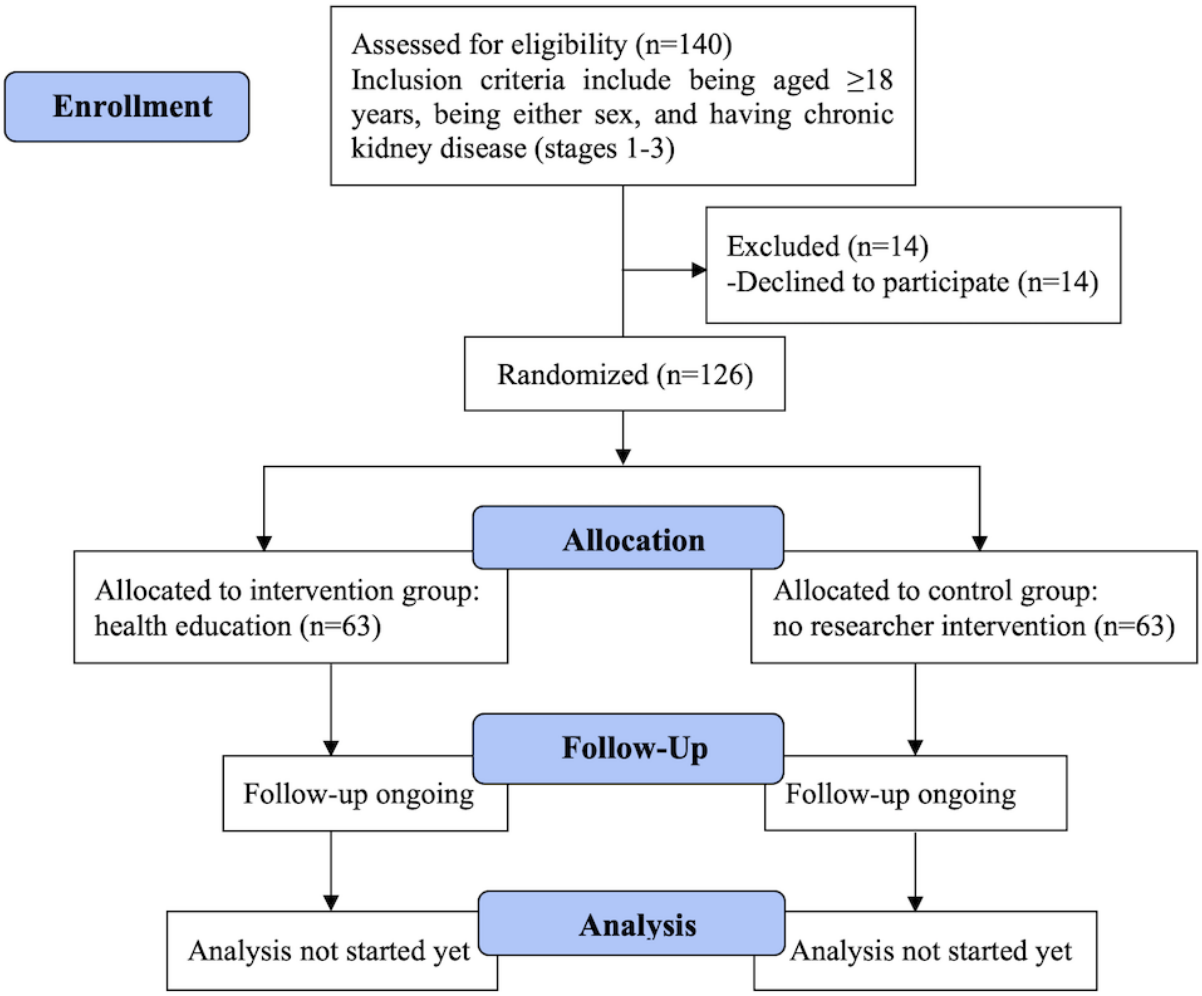
We hypothesize that the knowledge and health-related QOL of patients with CKD will be improved by health education provided by a CKD campaign and a mobile phone call–based intervention.

Methods

Design

This study is a community-based, single-centered, prospective, open-label, two-arm (1:1), randomized control trial involving patients with CKD and is being conducted in rural and periurban areas of Bangladesh. This study has been designed in accordance with the CONSORT (Consolidated Standards of Reporting Trials) [18] and SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [19]. The study flowchart is shown in Figure 1. The total study duration was planned to be 1 year; however, the intervention started in mid-November 2020 and the follow-up period was 6 months long. The last follow-up was completed in May 2021.

Figure 1. Flowchart of the study.



Study Site

This study was conducted in the demographic surveillance system (DSS) area of the Mirzapur subdistrict within the Tangail district, which is located about 60 km north of Dhaka, the capital city of Bangladesh. It has a mixed rural and periurban population [20]. The subdistrict has 13 unions—it is the smallest administrative unit—and 219 villages. Among the 10 unions in Mirzapur that comprise the DSS area, three unions—Mirzapur Sadar, Bhatgram, and Gorai—nearest to our sentinel health facility, which is popularly known as Kumudini Hospital, were selected purposively due to budgetary constraints and time limitations. The study participants were required to visit Kumudini Hospital Laboratory for their study-related investigations and had lower travel costs compared to other areas.

Study Population and Eligibility Criteria

We recruited patients for this study from among the residents of the DSS. Inclusion criteria for enrollment in the study were as follows: aged 18 years and older, either sex, diagnosed with CKD (stages 1-3: estimated glomerular filtration rate=30-59 mL/min/1.73 m^2 and/or albumin to creatinine ratio [ACR]≥30 mg/g for more than 3 months) [21], had lived steadily in the locality for at least 5 years, had a personal cell phone or access to a shared phone, and had given written informed consent to participate. The following were excluded from the study: individuals who were hospitalized at the time of enrollment; had any known serious illness with questionable prognosis, for example, stage 4 or 5 CKD, malignancy, mental illness, congenital disease, and physical disability, if they had prescriptions; and did not agree to give consent.

Randomization

A permuted block-randomization technique was performed using a block size of 6 based on a computer-generated random number sequence. An experienced statistician, not involved in the study in any way, prepared the randomization table and placed the study IDs of the patients with CKD, along with their corresponding intervention allocations, into serially numbered sealed envelopes according to the randomization schedule; these corresponded to the serial numbers of the patients with CKD. These envelopes were kept in an office locker. Allocations to intervention and control groups were concealed in identical sealed envelopes that were only to be opened when the study patient was ready for enrollment under the supervision of the principal investigator. This took place after a patient with CKD

was recruited to the study, after obtaining voluntary informed written consent and assignment of a study ID.

Study Activities and Content

During home visits, the CHWs used a Portable Health Clinic (PHC) box with the essential diagnostic equipment for this research; details are described elsewhere [22,23]. At baseline, CHWs performed home visits to obtain written informed consent and to interview the study patients by administering field-tested standardized questionnaires. The questionnaires collected the following data: sociodemographic information, such as age, gender, marital status, religion, occupation, educational background, and income per month; patients' current medical status, including medication use; patients' medical history; and patients' family history (3rd generation), including current and immediate-past medical status. The same information was collected at 3 months and at 6 months, in case of any changes from baseline. To evaluate the level of knowledge, awareness, and QOL on the part of the study patients, the CHWs also administered questionnaires at baseline to collect this data and administered the same questionnaire at 3 months and at 6 months.

CHWs also performed physical examinations at baseline and performed them again at 3 months and at 6 months to measure the following: BP, pulse, height, weight, waist and hip circumferences, and mid–upper arm circumference. However, during baseline measurements, the study patients were advised to visit Kumudini Hospital Laboratory for collection of blood and urine samples to estimate the condition of their kidneys and their related risk factors, such as serum creatinine, fasting blood sugar (FBS), hemoglobin, cholesterol, high-density lipoprotein cholesterol (HDL-c), triglyceride, serum uric acid, blood urea nitrogen (BUN), and ACR. The same laboratory investigations were done at the end of 6 months (Table 1).

Table 1. Study activities.

Schedule	Intervention group	Control group
Baseline sessions		
Week 1	• Interview • Administer questionnaires • Laboratory test (blood and urine)	• Interview • Administer questionnaires • Laboratory test (blood and urine)
Weeks 1 and 2	• CKD[a] health campaign (3-hour lecture and discussion by a nephrologist) • Provide health education materials (leaflet, short textbook, recording notebook, and a 5-gram salt measuring spoon) during campaign	• Usual care
Week 3 to month 3	• Mobile education: over the telephone once every 2 weeks (5 times) • Blood pressure check: once per week	• Usual care
Intermediate sessions		
Week 1 of month 4	• Interview • Administer questionnaires	• Interview • Administer questionnaires
Months 4 to 6	• Mobile education: over the telephone once every 2 weeks (5 times) • Blood pressure check: once per week	• Usual care
Final session		
End of month 6	• Interview • Administer questionnaires • Laboratory test (blood and urine)	• Interview • Administer questionnaires • Laboratory test (blood and urine)

[a]CKD: chronic kidney disease.

Training of CHWs

CHWs obtained written informed consent, performed physical examinations, interviewed the study participants after administering field-tested questionnaires, and provided health education. Training on the overall study procedure for CHWs was provided by the principal investigator. Training included the following: (1) general information about the study (ie, contact information, study overview, structure, and use of technology) and (2) role-specific information (ie, position description, recruitment, informed consent, data collection, use of an electronic database for data entry, proper use of backup paper copies, and self-evaluation form). Competency was assessed by practicing and role-playing in a private office. A nephrologist trained the CHWs, who then provided mHealth education to the study patients.

Intervention Group

The intervention group received health education through a CKD campaign using mHealth technology.

CKD Campaign

During the half-day CKD campaign, health education materials (ie, a leaflet as seen in Multimedia Appendix 1, a short textbook as seen in Multimedia Appendix 2, and a recording notebook) were provided to the study patients. A nephrologist facilitated

the health campaign: the contents of the textbook and leaflet were discussed, and patients were taught how to measure salt using the spoon during preparation of their daily meals. The research team have diverse professional backgrounds and have established the content of the CKD textbook and leaflet in the patients' native language (Bangla), based on the educational materials from the website of the National Kidney Foundation, New York, United States, after receiving permission. Important information related to CKD, such as basics of the kidney and kidney diseases, stages of disease, risk factors, and preventive measures, were used to develop the textbook and leaflet in the patients' native language (Bangla).

mHealth Technology

Basic health education information about CKD was included in the content to be delivered through a mobile phone call to help patients gain knowledge and awareness and to improve their behaviors. Discussion about the basics of kidney diseases, risk factors, and preventive measures of CKD was performed by CHWs over a mobile phone call with the study patients. The patients had the liberty to discuss their health-related issues with the CHWs over a period of 10 minutes (Table 2). A nephrologist trained the CHWs in the provision of mHealth education.

Table 2. Content of mobile health (mHealth) education that took place over a 10-minute mobile phone call.

Topic	Content of mHealth education
Kidneys	Kidneys are bean shaped and positioned near the middle of your back on either side of your backbone. Your kidneys are part of the body's urine system. Kidney functions include the following: • Remove waste products from the body • Remove drugs from the body • Balance the body's fluids • Release hormones that regulate blood pressure • Produce an active form of vitamin D that promotes strong and healthy bones • Control the production of red blood cells
Major risk factors for kidney disease	Some major risk factors include the following: • Diabetes • High blood pressure • Family history of kidney disease, diabetes, or high blood pressure • Age 50 years or older • Obesity • Long-time use of painkillers, such as aspirin and ibuprofen • Chronic kidney infection • Kidney stones • Smoking
Some ways to protect kidneys	Ways to protect kidneys include the following: • Keep blood sugar, blood pressure, and cholesterol under control • Lose weight, if needed • Eat healthy meals • Take all medicines as prescribed • Get regular exercise • Do not smoke • Avoid some over-the-counter medications, such as aspirin or ibuprofen, because they can harm kidneys
Diabetes	Diabetes damages your kidneys. Managing blood sugar level slows kidney damage. Some advice includes the following: • Maintain a healthy diet • Keep a healthy body weight • Perform at least 30 minutes of moderate-intensity physical exercise, 5 days per week • Take medication regularly if prescribed • Monitor your blood sugar regularly
Hypertension	Getting your blood pressure back to normal can reduce kidney damage, and some blood pressure tablets actually protect your kidneys. Some advice includes the following: • Reduce salt intake: excess salt in your body causes your blood pressure to go up; this damages your blood vessels and increases the risk of heart attack and stroke. Please consume 5 g of salt per day or less (1 teaspoon) • Check blood pressure at regular intervals. If possible, buy a blood pressure monitor and measure your blood pressure at home. This allows you to keep records of your blood pressure and you can see if it changes over time • Take medication regularly if prescribed

Blood Pressure Check

The CHWs performed home visits where they checked patients' BP once per week and continued over the study period.

Control Group

The control group received usual care and were followed up over the study period.

Sample Size

We assume that the average level of existing knowledge among patients with CKD (stages 1-3) is 40% [24], and that the average level of expected knowledge after the intervention will increase to 70% [25]. Therefore, considering 90% power and 20% loss to follow-up, the total sample size should be 126 (63 in each group). The sample size was estimated based on the following formula:

$$N = ([p1 \times q1 + p2q2] / [p2 - p1]2) \times \text{factor for } \alpha \text{ and } \beta$$

Here, p1=40%=0.40, the percentage of existing knowledge, and p2=70%=0.70, the percentage of expected knowledge after the intervention. In addition, q1 = 1 – p1 = 0.60; q2 = 1 – p2 = 0.30; power is equal to 90%; and loss to follow-up is equal to 20%.

Endpoints

The primary outcome is the evaluation of improved scores from the Chronic Kidney Disease Knowledge Questionnaire [24].

The secondary outcomes are as follows:

1. Improved QOL, as measured by the EuroQol 5-Dimension 5-Level (EQ-5D-5L) QOL questionnaire [26].
2. Improvements in the levels of BP, BMI, serum creatinine, FBS, hemoglobin, cholesterol, HDL-c, triglyceride, serum uric acid, BUN, and ACR.

Primary and secondary outcomes were measured at baseline, 3 months, and 6 months for both intervention and control groups, except for the laboratory investigation levels, which were measured at baseline and 6 months.

Measurements of Knowledge and QOL

Knowledge

Knowledge was measured using the Chronic Kidney Disease Knowledge Questionnaire, a 24-item scale with “true,” “false,” and “I don’t know” multiple-choice answer options, designed to assess CKD knowledge in patients with disease at stages 1 to 3. Knowledge scores were calculated by adding the number of correct answers divided by the total number of questions and multiplying by 100 to obtain a percentage score (Multimedia Appendix 3). For all questions, the answer “I don't know” was scored as incorrect.

The translation to Bangla was performed according to the state-of-the-art procedure of forward-backward translation. A physician and a university lecturer, both native speakers of Bangla and fluent in English, translated the questionnaire into Bangla first. The translated Bangla versions were compiled, and a single Bangla forward version was created. This forward version was then translated back into English by a professional translator with experience in medical translation and by one medical doctor who had not been involved in previous steps. The back-translated versions were then compiled and compared by the researcher, and all four versions were submitted to the expert committee that was formed for the validation study. The expert committee developed the questionnaire; pretesting was then conducted at the community level without any knowledge of diagnosis. The suggested changes were made accordingly based on the pretesting responses. Finally, the Bangla version of the CKD knowledge questionnaire was created.

Quality of Life

QOL was measured using the standardized EQ-5D-5L questionnaire (Multimedia Appendix 3). The EQ-5D-5L contains five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression [26,27]. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems, and unable to or extreme problems. A higher score indicates better QOL [28].

Ethical Considerations

This study has been approved by the Research Review Board and the Ethical Review Board of icddr,b. The study was registered at ClinicalTrials.gov (NCT04094831). This study is being conducted in accordance with the Declaration of Helsinki [29]. The study objectives; the importance, risks, and benefits of the research; and the patients’ rights were explicitly communicated to all participants before recruitment. Participation was completely voluntary and written informed consent was obtained from all patients. Each study patient’s identity will remain anonymous.

Statistical Analysis

The intention-to-treat analysis will be performed to compare the outcomes of the intervention and control groups. All baseline indicators at the time of registration will be analyzed to ensure the comparability of the randomized samples. Categorical variables will be expressed as means and SDs and will be analyzed by chi-square tests, discrete variables will be expressed as frequencies and percentages, and continuous variables will be analyzed by *t* tests or Mann-Whitney *U* tests. Multiple comparisons will be performed by two-way analysis of variance tests for the evaluation of the outcome variables, such as CKD knowledge, physical measurements, and QOL at baseline, 3 months, and 6 months. However, outcome variables for laboratory findings were measured at baseline and 6 months. Data will be analyzed using SPSS (version 22.0; IBM Corp) and the significance level will be set at the level of $P<.05$.

Results

The authors completed patient enrollment in November 2020, and the intervention and data collection were performed from November 2020 to May 2021. The results of the first analysis were made available in July 2021, as expected. We enrolled 126 patients (control group, n=63; intervention group, n=63) in the study. The mean age of the participants was 57.97 (SD 15.03) years for the control group and 57.32 (SD 14.37) years for the intervention group. A total of 71% (45/63) and 60% (38/63) of the patients were female in the control and intervention groups, respectively. A total of 67% (42/63) and 56% (35/63) of the patients were housewives in the control and intervention groups, respectively. A total of 79% (50/63) and 71% (45/63) of patients were married in the control and intervention groups, respectively. Furthermore, regarding the control and intervention groups, 60% (38/63) and 52% (33/63) of the patients were literate, 86% (54/63) and 78% (49/63) of the patients had a monthly income of US $100 per month or

higher, 13% (8/63) and 16% (10/63) of the patients were current tobacco users, and 43% (27/63) and 30% (19/63) were current smokeless tobacco users, respectively (Table 3).

Table 3. Demographic characteristics among the study participants.

Characteristic	Control group participants (n=63)	Intervention group participants (n=63)
Age in years, mean (SD)	57.97 (15.03)	57.32 (14.37)
Gender, n (%)		
Female	45 (71)	38 (60)
Male	18 (29)	25 (40)
Literacy, n (%)		
Illiterate	25 (40)	30 (48)
Literate	38 (60)	33 (52)
Occupation, n (%)		
Housewife	42 (67)	35 (56)
Farmer	3 (5)	4 (6)
Marital status, n (%)		
Married	50 (79)	45 (71)
Widowed	12 (19)	18 (29)
Income (US $), n (%)		
<100/month	9 (14)	14 (22)
≥100/month	54 (86)	49 (78)
Current tobacco smoker, n (%)		
Yes	8 (13)	10 (16)
No	55 (87)	53 (84)
Current smokeless tobacco user, n (%)		
Yes	27 (43)	19 (30)
No	36 (57)	44 (70)

Discussion

Overview

This study's overall effectiveness will be enhanced by the publication of this research protocol. A nephrologist-facilitated health campaign aims to increase knowledge and raise awareness about CKD-related health concerns by engaging people in discussions about important and influential health information. The aim of such events is to increase knowledge and understanding about CKD and its related risk factors, as well as to educate people on how they can avoid disease progression by living a healthy lifestyle. In addition, mHealth has been shown to enhance awareness, QOL, and behavior among low-income patients with chronic diseases, such as diabetes, and is currently being tested among low-income CKD patients [30]. While CKD management is a significant burden on health practitioners in low-capital settings, CHWs can be an important and underutilized resource for patient education. CHWs have been shown to be effective in assisting people in improving their health habits. A CHW intervention among patients with diabetes, for example, increased patients' awareness and helped them control their blood glucose levels and BP [31]. To the best of our knowledge, this is the first research study in Bangladesh to evaluate the outcome of health education through a CKD campaign and mobile phone calls to reduce CKD-related burden. mHealth shows a lot of potential in terms of raising patient awareness and understanding of kidney disease, as well as improving kidney knowledge [16]. Furthermore, studies from both developed and developing countries have demonstrated the efficacy and user acceptance of mHealth technologies in the management of CKD among patients; however, the majority of them were limited to dialysis patients [14].

Strengths

A nephrologist facilitated the health campaign in this study, and CHWs provided health education through mobile phone calls in the patients' native language (Bangla). Health education materials were developed using the same language for better understanding, even with minimum technical knowledge and skills. Furthermore, the study's strengths include the unbiased systematic sampling approach used to recruit patients and the standard laboratory facility used to identify patients with CKD.

Limitations

The patients in our study were randomly selected from the three unions of the Mirzapur subdistrict, and this does not represent the entire rural and periurban CKD population. In addition, data

contamination from study patients and family members could be another study limitation. Therefore, the CHWs received verbal consent from patients not to disclose any study details to their neighbors. Finally, due to budgetary limitations and time constraints, our 6-month follow-up duration was relatively brief.

Conclusions

If our results show an enhancement of the study outcomes among patients with CKD (stages 1-3), we suggest integrating health education via a campaign and mHealth as effective tools at the national level. Further, we can improve patient knowledge and motivate patients with CKD regarding their health practices to improve their QOL.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Health education material: leaflet.
[PNG File , 2314 KB - resprot_v10i11e30191_app1.png]

Multimedia Appendix 2
Health education material: short textbook.
[PDF File (Adobe PDF File), 1155 KB - resprot_v10i11e30191_app2.pdf]

Multimedia Appendix 3
Questionnaires.
[PDF File (Adobe PDF File), 412 KB - resprot_v10i11e30191_app3.pdf]

References

1. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet 2020 Feb 29;395(10225):709-733 [FREE Full text] [doi: 10.1016/S0140-6736(20)30045-3] [Medline: 32061315]
2. Lv J, Zhang L. Prevalence and disease burden of chronic kidney disease. Adv Exp Med Biol 2019;1165:3-15. [doi: 10.1007/978-981-13-8871-2_1] [Medline: 31399958]
3. George C, Mogueo A, Okpechi I, Echouffo-Tcheugui JB, Kengne AP. Chronic kidney disease in low-income to middle-income countries: The case for increased screening. BMJ Glob Health 2017;2(2):e000256 [FREE Full text] [doi: 10.1136/bmjgh-2016-000256] [Medline: 29081996]
4. Elshahat S, Cockwell P, Maxwell AP, Griffin M, O'Brien T, O'Neill C. The impact of chronic kidney disease on developed countries from a health economics perspective: A systematic scoping review. PLoS One 2020;15(3):e0230512 [FREE Full text] [doi: 10.1371/journal.pone.0230512] [Medline: 32208435]
5. White SL, Chadban SJ, Jan S, Chapman JR, Cass A. How can we achieve global equity in provision of renal replacement therapy? Bull World Health Organ 2008 Mar;86(3):229-237 [FREE Full text] [doi: 10.2471/blt.07.041715] [Medline: 18368211]
6. Duan J, Wang C, Liu D, Qiao Y, Pan S, Jiang D, et al. Prevalence and risk factors of chronic kidney disease and diabetic kidney disease in Chinese rural residents: A cross-sectional survey. Sci Rep 2019 Jul 18;9(1):10408 [FREE Full text] [doi: 10.1038/s41598-019-46857-7] [Medline: 31320683]
7. Peng S, Shen F, Wen A, Wang L, Fan Y, Liu X, et al. Detecting lifestyle risk factors for chronic kidney disease with comorbidities: Association rule mining analysis of web-based survey data. J Med Internet Res 2019 Dec 10;21(12):e14204 [FREE Full text] [doi: 10.2196/14204] [Medline: 31821152]
8. Schrauben SJ, Cavanaugh KL, Fagerlin A, Ikizler TA, Ricardo AC, Eneanya ND, et al. The relationship of disease-specific knowledge and health literacy with the uptake of self-care behaviors in CKD. Kidney Int Rep 2020 Jan;5(1):48-57 [FREE Full text] [doi: 10.1016/j.ekir.2019.10.004] [Medline: 31922060]

9. Baay S, Hemmelgarn B, Tam-Tham H, Finlay J, Elliott MJ, Straus S, et al. Understanding adults with chronic kidney disease and their caregivers' self-management experiences: A qualitative study using the theoretical domains framework. Can J Kidney Health Dis 2019;6:1-12 [FREE Full text] [doi: 10.1177/2054358119848126] [Medline: 31205731]
10. Tsai Y, Wang S, Tsai H, Chen T, Kung L, Hsiao P, et al. The interaction between self-care behavior and disease knowledge on the decline in renal function in chronic kidney disease. Sci Rep 2021 Jan 11;11(1):401 [FREE Full text] [doi: 10.1038/s41598-020-79873-z] [Medline: 33432037]
11. Ene-Iordache B, Perico N, Bikbov B, Carminati S, Remuzzi A, Perna A, et al. Chronic kidney disease and cardiovascular risk in six regions of the world (ISN-KDDC): A cross-sectional study. Lancet Glob Health 2016 May;4(5):e307-e319 [FREE Full text] [doi: 10.1016/S2214-109X(16)00071-1] [Medline: 27102194]
12. Ricardo AC, Yang W, Lora CM, Gordon EJ, Diamantidis CJ, Ford V, CRIC Investigators. Limited health literacy is associated with low glomerular filtration in the Chronic Renal Insufficiency Cohort (CRIC) study. Clin Nephrol 2014 Jan;81(1):30-37 [FREE Full text] [doi: 10.5414/CN108062] [Medline: 24219913]
13. Kidney Disease: Improving Global Outcomes (KDIGO) Work Group. Chapter 3: Management of progression and complications of CKD. Kidney Int Suppl (2011) 2013 Jan;3(1):73-90 [FREE Full text] [doi: 10.1038/kisup.2012.66] [Medline: 25598999]
14. Yang Y, Chen H, Qazi H, Morita PP. Intervention and evaluation of mobile health technologies in management of patients undergoing chronic dialysis: Scoping review. JMIR Mhealth Uhealth 2020 Apr 03;8(4):e15549 [FREE Full text] [doi: 10.2196/15549] [Medline: 32242823]
15. Hamine S, Gerth-Guyette E, Faulx D, Green BB, Ginsburg AS. Impact of mHealth chronic disease management on treatment adherence and patient outcomes: A systematic review. J Med Internet Res 2015 Feb 24;17(2):e52 [FREE Full text] [doi: 10.2196/jmir.3951] [Medline: 25803266]
16. Tuot DS, Boulware LE. Telehealth applications to enhance CKD knowledge and awareness among patients and providers. Adv Chronic Kidney Dis 2017 Jan;24(1):39-45 [FREE Full text] [doi: 10.1053/j.ackd.2016.11.017] [Medline: 28224941]
17. Narva AS, Norton JM, Boulware LE. Educating patients about CKD: The path to self-management and patient-centered care. Clin J Am Soc Nephrol 2016 Apr 07;11(4):694-703 [FREE Full text] [doi: 10.2215/CJN.07680715] [Medline: 26536899]
18. Grant S, Mayo-Wilson E, Montgomery P, Macdonald G, Michie S, Hopewell S, on behalf of the CONSORT-SPI Group. CONSORT-SPI 2018 Explanation and Elaboration: Guidance for reporting social and psychological intervention trials. Trials 2018 Jul 31;19(1):406 [FREE Full text] [doi: 10.1186/s13063-018-2735-z] [Medline: 30060763]
19. Chan A, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: Defining standard protocol items for clinical trials. Ann Intern Med 2013 Feb 05;158(3):200-207 [FREE Full text] [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
20. Sarker MHR, Moriyama M, Rashid HU, Chisti MJ, Rahman MM, Das SK, et al. Community-based screening to determine the prevalence, health and nutritional status of patients with CKD in rural and peri-urban Bangladesh. Ther Adv Chronic Dis 2021;12:1-13 [FREE Full text] [doi: 10.1177/20406223211035281] [Medline: 34377387]
21. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis 2014 May;63(5):713-735. [doi: 10.1053/j.ajkd.2014.01.416] [Medline: 24647050]
22. Ahmed A, Kabir L, Kai E, Inoue S. GramHealth: A bottom-up approach to provide preventive healthcare services for unreached community. In: Proceedings of the 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). 2013 Presented at: 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC); July 3-7, 2013; Osaka, Japan p. 1668-1671. [doi: 10.1109/EMBC.2013.6609838]
23. Islam R, Nohara Y, Rahman MJ, Sultana N, Ahmed A, Nakashima N. Portable Health Clinic: An advanced tele-healthcare system for unreached communities. Stud Health Technol Inform 2019 Aug 21;264:616-619. [doi: 10.3233/SHTI190296] [Medline: 31437997]
24. Gheewala PA, Peterson GM, Zaidi STR, Jose MD, Castelino RL. Public knowledge of chronic kidney disease evaluated using a validated questionnaire: A cross-sectional study. BMC Public Health 2018 Mar 20;18(1):371 [FREE Full text] [doi: 10.1186/s12889-018-5301-4] [Medline: 29554891]
25. Lang-Lindsey K, Yoon E. Measuring health-related outcomes after a peer-led educational intervention for African Americans with chronic kidney disease. J Nephrol Soc Work 2019;43(1):33-44 [FREE Full text]
26. van Hout B, Janssen MF, Feng Y, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health 2012;15(5):708-715 [FREE Full text] [doi: 10.1016/j.jval.2012.02.008] [Medline: 22867780]
27. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011 Dec;20(10):1727-1736 [FREE Full text] [doi: 10.1007/s11136-011-9903-x] [Medline: 21479777]
28. Jahan Y, Rahman MM, Faruque ASG, Chisti MJ, Kazawa K, Matsuyama R, et al. Awareness development and usage of mobile health technology among individuals with hypertension in a rural community of Bangladesh: Randomized controlled trial. J Med Internet Res 2020 Dec 07;22(12):e19137 [FREE Full text] [doi: 10.2196/19137] [Medline: 33284129]

29. Shrestha B, Dunn L. The Declaration of Helsinki on medical research involving human subjects: A review of seventh revision. J Nepal Health Res Counc 2020 Jan 21;17(4):548-552. [doi: 10.33314/jnhrc.v17i4.1042] [Medline: 32001865]
30. Krishna S, Boren SA. Diabetes self-management care via cell phone: A systematic review. J Diabetes Sci Technol 2008 May;2(3):509-517 [FREE Full text] [doi: 10.1177/193229680800200324] [Medline: 19885219]
31. Correia JC, Lachat S, Lagger G, Chappuis F, Golay A, Beran D, COHESION Project. Interventions targeting hypertension and diabetes mellitus at community and primary healthcare level in low- and middle-income countries: A scoping review. BMC Public Health 2019 Nov 21;19(1):1542 [FREE Full text] [doi: 10.1186/s12889-019-7842-6] [Medline: 31752801]

Abbreviations

ACR: albumin to creatinine ratio
BP: blood pressure
BUN: blood urea nitrogen
CHW: community health worker
CKD: chronic kidney disease
CONSORT: Consolidated Standards of Reporting Trials
DSS: demographic surveillance system
EQ-5D-5L: EuroQol 5-Dimension 5-Level
ESRD: end-stage renal disease
FBS: fasting blood sugar
HDL-c: high-density lipoprotein cholesterol
LMIC: low- and middle-income countries
mHealth: mobile health
PHC: Portable Health Clinic
QOL: quality of life
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Designing Ruby: Protocol for a 2-Arm, Brief, Digital Randomized Controlled Trial for Internalized Weight Bias

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Abstract

Background: Weight bias internalization, also known as *weight self-stigma*, is a serious health concern for individuals with higher body weight. Weight bias internalization is associated with the greater avoidance of health care and health-promoting activities, disordered eating, social isolation, and weight gain. Elevated weight bias internalization has been associated with low self-compassion, yet few investigations have explored self-compassion as a potential mechanism for reducing internalized weight bias.

Objective: Ruby is a 2-arm randomized controlled trial that was designed to test the efficacy of a 4-week digital self-compassion intervention to reduce internalized weight bias compared with a wait-list control.

Methods: Adults with elevated internalized weight bias and a BMI of >30 kg/m^2 (N=80) were recruited. Ruby is a standalone digital trial that will be delivered entirely via a smartphone and will involve web-based data collection and text messages. The intervention content will include psychoeducation and daily mindfulness practices with a focus on self-compassion and body concerns. We will use intent-to-treat analyses to examine changes in weight bias internalization throughout time by treatment arm. The analyses will be conducted by using one-way analysis of covariance models and linear mixed models.

Results: The protocol was designed in May 2020 and approved in December 2020. Data collection is currently underway.

Conclusions: Ruby will be the first digital standalone, self-compassion–based intervention designed to reduce internalized weight bias. Owing to its standalone digital delivery, Ruby may be a highly scalable treatment for internalized weight bias that can be delivered on its own or combined with other treatments. We expect Ruby to be accessible to many, as participants can access the digital intervention at times of the day that are the most convenient in their schedule and are not burdened by in-person time commitments, which can be a barrier for participants with competing demands on their time and resources. If efficacious, Ruby will be poised to expand a burgeoning body of literature related to psychological intervention in this area.

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International Registered Report Identifier (IRRID): DERR1-10.2196/31307

(JMIR Res Protoc 2021;10(11):e31307) doi:10.2196/31307

KEYWORDS

obesity; stigma; mHealth; mindfulness; self-compassion; mobile phone

Introduction

The physiological impact of obesity is often seen as the primary risk factor associated with obesity, but the *psychosocial* burden of obesity is harmful and may pose a greater risk. Weight stigma—the persistent devaluation, stereotyping, or discrimination of a person based on weight—is of paramount concern and a leading risk factor for adverse health outcomes [1].

Weight stigma is pervasive; experiences of weight stigma have been observed as early as at the age of 3 years [2]. Estimates of weight stigma experiences (ie, teasing, unfair treatment, or discrimination) across all demographics range from 20% to 40%. Rates tend to be higher in younger adults than older adults, women, individuals who self-identify as White, and people in higher weight classes [1]. Despite the myriad health consequences of weight stigma, these attitudes are commonly accepted in society because of the belief that body shame will result in motivation to lose weight [3]. However, evidence indicates that the opposite is true: experience of weight stigma is associated with weight gain, social isolation, increased binge eating episodes, and avoidance of health care services and physical activity [4].

Weight stigma (ie, social rejection because of weight) emanates from weight bias (ie, social prejudice regarding weight). Weight bias can also be internalized; that is, individuals can apply these societal beliefs about being overweight to themselves, begin to believe these stereotypes themselves, and self-stigmatize. This internalized weight bias (sometimes referred to as *weight self-stigma*) results in numerous serious health consequences, over and above those that may be associated with simply experiencing weight stigma [5].

In adults, internalized weight bias has been shown to result in an increased risk of metabolic syndrome, increased risk of eating disorder development, elevated triglycerides, and decreased quality of life after controlling for BMI [4,6]. The stress of internalized weight bias is often compared with other chronic discriminatory stressors (eg, racism). Dysregulation of the hypothalamic-pituitary-adrenal axis and consequent long-term elevation in cortisol levels have been observed in individuals who internalize weight bias, replicating findings in investigations of caregiver burden [7], employee burnout [8], childhood bullying [9], and persistent racism [10].

Internalized weight bias is associated with increased rates of maladaptive eating patterns and avoidance of healthy behaviors, such as physical activity [11,12]. Individuals with internalized weight bias are also less likely to attend preventive care visits to their physician, less likely to complete health screenings in accordance with guidelines, and more likely to switch health care providers [4]. This three-pronged issue—maladaptive eating patterns, physical inactivity, and fewer physician visits—may contribute to the poor health and well-being of those with internalized weight bias.

Recent evidence demonstrates that adaptive coping responses mediate the association between experiencing weight stigma and negative health outcomes [12]. Himmelstein et al [12] found that health outcomes were directly associated with how individuals responded to experiences of weight stigma. For instance, experiencing weight stigma was associated with greater depressive symptoms, but this effect was mediated by coping with negative affect. Furthermore, weight stigma was indirectly associated with lower depressive symptoms through the mediating effect of coping via healthy lifestyle behaviors such as eating healthy foods and exercising. This suggests that the consequences of weight stigma might be more readily attributed to an individual's response to stigma than to stigma alone. If internalization of weight bias is conceptualized as a response to experiences of weight stigma (in the way that Himmelstein et al [12] conceptualize negative affect), it becomes clear that intervention on the internalization of weight bias is possible and essential to improve health.

Acceptance- and mindfulness-based psychotherapies are well-positioned to disrupt the pathway from weight stigma to its negative health consequences. Recent investigations have begun to test the effects of acceptance- and mindfulness-based psychotherapies on weight stigma and related constructs (eg, body dissatisfaction), resulting in positive effects on reducing self-directed stigma [13]. Mindfulness skills are also known to increase several aspects of metacognition, including decentering from thoughts and emotions and reperceiving negative experiences, which could significantly impact an individual's response to experiences of weight stigma and thus, the development of internalized weight bias.

One such mindfulness skill is self-compassion. Self-compassion is a multidimensional mindfulness-based construct consisting of 3 parts: self-directed kindness, a sense of common humanity, and mindfulness [14]. Recent investigations have highlighted self-compassion as an important treatment target in patients with internalized weight bias and related concerns. Self-compassion is associated with greater overall psychological health [15], and a more recent systematic review suggests that amplifying self-compassion can ameliorate body image disturbance and eating pathology [16]. Both experienced and internalized weight bias have been linked to low self-compassion and low self-kindness in young adults [17] and adults [11]. In a clinical trial, self-compassion intervention was associated with greater reductions in body dissatisfaction than in wait-list control [18]. Overall, these findings suggest that self-compassion may improve well-being and reduce internalized weight bias. To date, no intervention has tested the efficacy of a brief self-compassion intervention on internalized weight bias. We aim to fill this gap by developing and testing a digitally delivered self-compassion mindfulness intervention called Ruby.

Methods

Overview

Ruby is a 2-arm, 4-week randomized controlled trial (N=80) testing the efficacy of a digital mindfulness-based self-compassion intervention for internalized weight bias compared with a wait-list control. The primary outcome is a 4-week change in self-reported weight bias internalization, as measured by the Weight Bias Internalization Scale [5]. Secondary outcomes include 4-week changes in

self-compassion, body appreciation, cognitive flexibility related to weight, and other related constructs. The Duke University institutional review board approved this protocol in December 2020.

Population

Overview

Ruby will enroll adults with obesity and internalized weight bias. Eligible participants will be at least 18 years old, report a BMI of at least 30 kg/m^2, have experienced weight bias, report elevated internalized weight bias as determined by a score of at least 4.0 on the Weight Bias Internalization Scale, have a smartphone, be willing to receive multiple text messages per day and engage in mindfulness practice for up to 20 minutes per day, live in the United States EST zone, and be able to read and write in English fluently. A Weight Bias Internalization Scale cutoff score of 4.0 has been used in prior research to determine *high* internalization of weight bias [19]. Reports on population norms of this measure indicate a cutoff score of 4.0 will capture women in the 80th percentile and men in the 90th percentile of internalized weight bias [20]. Participants will be excluded if they do not meet the eligibility criteria listed above, if they are already regular meditators (ie, meditate for at least 1 day per week for more than 1 week), are currently engaged in other treatments similar to Ruby (ie, in a mindfulness program, working on weight-related distress, or actively trying to lose weight), or have recently undergone bariatric surgery.

Power and Sample Size

We will recruit 80 adults aged >18 years who have English language proficiency, a BMI higher than 30 kg/m^2, and report weight bias internalization equal to or greater than a score of 4.0. The sample size was calculated based on the primary outcome using G*Power with a medium effect size determined based on the literature (effect size=0.5; power=0.95). We predict a 1-point reduction in the Weight Bias Internalization Scale score, based on prior literature in this field. We will need a minimum of 55 participants to be adequately powered; we estimate a retention rate of 70% and thus inflated sample size to account for attrition for a final sample size of 80 participants.

Recruitment

The target enrollment for this trial is 80 participants, with 40 participants in each group. Participants will be recruited from anywhere within the EST zone in the United States to ensure consistent timing of text messages across participants while maximizing reach. To recruit eligible participants, we will use a multipronged web-based approach. We will list information about Ruby on a clinical trial registry from the National Institutes of Health and use social media platforms (ie, Instagram, Twitter, and Facebook) and professional networks to distribute recruitment materials. We will also use ResearchMatch, a national health volunteer registry, to identify potentially eligible participants and notify them about Ruby. Of note, 75% of ResearchMatch registrants are White individuals, 70% are female, and 90% are non-Hispanic or Latino individuals. All recruitment sources will direct interested participants to the study website to provide details about the intervention, eligibility criteria, and contact information for study staff should they have questions about Ruby before continuing to the remaining screening procedures.

Screening, Consent, and Baseline Assessments

The prescreening eligibility survey will be administered through the REDCap (Research Electronic Data Capture) website (Vanderbilt University), a secure web-based software platform designed for data collection and management in research studies. The survey will collect participant contact information, recruitment sources, and questions to determine eligibility based on the criteria listed above. The participant will be automatically notified of their eligibility status and, if eligible, will be directed to the web-based consent form. If ineligible, they will be directed to nationally available resources for body image concerns, mental health resources, and reading materials that they might find supportive.

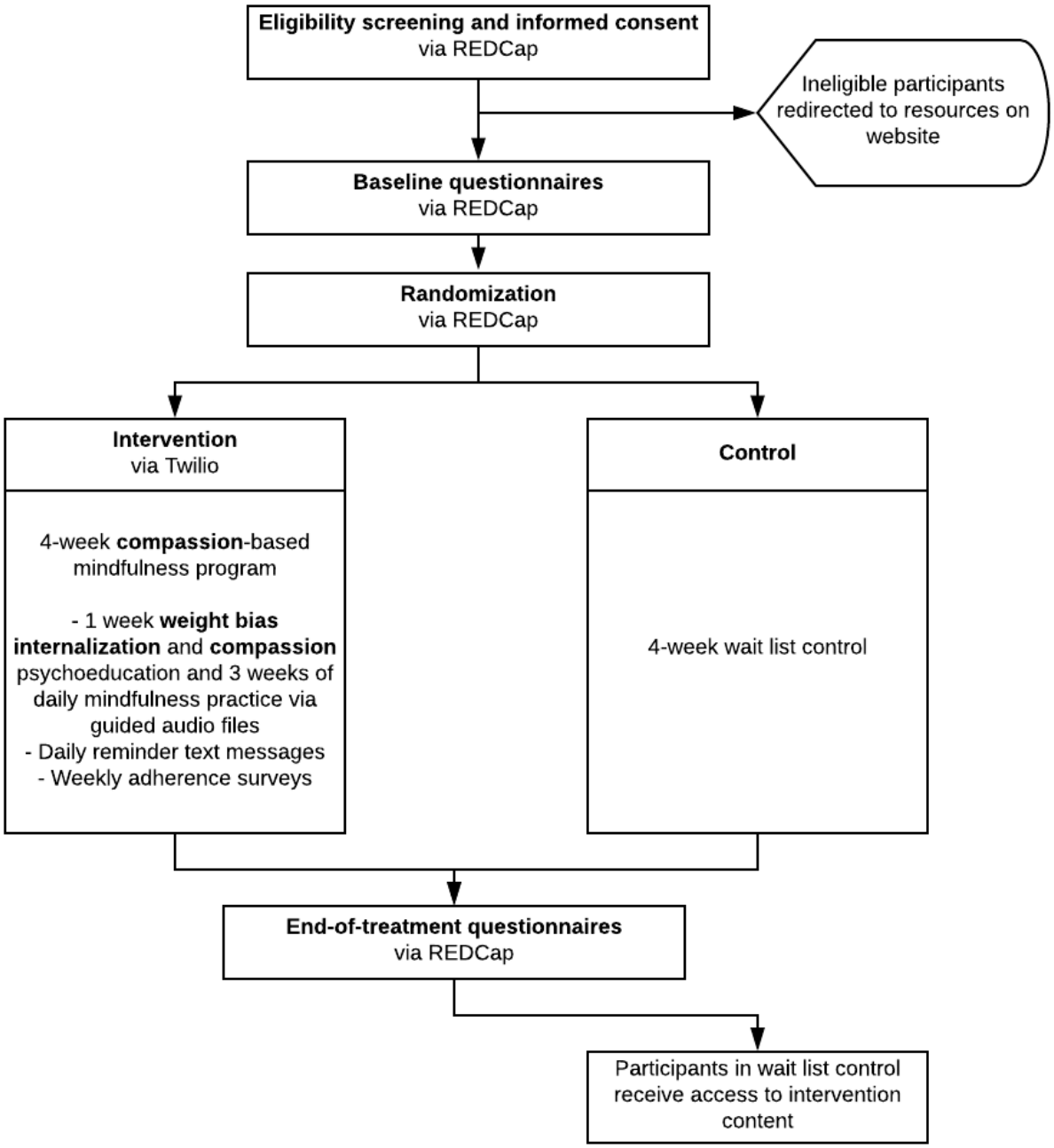
Eligible participants will proceed to the informed consent document hosted on the REDCap platform. Participants will be encouraged to read the informed consent document carefully and contact study staff via email if they have any questions or hesitations about participating in Ruby. If they are interested and agree to the study procedures, they will provide their electronic signatures to indicate their informed consent.

Participants who provide informed consent will be automatically emailed a unique link to their baseline surveys and instructed to complete them within 24 hours. The baseline surveys will include several instruments to measure baseline values on a variety of constructs, as described in more detail below. These surveys can be completed in a web browser using smartphones or personal PCs. Once participants complete their final baseline assessment survey, REDCap will automatically send an email to a study staff member to indicate that a new participant is ready for randomization.

Randomization

Participants who are eligible, provide informed consent, and complete baseline questionnaires will be randomized to one of two trial arms: intervention or wait-list control. Randomization will be conducted using simple random sampling; a randomization allocation table will be created using Microsoft Excel and uploaded to REDCap. Once the study staff is notified of a new participant eligible to be randomized, they will complete a random assignment using the randomization module in REDCap, which automatically assigns the participant to 1 of 2 groups and locks their randomization data fields. Study staff will not be blinded to randomization; however, this is not expected to impact trial outcomes as both treatment arms are completely preprogrammed, and thus, the potential bias of study staff could not impact intervention delivery. Randomization in REDCap will automatically trigger the delivery of text messages to provide notifications to the participant of their assigned group and orientation about what to expect. Figure 1 shows a summary of the study flow.

Figure 1. Study flow. REDCap: Research Electronic Data Capture.



Intervention Delivery

As described above, Ruby will be delivered as a standalone digital health intervention via a smartphone. All data collection, similar to screening and baseline assessments, will be automated and completed via a web browser. Intervention content is delivered via text messages with links to additional intervention content. Given the known nonuse attrition common in mobile apps, text messages provide an excellent delivery method for Ruby [21]. Unlike a mobile app, text messages cannot be uninstalled by the user nor can they be offloaded by the mobile operating system because of the lack of available storage on the smartphone. Although the user can go to additional lengths to block text messages, we presume this will only occur for a small subset of Ruby participants. Ruby is preprogrammed and automated and thus requires no synchronous human contact from a clinician or study team member.

Treatment Arms

Wait-list Control Group

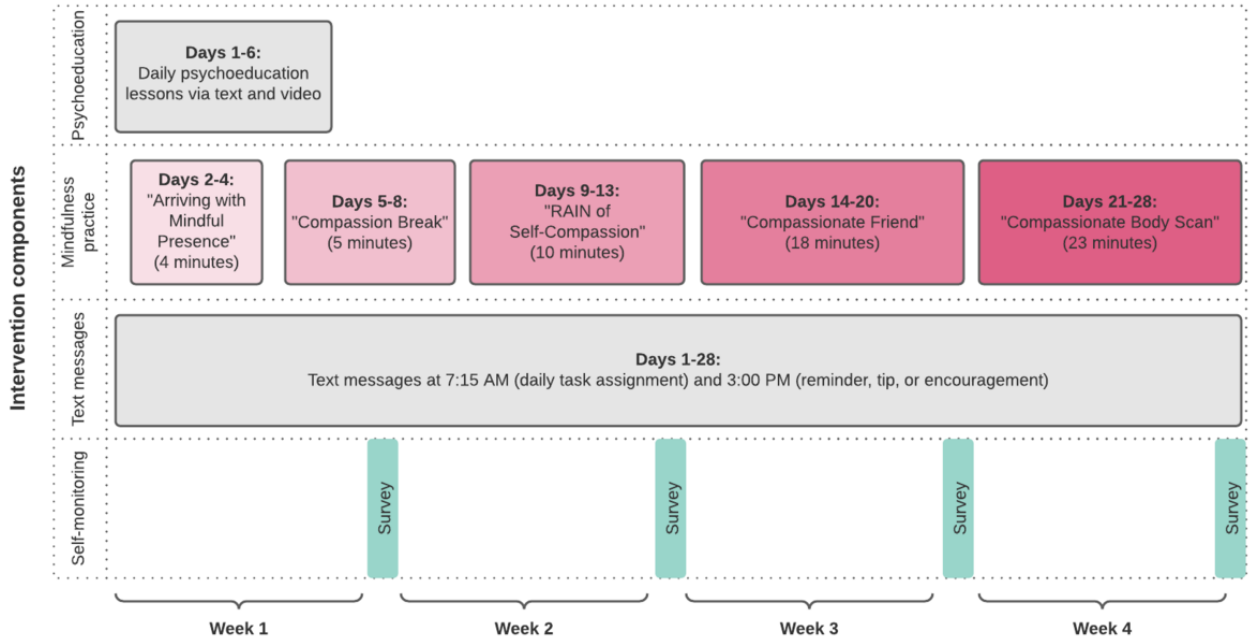
Immediately following randomization, participants randomized to the control group will receive 2 brief text messages notifying them of their group assignment and extending gratitude for their patience. The control group participants will receive one text message halfway through their waiting period (ie, on day 14) and one text message at the end of their waiting period (ie, on day 28). The text on day 14 will notify them of the halfway

point, and the text on day 28 will ask them to complete their end-of-treatment surveys. No additional intervention content or resources will be provided to the control group participants during the trial period. After completion of their end-of-treatment surveys, participants will be entered into a raffle to win study compensation and will be offered access to the Ruby intervention. If they opt in, they will begin receiving the intervention the next day.

Intervention Group

Immediately following randomization, participants randomized to the intervention group will be sent a series of text messages notifying them of their group assignment. They will also receive a link to a Ruby orientation page on the study website. The orientation page will outline participation expectations and study details, including when text messages will be sent and from what phone number, what participants' daily time commitment will be, and how to get in touch with study staff if they need technical assistance. An outline of the intervention activities each day has been provided in Figure 2; the duration of each mindfulness recording is provided.

Figure 2. Overview of the intervention components and delivery schedule.



Psychoeducation

Participants in the intervention group will receive a text message from day 1 to day 6 of the intervention that includes a link to psychoeducation material (Figure 2). These materials will be hosted on a hidden page on the study website. The purpose of the psychoeducation material is to orient users to their upcoming experience, provide education about internalized weight bias, the nervous system, and weight bias as a chronic stressor, the utility of self-compassion practice to regulate physiological and psychological targets, and guidance on establishing and maintaining a mindfulness practice. Psychoeducation will be delivered in written and animated video formats. A sample of these materials can be viewed in Multimedia Appendix 1. Each lesson will end with a reflection prompt that participants are encouraged to respond to in a journal to help generalize each lesson and apply them to their daily lives.

Mindfulness Practices

Beginning on day 2 of the intervention, participants will also receive a link to an audio file of a guided mindfulness practice via an automated text message each day. These mindfulness audio files will be hosted on SoundCloud, and a link will be texted to participants every morning. Mindfulness practices will range in duration and focus in an effort to build intensity slowly over the course of the intervention. For example, day 2 will include a 4-minute mindfulness of breath practice to complete after reading psychoeducation materials. Participants will be instructed to use the brief mindfulness practices during week 1 to get acquainted with what it feels like to be engaged in mindfulness, troubleshoot logistical barriers (eg, finding the ideal location and time of day), and identify additional barriers that may arise during their participation in Ruby (eg, noticing more unwanted unpleasant emotions) while engaging in supportive psychoeducation. As participants progress, mindfulness practices will begin to focus on self-compassion and finally, self-compassion as applied to body concerns. These practices are publicly available mindfulness practices written and recorded by Brach [22] and Neff [23]. Several of these practices were previously used in other investigations of compassion and body image concerns [18].

Daily Prompts

Daily tasks through days 1 to 28 will be automatically texted to every participant at 7:15 AM each morning. This will include links to psychoeducation materials and the accompanying animated video and mindfulness practice. Because of technical constraints, it is necessary for all participants to receive their

daily prompts at the same time rather than allowing them to select the most convenient time for them. Participants will be instructed to complete their daily tasks or mindfulness practice at the most convenient time each day. There is little extant literature providing guidance on the preferred timing of text messages in clinical trials. There is some evidence that participants respond more favorably to text message prompts sent during waking hours rather than during sleeping hours [24]; thus, 7:15 AM was chosen as the ideal time as many people are awake and not yet at work at this hour. Participants will be encouraged to reach out to study staff if they would like assistance with troubleshooting the best time of day for completing their daily practice (eg, if they are shift workers or otherwise have an atypical schedule).

Participants will receive an additional text daily at 3 PM, which includes a reminder of their reflection for the day, a tip to troubleshoot mindfulness practice, a poem, or a note of compassion. In orientation materials, participants will be instructed to continue to follow the daily prompts even if they miss a day (rather than try to catch up on missed material). The additional texts (at 3 PM) will remind them of this instruction on an approximately weekly basis, and they will be reoriented to these instructions during their weekly self-monitoring feedback.

Weekly Self-monitoring

At the end of each week (ie, days 6, 13, 21, and 28), participants will be sent an automated text at 7 PM with a link to a weekly self-monitoring survey hosted on REDCap. Participants will report how many days that week they were able to complete their assigned tasks and will be provided automated feedback based on their responses.

If they practice for 0 to 3 days, they will provide feedback that includes encouraging messages and prompts to use self-compassion, identify specific barriers that got in the way of their practice, and create an action plan for how they could improve their adherence in the coming week. If they practice for 4 to 6 days, they will be provided with reinforcement and praise for completing their practice at least half of the week and will be asked to identify specific barriers and create an action plan for the coming week. If they practice every day, they will be provided with reinforcement and praise and will be asked to identify how they were able to practice every day and commit to doing the same in the coming week. If the participant does not respond to this survey, they will automatically be sent the survey again the following evening.

Compensation

Participants who complete all required study tasks (ie, informed consent, randomization, baseline surveys, and end-of-treatment surveys) will be entered into a raffle to win one of 20 Amazon e-gift cards valued at US $45 each. Participants will have a 25% chance of winning compensation. After completion of the study, 20 participant identifiers will be randomly selected using a random number generator. The participants will then have 72 hours to claim their compensation; if they are not responsive to emails in <72 hours, additional participant identifiers will be selected to maximize the number of participants who can receive compensation.

Data Collection

Data collection for primary and secondary outcomes will be assessed at baseline (day 0) and end-of-treatment (day 28). All surveys will be administered via REDCap and are estimated to take 15-30 minutes to complete. A complete list of the surveys administered is presented in Table 1. Participants will be expected to complete their baseline assessments on the same day as they are deemed eligible. If a participant does not complete the baseline assessments that day, they will receive an automated email reminder that includes the link to the assessments. This reminder will be sent every 24 hours up to 3 times. If a participant does not complete the baseline assessments during the four-day window, they will be deemed no longer interested.

After completing the intervention, participants will receive additional text messages with instructions to complete the end-of-treatment surveys and receive a link to their surveys in their email. Participants will be encouraged to respond to the surveys within 24 hours. If a participant does not complete the surveys that day, they will receive an automated email reminder that includes the link to the surveys every 24 hours up to 5 more times. After 5 days of automated email attempts, study staff will personally reach out to participants via email to provide context about end-of-treatment surveys, remind them of the compensation they would be eligible to receive if they completed these surveys, and provide an opportunity for the participant to voice questions or concerns they may have about completing these surveys.

Table 1. Surveys administered at each timepoint.

Instrument	Time point					
	Screening	Day 0 (baseline)	Day 7	Day 14	Day 21	Day 28 (end-of-treatment)
Date of birth	✓[a]					
Anthropometric data	✓					
Modified weight bias internalization scale [5]	✓					
Demographics		✓				
Self-compassion scale [25]		✓				✓
Weight self-stigma questionnaire [26]		✓				✓
Fear of compassion scale [27]		✓				✓
Patient health questionnaire [28]		✓				✓
Weight and dieting history [29]		✓				
Intuitive eating scale [30]		✓				✓
International physical activity questionnaire (short form) [31]		✓				✓
Five facet mindfulness questionnaire (short form) [32]		✓				✓
Body appreciation scale [33]		✓				✓
Acceptance and action questionnaire for weight [34]		✓				✓
Childhood trauma questionnaire [35]		✓				
Weekly adherence survey			✓	✓	✓	✓
Acceptability and feasibility ratings						✓
Engagement and feedback report						✓

[a]Variable assessed.

Measurements

Primary Outcomes

Weight Bias Internalization

Participants will complete the Modified Weight Bias Internalization Scale [5], a 10-item version of the prior Weight Bias Internalization Scale. This is a psychometrically validated assessment of weight bias internalization in people of all weight statuses, and the 10-item version of the original scale [36] was created to capture weight bias internalization regardless of whether the respondent was identified as overweight or obese [37]. Participants will be asked to rate their agreement with statements such as "My weight is a major way that I value myself as a person." The Modified Weight Bias Internalization Scale is scored by computing the mean of 10 item responses rated on a 1 to 7 scale, with higher scores signifying greater weight bias internalization.

Weight Self-Stigma

Participants will complete the Weight Self-Stigma Questionnaire [26], a 12-item assessment of self-directed weight stigma. The Weight Self-Stigma Questionnaire captures different aspects of weight bias internalization and self-directed stigma compared with the Weight Bias Internalization Scale. Notably, in addition to the total score, the Weight Self-Stigma Questionnaire measures 2 distinct subscales: fear of enacted stigma and self-devaluation. Although both instruments are sound measures of weight bias internalization [38], they demonstrate different sensitivities to change in recent interventions of weight bias internalization [19]. Participants will be asked to rate their agreement with statements such as "I became overweight because I'm a weak person."

Self-Compassion

Participants will complete the Self-Compassion Scale [25], a 26-item assessment of an individual's capacity to direct compassion toward themselves. Participants will be asked how frequently they behave in a self-compassionate manner by responding to statements such as "I try to be loving toward myself when I am feeling emotional pain." Per the recommendations by Neff [25], we will use the total score comprising all 6 factors in our primary outcome analysis. To understand the specific mechanisms that conferred changes in self-compassion global score, we will also analyze each of the 6 subfactors: the 3 compassionate self-responding factors (self-kindness, common humanity, and mindfulness) and the 3 uncompassionate self-responding factors (ie, self-judgment, isolation, and overidentification).

Secondary Outcomes

Mindfulness Constructs

The mindfulness constructs are as follows:

- Mindfulness: Participants will complete the Short Form Five Facet Mindfulness Questionnaire [32], a 24-item instrument that measures 5 facets of a tendency to be mindful in daily life. The 5 facets assessed are observing internal experience, describing internal experience, acting with awareness, nonjudging of inner experience, and nonreactivity to inner experience. Participants will rate their agreement with statements such as "When I have distressing thoughts or images, I don't let myself be carried away by them." Items are rated on a scale of 1 to 5, with higher scores indicating greater mindfulness.
- Weight-related experiential avoidance: Participants will complete the Acceptance and Action Questionnaire for Weight-Related Difficulties–Revised [34], a 10-item measure of experiential avoidance of unwanted thoughts, feelings, and actions related to weight. Data suggest that using a domain-specific inventory of experiential avoidance is more accurate than using the general Acceptance and Action Questionnaire. On this instrument, participants will be asked to rate their agreement with statements such as "When I evaluate my weight or appearance negatively, I am able to recognize that this is just a reaction, not an objective fact." Items are rated from 1 (never true) to 7 (always true). Higher global scores reflect greater experiential avoidance. Three subfactors will also be analyzed: food as control (the tendency to use food as coping), weight as a barrier to living (tendency to move away from a valued life due to one's body shape or weight), and internalized weight stigma.
- Fear of compassion: Participants will complete one subscale from the Fear of Compassion Scale [27]. The Fear of Compassion Scale measures compassion in the following three domains: compassion from others, compassion for others, and compassion for self. We will administer the 17-item fear of compassion for the self-subscale. Participants will rate their agreement with statements such as "I feel that I don't deserve to be kind and forgiving to myself." Items are rated from 0 (do not agree at all) to 4 (completely agree) and summed, with lower scores indicating lower fear of compassion.

Weight and Eating Constructs

The weight and eating constructs are as follows:

- Body appreciation: Participants will complete the Body Appreciation Scale 2 [33], a 10-item inventory assessing a sense of gratitude, appreciation, and positive attitudes toward the body. The original Body Appreciation Scale was updated to eliminate gendered language and update language, assuming that all respondents had
  body flaws
  that were inherently negative or looked upon unfavorably by the respondent. Participants will rate their agreement with statements such as "I appreciate the different and unique characteristics of my body." Items are rated on a scale of 1 (never) to 5 (always); responses are averaged for a total score, with higher scores indicating higher body appreciation.
- Intuitive eating: Participants will complete the Intuitive Eating Scale-2 [30], a 23-item assessment of an individual's tendency to eat in alignment with internal versus external cues. Participants will rate their agreement with statements such as "When I am craving a certain food, I allow myself to have it" on a scale of 1 (strongly disagree) to 5 (strongly agree), and a global score will be calculated, with higher scores indicating more intuitive eating patterns. We will also calculate each of the 4 subscales: unconditional permission to eat, eating for physical rather than emotional reasons, reliance on hunger and satiety cues, and body-food choice congruence.
- Weight and dieting history: Participants will respond to a series of questions selected from the Weight and Lifestyle Inventory [29]. We will select items that inquire about the frequency of dieting across their life span, age of first dieting experience, frequency of weight cycling episodes, history of eating disorder diagnosis or treatment, and specific dieting behaviors used (eg, caloric restriction and prescription medications). One weight cycle will be defined as a loss and regain of at least 10 pounds [39].
- Physical activity: Participants will complete the International Physical Activity Questionnaire–Short Form [31], a self-report inventory of recent physical activity across different domains (vigorous activity, moderate activity, walking, and leisure) in the past week.

Psychopathology and Trauma Constructs

The psychopathology and trauma constructs are as follows:

- Depression: Participants will complete the Patient Health Questionnaire 2 [28], a self-report instrument measuring depressive symptoms derived from the diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders-IV. The 2-item version (abbreviated from the original 9-item Patient Health Questionnaire) does not include the suicidal ideation item and demonstrates good predictive validity with a cutoff score of ≥2 [40].
- Adverse childhood experiences: Participants will complete the Childhood Trauma Questionnaire [35], a 28-item retrospective assessment of childhood experiences of abuse, neglect, and maltreatment. The Childhood Trauma Questionnaire assesses experiences that are often not captured, such as chronic neglect, invalidation, psychological abuse, and other experiences that may not meet Diagnostic and Statistical Manual of Mental Disorders Criterion A trauma thresholds, yet significantly impact an individual's capacity for healthy attachment, sense of self, and other measures of well-being. The Childhood Trauma Questionnaire has the following five subscales: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect.
- Engagement and feedback: We will assess study adherence using weekly surveys in which participants will be asked to report the number of days they practiced mindfulness. Self-report adherence will also be assessed in the engagement and feedback surveys provided at study completion. In these surveys, we will ask participants to report what percentage of Ruby they believe they completed, which psychoeducation lessons and mindfulness practices they completed, and provide feedback on

intervention content. We will also assess the usability and acceptability of Ruby at the end of the treatment.

Analytic Approach

To describe baseline characteristics, we will compute descriptive statistics stratified by the treatment arm. To determine whether baseline characteristics differ by group assignment or retention status, we will use Pearson chi-square tests for categorical variables and analysis of variance for continuous variables.

We will use intent-to-treat analyses to test our primary study aim using one-way analysis of covariance models and linear mixed models to examine changes in weight bias internalization over time by treatment arm. Linear mixed models will be fitted with a full maximum likelihood estimation, and we will assume missingness at random. We will use an unstructured covariance matrix. We will not control for any additional variables. If the distribution of any outcome is heavily skewed, we will apply transformations to the data to conduct these analyses. We will assess the impact of moderating variables using analysis of covariance and linear mixed models. We hypothesize that the intervention effect may be moderated by certain demographic variables (ie, race or gender) or psychological variables (ie, fear of self-compassion or adverse childhood experiences determined by scores on the Childhood Trauma Questionnaire). We also hypothesize that the effect of the intervention will be partially mediated by an increase in self-compassion, measured using the Self-Compassion Scale. We will conduct mediation analyses using the SPSS PROCESS macro (IBM Corp) with 5000 bootstrap samples. Exploratory analyses will assess the moderating impact of additional constructs (eg, baseline depression scores) and the impact of the intervention on tertiary outcome variables (eg, body appreciation score and intuitive eating score). The sample size will likely not be large enough to be fully powered for these exploratory analyses, although they are worthy of investigation given the lack of clinical trials in this area. We will also conduct a per-protocol analysis with participants who report completing at least 60% of Ruby components for all analyses.

Results

This protocol was designed in May 2020 and approved by the Duke University Institutional Review Board in December 2020. Data collection began in January 2021 and was completed in August 2021. Data analyses are underway, and the results are expected to be published in December 2021.

Discussion

Comparison With Prior Work

Ruby will be the first self-compassion-based intervention designed to reduce internalized weight bias. Although several cross-sectional investigations have indicated that self-compassion may be a construct of interest concerning internalized weight bias, Ruby is the first to test its efficacy in a randomized controlled trial. If efficacious, Ruby will be poised to expand a burgeoning body of literature related to psychological intervention in this area of need.

The nascent body of intervention research on internalized weight bias has demonstrated several promising results. Cognitive-behavioral strategies, such as the Weight Bias Internalization and Stigma (BIAS) program, have been tested to reduce internalized weight bias. The BIAS program has been tested in a pilot trial and a randomized controlled trial [19,41], testing an 8-week cognitive-behavioral intervention to reduce internalized weight bias compared with a quasi-control. The results of the pilot study suggest that the BIAS program can reduce weight bias internalization using cognitive-behavioral strategies. This program was then modified and tested in a randomized controlled trial with a longer duration (12 weeks) and combined with behavioral weight loss, compared with a behavioral weight loss program alone. No difference was observed between the 2 groups in the reduction of weight bias internalization when measured using the Weight Bias Internalization Scale, and some group differences were observed when weight bias internalization was measured using the Weight Self-Stigma Questionnaire. Overall, these results indicate that cognitive-behavioral interventions for internalized weight bias show some promise and require additional investigation. Further, differential results—depending on the self-report instrument used—raise important questions about measurements of this construct that should be explored in future work.

Acceptance- and mindfulness-based interventions for internalized weight bias show additional efficacy. Mindfulness strategies have been used several times to aid in obesity interventions, weight-related quality of life interventions, and recently, to improve body image concerns. Ruby is the first study to specifically test the efficacy of self-compassion mindfulness practices in reducing internalized weight bias. Albertson et al [18] demonstrated preliminary evidence that self-compassion could be useful in treating body image concerns, and the design of Ruby was inspired by their work, although there are some key differences. Albertson et al [18] trial was a 3-week intervention that provided self-compassion mindfulness audio files via podcast compared with a wait-list control. Ruby aims to provide additional psychoeducation about mindfulness, internalized weight bias, and the health effects of each.

Furthermore, the schedule of mindfulness practices differs when comparing Ruby with the Albertson et al [18] intervention; Ruby aims to build mindfulness skills slowly, beginning with brief practices (ie, 4 minutes) to improve accessibility for new meditators. Although both trials encourage daily mindfulness practice, Ruby's mindfulness practices slowly increase in duration until they reach 20 minutes per day, whereas Albertson et al [18] opted to provide 20 minutes mindfulness recordings throughout the intervention. These key differences may or may not affect the efficacy of the intervention. Participants in the trial by Albertson et al [18] reported significant reduction in body dissatisfaction, reduction in body shame, and increase in body appreciation at 3 weeks. Moreover, these improvements remained 3 months after the completion of the study. Other studies have begun to explore the associations between acceptance-based strategies and body image concerns, such as the KgFree study [13].

Strengths and Limitations

To date, most interventions for internalized weight bias have been lengthy and in-person interventions. Ruby may be an especially promising treatment for internalized weight bias for many reasons because of its remote, standalone digital delivery. First, remote, digital interventions can reach large portions of the population, given near-universal access to smartphones and other internet-capable devices across sociodemographically diverse communities. Even among individuals earning less than US $30,000 annually, more than 85% of US adults own smartphones, and rates of ownership increase among higher income levels [42]. This is particularly important because individuals living on lower incomes can have especially limited access to traditional in-person treatments for myriad reasons. Second, standalone digital interventions are more scalable than in-person or human-supported digital interventions, as they are not constrained by the availability of a finite number of health care providers.

Similarly, digital interventions may be more accessible than in-person treatment, as participants can access a digital intervention at times of the day most convenient in their schedule and are not burdened by in-person time commitments, which can be a barrier for participants with shift jobs, caregiver responsibilities, lack of transportation, and so on. Finally, the standalone digital delivery approach allows Ruby to operate at a much lower cost than human-supported treatments for weight bias. Although a standalone remote intervention may not be sufficient for all individuals, Ruby's comparatively low resource footprint may make it a viable first option in a stepped care model. Remote, standalone digital interventions may be a particularly promising first-step intervention given the negative impact of internalized weight bias on help-seeking [4] and may be a useful alternative to group-based treatment that may prime individuals for comparison with others.

Owing to the brief, digital, standalone design of this trial, we believe Ruby could be easily disseminated and integrated into other evidence-based care packages to enhance their effects. Self-compassion training would make an excellent adjunctive treatment in populations that tend to have higher body weights, such as for interventions concerning physical activity, diabetes management, hypertension, or weight loss. Future investigations should explore the efficacy of Ruby in tandem with such treatments. If efficacious, Ruby may be able to improve treatment engagement and reduce downstream markers of chronic stress in these populations and improve overall treatment outcomes.

Recent popular media outlets have suggested that weight loss medications, such as semaglutide, may also result in reductions in weight stigma. Although any reduction in weight stigma is welcomed, we posit that reductions in weight stigma need not be tied to weight loss. It is well known that weight-related reductions in weight stigma in some populations are often reversed when weight is regained; thus, these reductions may be temporary and may send a message that patients must be thin to be free of weight stigma. Furthermore, investigations of stigma following bariatric surgery suggest that many patients experience lingering internalized weight bias even after losing significant amounts of weight because of the lasting effects of chronic stress and discrimination based on their weight. Finally, weight loss is not mandatory. Many Americans live long, healthy, and values-consistent lives at higher weights and should have access to low-cost, effective treatments to reduce internalized weight bias without inducing weight loss. For these individuals, Ruby may hold a promise.

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Conflicts of Interest

GGB holds equity in Coeus Health and serves the Scientific Advisory Board of WW (formerly Weight Watchers) and Wondr Health. DMS holds equity in Equip Health. These organizations had no role in the study design, data collection, data analysis, interpretation of data, the writing of the report, or the decision to submit the article for publication. The remaining authors declare no conflicts of interest.

Multimedia Appendix 1
Sample psychoeducation video delivered on day 1.
[MP4 File (MP4 Video), 16119 KB - resprot_v10i11e31307_app1.mp4]

References

1. Puhl RM, Himmelstein MS, Quinn DM. Internalizing weight stigma: prevalence and sociodemographic considerations in US adults. Obesity (Silver Spring) 2018 Jan;26(1):167-175. [doi: 10.1002/oby.22029] [Medline: 29082666]
2. Andreyeva T, Puhl RM, Brownell KD. Changes in perceived weight discrimination among Americans, 1995-1996 through 2004-2006. Obesity (Silver Spring) 2008 May;16(5):1129-1134 [FREE Full text] [doi: 10.1038/oby.2008.35] [Medline: 18356847]
3. Callahan D. Obesity: chasing an elusive epidemic. Hastings Cent Rep 2013;43(1):34-40. [doi: 10.1002/hast.114] [Medline: 23254867]

4. Puhl R, Suh Y. Health consequences of weight stigma: implications for obesity prevention and treatment. Curr Obes Rep 2015 Jun;4(2):182-190. [doi: 10.1007/s13679-015-0153-z] [Medline: 26627213]
5. Pearl RL, Puhl RM. Measuring internalized weight attitudes across body weight categories: validation of the modified weight bias internalization scale. Body Image 2014 Jan;11(1):89-92. [doi: 10.1016/j.bodyim.2013.09.005] [Medline: 24100004]
6. Pearl RL, Wadden TA, Hopkins CM, Shaw JA, Hayes MR, Bakizada ZM, et al. Association between weight bias internalization and metabolic syndrome among treatment-seeking individuals with obesity. Obesity (Silver Spring) 2017 Feb 26;25(2):317-322 [FREE Full text] [doi: 10.1002/oby.21716] [Medline: 28124502]
7. Potier F, Degryse J, Bihin B, Debacq-Chainiaux F, Charlet-Renard C, Martens H, et al. Health and frailty among older spousal caregivers: an observational cohort study in Belgium. BMC Geriatr 2018 Nov 26;18(1):291 [FREE Full text] [doi: 10.1186/s12877-018-0980-3] [Medline: 30477431]
8. Penz KL, Kosteniuk JG, Stewart NJ, MacLeod ML, Kulig JC, Karunanayake CP, et al. Development and psychometric evaluation of the job demands in nursing scale and job resources in nursing scale: results from a national study. Nurs Open 2018 Nov 13;6(2):348-366 [FREE Full text] [doi: 10.1002/nop2.215] [Medline: 30918685]
9. Ouellet-Morin I, Wong CC, Danese A, Pariante CM, Papadopoulos AS, Mill J, et al. Increased serotonin transporter gene (SERT) DNA methylation is associated with bullying victimization and blunted cortisol response to stress in childhood: a longitudinal study of discordant monozygotic twins. Psychol Med 2013 Sep;43(9):1813-1823. [doi: 10.1017/s0033291712002784] [Medline: 23217646]
10. Richman LS, Jonassaint C. The effects of race-related stress on cortisol reactivity in the laboratory: implications of the Duke lacrosse scandal. Ann Behav Med 2008 Feb;35(1):105-110 [FREE Full text] [doi: 10.1007/s12160-007-9013-8] [Medline: 18347910]
11. Braun TD, Gorin AA, Puhl RM, Stone A, Quinn DM, Ferrand J, et al. Shame and self-compassion as risk and protective mechanisms of the internalized weight bias and emotional eating link in individuals seeking bariatric surgery. Obes Surg 2021 Jul;31(7):3177-3187. [doi: 10.1007/s11695-021-05392-z] [Medline: 33905070]
12. Himmelstein MS, Puhl RM, Quinn DM. Weight stigma and health: the mediating role of coping responses. Health Psychol 2018 Feb;37(2):139-147. [doi: 10.1037/hea0000575] [Medline: 29120192]
13. Palmeira L, Pinto-Gouveia J, Cunha M. Appetite 2017 May 01;112:107-116. [doi: 10.1016/j.appet.2017.01.027] [Medline: 28119138]
14. Neff K. Self-compassion: an alternative conceptualization of a healthy attitude toward oneself. Self Identity 2003 Apr;2(2):85-101. [doi: 10.1080/15298860309032]
15. MacBeth A, Gumley A. Exploring compassion: a meta-analysis of the association between self-compassion and psychopathology. Clin Psychol Rev 2012 Aug;32(6):545-552. [doi: 10.1016/j.cpr.2012.06.003] [Medline: 22796446]
16. Braun TD, Park CL, Gorin A. Self-compassion, body image, and disordered eating: a review of the literature. Body Image 2016 Jun;17:117-131. [doi: 10.1016/j.bodyim.2016.03.003] [Medline: 27038782]
17. Puhl RM, Telke S, Larson N, Eisenberg ME, Neumark-Stzainer D. Experiences of weight stigma and links with self-compassion among a population-based sample of young adults from diverse ethnic/racial and socio-economic backgrounds. J Psychosom Res 2020 Jul;134:110134 [FREE Full text] [doi: 10.1016/j.jpsychores.2020.110134] [Medline: 32413612]
18. Albertson ER, Neff KD, Dill-Shackleford KE. Self-compassion and body dissatisfaction in women: a randomized controlled trial of a brief meditation intervention. Mindfulness 2014 Jan 25;6(3):444-454. [doi: 10.1007/s12671-014-0277-3]
19. Pearl RL, Wadden TA, Bach C, Gruber K, Leonard S, Walsh OA, et al. Effects of a cognitive-behavioral intervention targeting weight stigma: a randomized controlled trial. J Consult Clin Psychol 2020 May;88(5):470-480 [FREE Full text] [doi: 10.1037/ccp0000480] [Medline: 31971410]
20. Hilbert A, Baldofski S, Zenger M, Löwe B, Kersting A, Braehler E. Weight bias internalization scale: psychometric properties and population norms. PLoS One 2014 Jan 29;9(1):e86303 [FREE Full text] [doi: 10.1371/journal.pone.0086303] [Medline: 24489713]
21. Linardon J, Fuller-Tyszkiewicz M. Attrition and adherence in smartphone-delivered interventions for mental health problems: a systematic and meta-analytic review. J Consult Clin Psychol 2020 Jan;88(1):1-13. [doi: 10.1037/ccp0000459] [Medline: 31697093]
22. Guided Meditations. Tara Brach. URL: https://www.tarabrach.com/guided-meditations/ [accessed 2021-08-21]
23. Kristin Neff. Self-compassion guided practices and exercises. Self-Compassion Exercises. URL: https://self-compassion.org/category/exercises/ [accessed 2021-08-21]
24. Mohr DC, Cuijpers P, Lehman K. Supportive accountability: a model for providing human support to enhance adherence to ehealth interventions. J Med Internet Res 2011 Mar 10;13(1):e30 [FREE Full text] [doi: 10.2196/jmir.1602] [Medline: 21393123]
25. Neff KD. The development and validation of a scale to measure self-compassion. Self Identity 2003 Jul;2(3):223-250. [doi: 10.1080/15298860309027]
26. Lillis J, Luoma JB, Levin ME, Hayes SC. Measuring weight self-stigma: the weight self-stigma questionnaire. Obesity (Silver Spring) 2010 May;18(5):971-976 [FREE Full text] [doi: 10.1038/oby.2009.353] [Medline: 19834462]

27. Gilbert P, McEwan K, Matos M, Rivis A. Fears of compassion: development of three self-report measures. Psychol Psychother 2011 Sep;84(3):239-255. [doi: 10.1348/147608310X526511] [Medline: 22903867]
28. Kroenke K, Spitzer RL, Williams J. The patient health questionnaire-2: validity of a two-item depression screener. JSTOR 2003 Nov;41(11):1284-1292 [FREE Full text] [doi: 10.1097/01.mlr.0000093487.78664.3c]
29. Wadden TA, Foster GD. Weight and lifestyle inventory (WALI). Surg Obes Relat Dis 2006 Mar;2(2):180-199. [doi: 10.1016/j.soard.2006.03.017] [Medline: 16925345]
30. Tylka TL, Kroon Van Diest AM. The Intuitive Eating Scale-2: item refinement and psychometric evaluation with college women and men. J Couns Psychol 2013 Jan;60(1):137-153. [doi: 10.1037/a0030893] [Medline: 23356469]
31. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003 Aug;35(8):1381-1395. [doi: 10.1249/01.MSS.0000078924.61453.FB] [Medline: 12900694]
32. Bohlmeijer E, ten Klooster PM, Fledderus M, Veehof M, Baer R. Psychometric properties of the five facet mindfulness questionnaire in depressed adults and development of a short form. Assessment 2011 Sep 17;18(3):308-320. [doi: 10.1177/1073191111408231] [Medline: 21586480]
33. Tylka TL, Wood-Barcalow NL. The body appreciation scale-2: item refinement and psychometric evaluation. Body Image 2015 Jan;12:53-67. [doi: 10.1016/j.bodyim.2014.09.006] [Medline: 25462882]
34. Palmeira L, Cunha M, Pinto-Gouveia J, Carvalho S, Lillis J. New developments in the assessment of weight-related experiential avoidance (AAQW-revised). J Contextual Behav Sci 2016 Jul;5(3):193-200. [doi: 10.1016/j.jcbs.2016.06.001]
35. Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T, et al. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. Child Abuse Negl 2003 Feb;27(2):169-190. [doi: 10.1016/S0145-2134(02)00541-0]
36. Durso LE, Latner JD. Understanding self-directed stigma: development of the Weight Bias Internalization Scale. Obesity (Silver Spring) 2008 Nov;16(Suppl 2):S80-S86 [FREE Full text] [doi: 10.1038/oby.2008.448] [Medline: 18978768]
37. Lee MS, Dedrick RF. Weight bias internalization scale: psychometric properties using alternative weight status classification approaches. Body Image 2016 Jun;17:25-29. [doi: 10.1016/j.bodyim.2016.01.008] [Medline: 26907913]
38. Hübner C, Schmidt R, Selle J, Köhler H, Müller A, de Zwaan M, et al. Comparing self-report measures of internalized weight stigma: the weight self-stigma questionnaire versus the weight bias internalization scale. PLoS One 2016 Oct 28;11(10):e0165566 [FREE Full text] [doi: 10.1371/journal.pone.0165566] [Medline: 27792772]
39. Stevens VL, Jacobs EJ, Sun J, Patel AV, McCullough ML, Teras LR, et al. Weight cycling and mortality in a large prospective US study. Am J Epidemiol 2012 Apr 15;175(8):785-792. [doi: 10.1093/aje/kwr378] [Medline: 22287640]
40. Manea L, Gilbody S, Hewitt C, North A, Plummer F, Richardson R, et al. Identifying depression with the phq-2: a diagnostic meta-analysis. J Affect Disord Rep 2016 Oct;203:382-395. [doi: 10.1016/j.jad.2016.06.003]
41. Pearl RL, Hopkins CM, Berkowitz RI, Wadden TA. Group cognitive-behavioral treatment for internalized weight stigma: a pilot study. Eat Weight Disord 2018 Jun 27;23(3):357-362. [doi: 10.1007/s40519-016-0336-y] [Medline: 27787772]
42. Mobile technology and home broadband 2021. Pew Research Center. 2021. URL: https://www.pewresearch.org/internet/2021/06/03/mobile-technology-and-home-broadband-2021/ [accessed 2021-06-16]

Abbreviations

BIAS: Weight Bias Internalization and Stigma
REDCap: Research Electronic Data Capture

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Protocol

Association of Innate and Acquired Aerobic Capacity With Resilience in Healthy Adults: Protocol for a Randomized Controlled Trial of an 8-Week Web-Based Physical Exercise Intervention

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Abstract

Background: Physical activity alleviates chronic stress. The latest research suggests a relationship between resilience and physical fitness. Beneficial adaptations of the hypothalamic-pituitary-adrenal axis, sympathetic nervous system, endocannabinoid system, and tryptophan pathway, which are induced by an active lifestyle, are considered to be conducive to resilience. However, detailed knowledge on the molecular link between the effects of acute and chronic physical exercise and improved resilience to stress in humans is missing. Moreover, the relationship between innate and acquired aerobic capacity and resilience is poorly understood.

Objective: The aim of this study is to implement a human exercise intervention trial addressing the following main hypotheses: a high innate aerobic capacity is associated with high resilience to stress, and web-based physical exercise training improves aerobic capacity of physically inactive adults, which is accompanied by improved resilience. In this setting, we will analyze the relationship between resilience parameters and innate and acquired aerobic capacity as well as circulating signaling molecules.

Methods: A total of 70 healthy, physically inactive (<150 minutes/week of physical activity) adults (aged 18-45 years) will be randomly assigned to an intervention or control group. Participants in the intervention group will receive weekly training using progressive endurance and interval running adapted individually to their remotely supervised home training performance via web-based coach support. A standardized incremental treadmill exercise test will be performed before and after the intervention period of 8 weeks to determine the innate and acquired aerobic capacity (peak oxygen uptake). Before and after the intervention, psychological tests and questionnaires that characterize parameters implicated in resilience will be applied. Blood and saliva will be sampled for the analysis of cortisol, lactate, endocannabinoids, catecholamines, kynurenic acid, and further circulating signal transducers. Statistical analysis will provide comprehensive knowledge on the relationship between aerobic capacity and resilience, as well as the capacity of peripheral factors to mediate the promoting effects of exercise on resilience.

Results: The study was registered in October 2019, and enrollment began in September 2019. Of the 161 participants who were initially screened via a telephone survey, 43 (26.7%) fulfilled the inclusion criteria and were included in the study. Among the 55% (17/31) of participants in the intervention group and 45% (14/31) of participants in the control group who completed the study, no serious adverse incidents were reported. Of 43 participants, 4 (9%) withdrew during the program (for individual reasons)

and 8 (19%) have not yet participated in the program; moreover, further study recruitment was paused for an indeterminate amount of time because of the COVID-19 pandemic.

Conclusions: Our study aims to further define the physiological characteristics of human resilience, and it may offer novel approaches for the prevention and therapy of mental disorders via an exercise prescription.

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KEYWORDS

stress resilience; eHealth; aerobic capacity; peak oxygen uptake; cortisol; kynurenic acid; endocannabinoids

Introduction

Background

Physical inactivity is one of the major risk factors for global mortality; therefore, an active lifestyle is highly important to promote health and longevity. The risk for cardiovascular diseases, type 2 diabetes, osteoporosis, metabolic syndrome, specific cancers, and several other diseases is reduced by being physically active [1], and physical exercise can be prescribed as a medicine for 26 common chronic diseases [2]. In addition, mental health is positively affected by regular physical activity. Physical exercise induces the preservation of brain volume, which is associated with cognitive benefits [3,4]; it promotes blood-brain barrier integrity and protects against central nervous system infiltration of immune cells [5], and neurodegenerative diseases, such as Alzheimer and Parkinson disease, are counteracted by an active lifestyle [6].

To show the influence of exercise type, frequency, duration, and intensity on mental health, a cross-sectional study was conducted with 1.2 million individuals in the United States between 2011 and 2015 [7]. It was shown that regularly physically active persons have approximately half as many days of poor mental health than physically inactive persons. Furthermore, it was demonstrated that any kind of exercise had a reduced mental health burden compared with not exercising. A duration of at least 45 minutes with a frequency of 3 to 5 times a week is recommended. However, the authors also cautioned that more exercise is not always better [7].

To improve peak oxygen uptake (VO_2peak), it has been shown that individuals who perform interval training have a higher increase in VO_2peak [8] or have a shorter exercise duration with similar increases in VO_2peak compared with those who perform continuous exercise [9-11]. The comparison between low- and high-fit groups showed that the high-fit participants reacted and recovered faster within and after a psychological stress situation [12,13]. Furthermore, high-fit individuals had a lower cortisol concentration at rest and higher variability during the stressor compared with low-fit individuals. Moreover, a low cardiorespiratory fitness at the age of 18 years is associated with serious depression in later life [14], whereas implementing regular physical exercise training induces comparable efficacy in the treatment of major depression as antidepressant medication [15]. The described positive effects of physical exercise on mental health are accompanied by increased overall resilience [16].

Currently, there is no uniform and stringent definition of resilience [17-19]. A common psychological definition of resilience is “a person’s ability to adapt successfully to acute stress, trauma or more chronic forms of adversity” [20]. According to Kalisch et al [17], it is defined as the “empirically observable phenomenon [...] that someone does not develop lasting mental health problems although he or she is subject to adversity.” Recent resilience theories suggest a distinction to be made between resilience as an outcome, that is, the change in mental health relative to the stressor burden in a certain period, and resilience mechanisms, that is, variables that directly affect resilient outcomes [17]. By now, several psychosocial characteristics of a resilient phenotype (eg, lower levels of denial, avoidant coping behavior, and high positive emotionality) and multiple ways of promoting it (eg, improving problem-solving and planning skills) have been described [16]. Emotion regulation ability is considered a potential resilience mechanism and finds prominence in dynamic resilience theories [17,21]. Previous cross-sectional studies have indicated a positive relationship between physical activity and emotion regulation [22,23]. However, the driving neural circuits and underlying molecular pathways in resilience, especially in the context of physical exercise, are only beginning to be unraveled [16].

The major neuroendocrine and neural drivers of the responses to stress are the hypothalamic-pituitary-adrenal (HPA) axis, which mediates glucocorticoid (cortisol) release, and the sympathetic nervous system, which initiates the release of catecholamines (epinephrine and norepinephrine) in interaction with the immune system. Adequate activation of these systems in response to psychological or physical stress and subsequent restoration of homeostasis is critical to physical and mental health [16,24]. Malfunction of this responsive orchestration is associated with the development of several chronic diseases, including psychiatric diseases, autoimmune diseases, and cardiovascular diseases, contributing to mortality worldwide [25-27]. Acute bouts of physical exercise activate the HPA axis and the sympathetic nervous system, leading to increased stress hormone release followed by immune cell mobilization in a dose-responsive fashion [28-30]. When cessation of the physical stressor and the ensuing reconstitution of a homeostatic state occurs after a moderate period, adaptive mechanisms may result in improved stress reactivity. These adaptations include neurogenesis, improved synaptic plasticity and neuroprotection (eg, by increased levels of brain-derived neurotrophic factor [30,31]), and the promotion of an anti-inflammatory state (eg, by enhanced anti-inflammatory cytokines and reduced c-reactive

protein release [32]). Consequently, regular physical exercise may increase resilience by promoting a more adaptive activation of the HPA axis. Similarly, an exercise-induced shift in the tryptophan pathway, resulting in decreased kynurenine and increased kynurenic acid plasma levels, is considered to promote neuroprotection and resilience [33,34]. Furthermore, physical exercise activates the endocannabinoid system, which is considered to result in cognitive benefits and an antidepressant effect [35-37]. Thus, exercise prescription constitutes a useful means for the prevention and treatment of psychological and neurodegenerative diseases and moreover offers the possibility to enhance resilience in the general population.

Structured physical exercise interventions have been successfully implemented to improve disease states in brain diseases, such as major depression, Alzheimer disease, and Parkinson disease [15,38,39]. However, personalized training in a face-to-face fashion requires a high workload for coaches, and participants need to adhere to a strict time schedule. Individualized web-based physical exercise interventions allow trainers to remotely supervise multiple participants in a time- and cost-effective manner, for example, by providing weekly feedback. In turn, participants are highly flexible when integrating the training sessions into their daily routines and still receive individualized training programs from a coach. Our research group had previously shown in different types of patients that a web-based exercise program is useful, does not harm any participant, and improves physiological parameters, such as VO_2peak [40,41], and clinically relevant parameters [42-45].

Physical activity is positively associated with blunted stress reactivity and shorter stress recovery in response to various stressors [46,47]. To investigate acute stress reactivity and recovery in a psychophysiological laboratory, an experimental paradigm that significantly induces stress at the psychological and physiological levels is needed. Dickerson and Kemeny [48] identified several elements that reliably elicit significant HPA axis responses in participants: (1) physical stressors (eg, heat or cold), (2) mental challenges (eg, arithmetic tasks and working memory tasks), and (3) social evaluation (eg, giving a speech in front of a jury). In psychological stress research, there are several established stress paradigms that make use of these elements. The Socially Evaluated Cold Pressor Task (SECPT) [49] and the ScanSTRESS-C [50] for acute stress induction are experimental paradigms that have previously been proven effective in eliciting acute stress responses at the psychological (ie, decreases in well-being), endocrine (ie, high levels of catecholamines and cortisol), and physiological (ie, higher heart rate levels) levels [50-52].

Objectives

In this study, we implement an 8-week randomized controlled trial of a web-based, individualized physical exercise training intervention to evaluate the link between aerobic capacity and resilience in healthy untrained adults. Therefore, baseline values of performance diagnostics to determine the innate aerobic capacity (VO_2peak) as well as emotion regulation abilities, stress reactivity, and stress recovery (saliva cortisol) as potential resilience mechanisms are estimated. We hypothesize that (1) participants with a high innate aerobic capacity will show a higher resilience to stress compared with participants with low aerobic capacity. This will be followed by 8 weeks of individualized web-based physical exercise training combining continuous and interval-type running exercises with the aim of progressively increasing aerobic capacity. After completion of the exercise intervention, performance diagnostics will be repeated to estimate the acquired aerobic capacity, as well as to assess the psychological parameter. In addition, secondary outcomes of molecular factors, including hair cortisol levels, endocannabinoids, catecholamines, cytokines, and cell-free DNA, and results of several questionnaires will be determined throughout the study. We hypothesize that (2) the exercise intervention will improve the aerobic capacity of the intervention group, which (3) will be accompanied by improvements in resilience factors. This will offer the possibility to exploratively study the underlying molecular mechanism (stress hormone release and immune reactions) in the promotion of resilience by regular physical activity.

Methods

Trial Design and Participants

This study is designed as a prospective randomized controlled trial with 2 phases of data collection before (baseline examination; time point 0 [T0] and time point 1 [T1]) and after (final examination; time point 2 [T2] and time point 3 [T3]) 8 weeks of web-supervised physical exercise training intervention (T1-T2; Figure 1). The multidisciplinary single-center trial is a collaboration among the Institute of Physiological Chemistry, Department of Psychiatry and Psychotherapy, Department of Clinical Psychology and Neuropsychology, and Department of Sports Medicine, Disease Prevention and Rehabilitation. The medical association Rhineland-Palatinate approved the study (July 29, 2019, ID: 2019-14305), and the study was registered with the German Clinical Trials Register (DRKS; DRKS00018078; October 2, 2019) and conformed to the standards of the Declaration of Helsinki of the World Medical Association. Administrative changes of the protocol, if needed, are minor corrections and clarifications that have no effect on the way the study is to be conducted. An amendment will be approved by the Ethics Committee Landesärztekammer Rhineland-Palatinate before implementation. This protocol follows the guidelines from the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) [53] and the CONSORT-eHEALTH checklist (Multimedia Appendix 1) [54]. A SPIRIT diagram of enrollment, interventions, and assessments is provided in Figure 1.

Figure 1. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) diagram of enrollment, interventions, and assessments. ADS: Allgemeine Depressionsskala; ASI: Anxiety Sensitivity Index; BRS: Brief Resilience Scale; BSI: Brief Symptom Index; CERQ: Cognitive Emotion Regulation Questionnaire; CG: Control Group; CTQ: Childhood Trauma Questionnaire; ECG: electrocardiogram; ERQ: Emotion Regulation Questionnaire; GOT: Glutamate Oxalacetate Transaminase; GPT: Glutamate Pyruvate Transaminase; GSE: General Self-Efficacy Scale; HPA: Habitual Physical Activity Questionnaire; IG: Intervention Group; IPAQ: International Physical Activity Questionnaire; MDBF: Mehrdimensionaler Befindlichkeitsfragebogen; PAR-Q: Physical Activity Readiness Questionnaire; PSS-10: Perceived Stress Scale–10; SCS-D: Self-compassion Scale–German Version; SECPT: socially evaluated cold pressor test; SF-36: Short-Form Health Survey; SRS: Stress Reactivity Scale; TICS-SSCS: Trier Inventory for the assessment of Chronic Stress–Screening Scale For Chronic Stress.

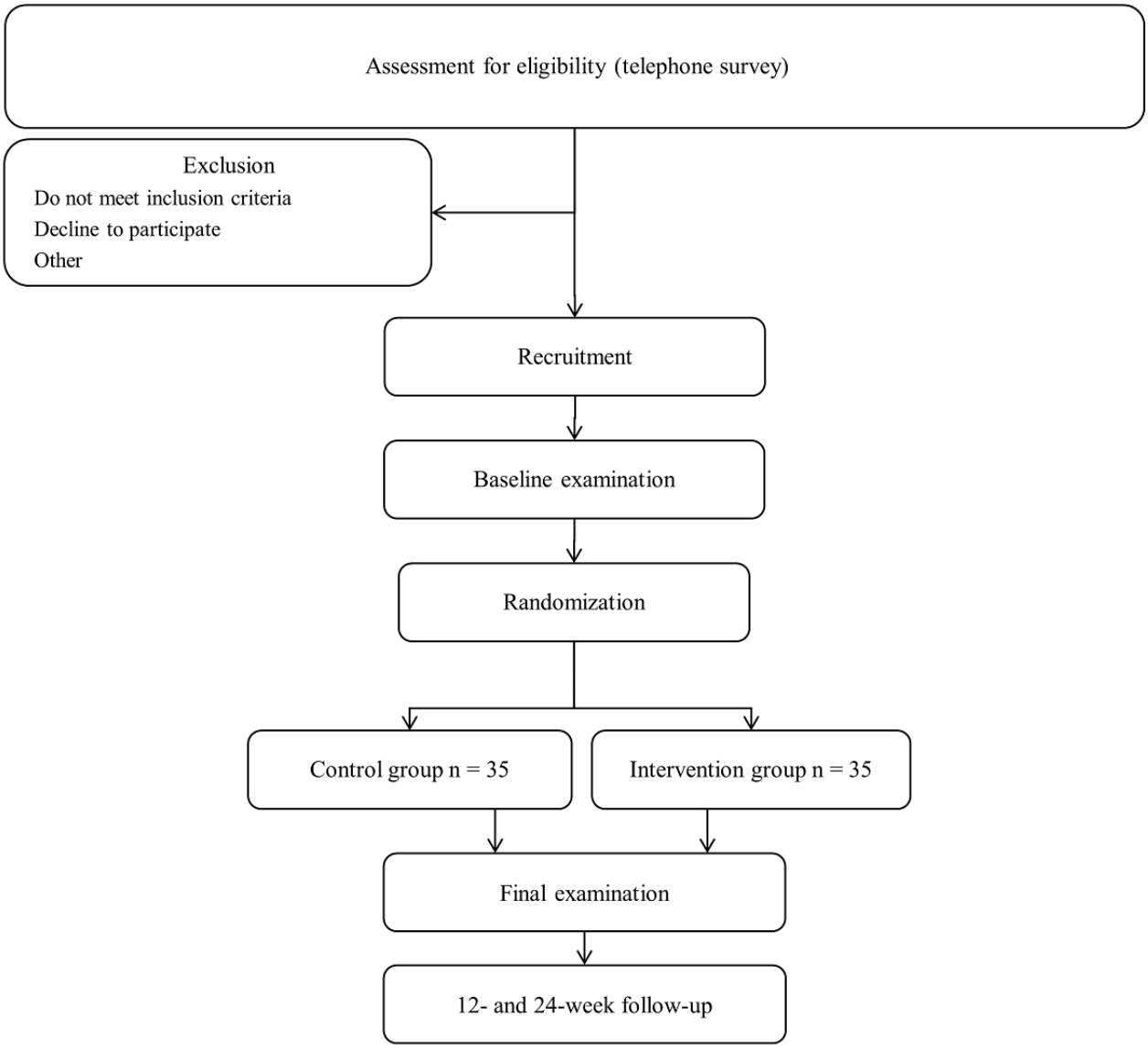
	Study period							
	Enrollment	Baseline		Intervention	Post-allocation		Follow-up 12 & 24w.	
TIMEPOINT	- T1	T0	T1	T1-T2	T2	T3	T4	T5
ENROLMENT:								
Telephone screening	X							
Eligibility screen	X	X	X					
Informed consent (Pre)		X						
Informed consent (Post)						X		
PRELIMINARY INVESTIGATION:								
Bioelectric impedance analysis			X			X		
Pulmonary function test		X				X		
Anthropometric data		X				X		
Blood pressure		X				X		
Resting-ECG (supine position)		X				X		
Survey by the doctor		X				X		
PSYCHOLOGICAL STRESS TESTS:								
Cold Pressure Task (SECPT)		X						
ScanSTRESS-C					X			
Saliva cortisol		X			X			
Cognitive Emotion Regulation Task (CERT)		X						
Script-based Reappraisal Test (SRT)					X			
PERFORMANCE DIAGNOSIS:								
Spiroergometry (peak oxygen uptake [VO_2peak])			X			X		
Capillary blood (lactate, cell-free DNA)			X			X		
Venous blood (adrenalin, noradrenalin, cfDNA, extracellular vesicles, endocannabinoids, kynurenic acid, electrolytes, glucose, GOT, GPT, creatinine, urea)			X			X		
Determination of the training intensities based on the lactate kinetic			X					
INTERVENTIONS:								
Randomization		X						
Intervention group (IG)			◊	—	◊			
Control group (CG)			◊	—	◊			
Continuous interval-based endurance training (IG)				X				
Weekly training adjustment (IG)				X				
ASSESSMENTS:								
Medical history sheet, BRS, CTQ		X						
BSI, ADS-long, CERQ, ERQ, ASI, SCS-D, PSS-10, TICS-SSCS, SRS, SF-36, HPA, IPAQ long version, German-PAQ-50+, GSE, MDBF		X			X			
Voluntary web-based survey							X	X

The primary (VO_2peak and saliva cortisol) and key secondary outcomes, trial methods, and designs are summarized in the World Health Organization trial registration data set (Textbox 1). This study includes 4 time points of investigation of physiological and psychological parameters, including the primary end points of a change in VO_2peak and saliva cortisol

from the baseline: at T0 and T1, baseline values will be estimated, and at T2 and T3, data collection following the control or exercise intervention will be performed. T0 and T2, as well as T1 and T3, are structured in the same way, except for the separately listed psychological examinations at the measurement points. T1 and T3 will be performed after a maximum of 10 days after T0 and T2, respectively. Written consent after a detailed oral explanation will be obtained from all participants at the beginning and after completion of the study by the responsible study physician. At the beginning of the study (T0), the participants will not be fully informed about the purpose and aim of the psychological stress tests. Full clarification will take place at T3. If a participant wishes to discontinue the study prematurely, they will be fully informed about the purpose and aim of the psychological stress tests.

Participant recruitment commenced in September 2019. Participants were and will be recruited via flyer announcements for the study (Multimedia Appendix 2) at multiple locations at the Johannes Gutenberg-University of Mainz and the University Medical Center campuses, as well as diverse places for leisure activities, as impersonal recruitment. Inclusion into the study is a two-step procedure beginning with a telephone survey according to the eligibility criteria (Textbox 2). At the first visit, sport capability will be confirmed and the participants will be included in the study. Blinding of participants will not take place. After telephone screening and recruitment, participants will be randomized (Figure 2) into the intervention group (IG) or control group (CG). The IG will participate in the 8-week sports intervention based on a combination of continuous and interval-type running exercises. Participants in the IG will be told not to engage in further high-intensity sports activities. Participants in the CG will be told not to change their daily lifestyles during the intervention period.

Figure 2. Study design flow diagram.



Textbox 1. World Health Organization trial registration data set.

Trial registration data set

- Primary registry and trial identifying number: German Clinical Trials Register DRKS00018078
- Date of registration in primary registry: October 2, 2019
- Secondary identifying numbers: none
- Source of monetary or material support: Boehringer Ingelheim Foundation
- Primary sponsor: Boehringer Ingelheim Foundation
- Secondary sponsor(s): not applicable
- Contact of public queries: ochmann@uni-mainz.de (DO); albrahme@uni-mainz.de (AB)
- Contact for scientific queries: albrahme@uni-mainz.de (AB)
- Public title: mediators of a link between innate or acquired aerobic capacity and stress resilience
- Scientific title: The association of innate and acquired aerobic capacity with resilience in healthy adults: Protocol for an 8-week randomized controlled, web-based, physical exercise intervention study
- Countries of recruitment: Germany
- Health condition(s) or problem(s) studied: healthy participants
- Intervention(s): web-based exercise intervention; control
- Key inclusion criteria:
  - Age: 18-45 years
  - Healthy
  - Suitable for sports
  - Physically inactive (<150 minutes/week physically active)
  - Gender: male and female
- Key exclusion criteria:
  - Absolute contraindications to exercise
  - Smoker or other tobacco consumption
  - High blood pressure
  - Long-term medication intake
  - Hairless participants (<1 cm)
  - Shift worker
  - Participation in another study
  - Psychological disorders
- Study type:
  - Interventional
  - Allocation: randomized, controlled
  - Intervention model: parallel assignment
  - Primary purpose: prevention
- Date of first enrollment: September 10, 2019
- Target sample size: 70
- Recruitment status: Recruiting
- Primary outcome(s):
  - Improvement of the maximum oxygen uptake through an 8-week web-based training intervention.
  - Investigation of the link between the changes in maximum oxygen uptake induced during training intervention and the associated changes in salivary cortisol induced during a stress test.

- Key secondary outcomes:
  - Investigation of the link between maximum oxygen uptake and resilience by determining physiological and biochemical markers in the untrained state before an 8-week web-based training intervention.
  - Investigation of the link between the changes in maximum oxygen uptake and resilience induced through training intervention by determining physiological and biochemical markers.
  - Sustainability of the change in resilience 12 and 24 weeks after 8 weeks of web-based training intervention.

Randomization

The included participants will be randomly assigned with a 50%-50% allocation to the IG or CG. Randomization will be performed using the EXCEPT NUMBER command in Microsoft Excel. In addition, randomization will be stratified by gender with an expected ratio of 50%-50% and BMI with an expected ratio of 33% overweight (BMI ≥25) and 67% normal weight (BMI <25) to recruit CG and IG participants with homogeneous baseline characteristics.

Eligibility Criteria

To work with a homogenous study population and to reduce the influence of different characteristics of the study population on study outcomes, the inclusion and exclusion criteria for participating in the study were chosen as listed in Textbox 2. It is known that both neural and behavioral processing of stress is altered in clinical samples with conditions such as depression [55] or anxiety disorders [56]. To minimize differences between participants, we excluded individuals with current or past psychological treatment as assessed in our standardized telephone screening. To reduce the impact of hormonal contraceptives in women on stress reactivity (saliva cortisol) and emotional memory [57], only women taking no hormonal contraceptives are included in our study. Alcohol abuse was defined according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) [58] as a regular or daily drinking routine.

Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- Age: 18-45 years
- Nonsmokers
- Normal blood pressure (≤140/90 mm Hg)
- Suitable for sports
- Voluntary participation
- No medication
- Physically inactive (<150 minutes/week physically active)
- Time for 8-week intervention
- Signing the consent form
- Gender: male and female

Exclusion criteria

- Age: <18 or >45 years
- Smoker or other tobacco consumption
- High blood pressure
- Not suitable for sports
- Constrained participation
- Long-term medication intake
- Trained (>150 minutes/week physically active)
- Probably no time for intervention
- Rejection by the participant
- Lack of ability to consent or doubts about the ability to consent
- Hairless participants (<1 cm)
- Shift worker
- Clinically significant 12-channel electrocardiogram abnormality determined by the physician
- Alcohol or drug abuse within the past year before screening, positive urine drug test, or positive alcohol test during screening
- Infection with HIV, Hepatitis C virus, or Hepatitis B virus
- Participation in another study
- Other unspecified reasons that, from the investigator's point of view, militate against participation in the study
- Cardiovascular, metabolic, pulmonary, and muscular diseases after the *International Classification of Diseases, Tenth Revision*, acute or anamnestic
- Psychological disorders diagnosed according to *International Classification of Diseases, Tenth Revision* or *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition), acute or anamnestic (last 24 months)
- Female participants taking hormonal contraceptives

Preliminary Investigation (T0/T1 and T2/T3)

The first visit (T0) includes the initial screening of the participant's height and weight. A pulmonary function test will be used to determine vital capacity, forced expiratory volume in 1 second (Spirometry, Bodybox 5500, Medisoft Group) and, if applicable, to identify the presence of undiagnosed restrictive or obstructive respiratory abnormalities [59]. Furthermore, the cardiological values of resting blood pressure and resting electrocardiogram (Schiller AT-60) will be measured in a supine position to ensure proper cardiovascular function. To determine the long-term cortisol value over 2 months, a 2 cm–long strand of hair will be cut off at the back of the head directly from the skin [60]. A bioelectric impedance analysis (In Body 3.0, Biospace) and blood counts will be conducted during the second visit (T1) in the morning before the incremental running test after a minimum of 8 hours of overnight fasting. After the completion of the control or exercise intervention, the described parameters will be reassessed during the third or fourth visit (T2 or T3).

Questionnaires (T0 and T2)

Owing to the multidimensional approach to stress resilience outlined above, we required a lot of information about the

participants' lifestyle as well as psychological and medical anamnesis with the help of several questionnaires. To minimize the total experimental time, participants will complete part of the questionnaires on the web before their arrival at T0. Further questionnaires will be completed within the resting and recovery periods during the on-site appointments.

Psychological Questionnaires

Brief Resilience Scale (Only T0)

The Brief Resilience Scale is a 6-item questionnaire that considers the dimension *bounce back* from stress on a 5-point Likert scale. The scale exhibits good psychometric properties with high internal consistency and retest reliability [61]. The German version of the Brief Resilience Scale was validated in 2018 [62].

Childhood Trauma Screener (Only T0)

The Childhood Trauma Screener (CTS) is a 5-item brief instrument for the assessment of childhood abuse and neglect on a 5-point Likert scale [63]. The CTS is based on the Childhood Trauma Questionnaire, which includes 28 items on physical, emotional, and sexual abuse as well as emotional and physical neglect [64,65]. These questions of the CTS deal with experiences during childhood and youth. The CTS showed a high correlation (r=.88; P<.001) with the total Childhood Trauma Questionnaire score. The internal consistency was .757 (Cronbach α; n=499).

Brief Symptom Index-18

The Brief Symptom Index-18 is an 18-item scale, which is divided into 3 syndromes—somatization, depression, and anxiety—with 6 items each on a 5-point Likert scale [66]. The German version of the Brief Symptom Index-18 was validated in 2011. It showed a satisfactory-to-high consistency of the different syndromes (Cronbach α between .63 and .93) [67].

General Depression Scale (Long Version)

The General Depression Scale (German translation: *Allgemeine Depressionsskala* [ADS]) is the most common German version of the Center for Epidemiologic Studies Depression Scale [68]. The first test publication of ADS was in 1993 [69]. The second edition of the manual with new samples and standard data was published in 2012 [70]. No changes were made to the items. Only the critical threshold value of the long version (ADS-L) for the screening of depression was corrected from >23 to >22 [70]. With its 20 items, the ADS-L considers affective, cognitive, somatic, and social depression symptoms, among others. The answers are given on a 4-point scale from 0 (rarely or not at all [<1 day]) to 3 (mostly all the time [5-7 days]). The internal consistency (Cronbach α) of the ADS-L in adults in multiple population samples is between .85 and .92, and the test-retest reliability (2-8 weeks) is .51-.67.

Cognitive Emotion Regulation Questionnaire

The Cognitive Emotion Regulation Questionnaire covers 9 strategies (self-blame, blaming others, acceptance, refocusing on planning, positive refocusing, rumination or focus on thought, positive reappraisal, putting into perspective, and catastrophizing) and 36 items of cognitive emotion regulation with a range from 1 ([almost] never) to 5 ([almost] always) [71]. The German version differs in the item number. Here the questionnaire was shortened to 27 items (3 items per dimension) [72,73]. A good psychometric quality (factorial validity and acceptable-to-good reliability [.70<α<.84]) could be shown in a clinical sample [72].

Emotion Regulation Questionnaire

The Emotion Regulation Questionnaire deals with the most common preferences of 2 applied strategies for emotion regulation: suppression (4 items) and reappraisal (6 items) [74]. The German version was first published in 2009 [75]. On a 7-point Likert scale from 1 to 7 (1=not correct at all; 4=neutral; and 7=completely correct), the participants can choose a number. Internal consistency (Cronbach α) for reappraisal was .79, and for suppression, .73 [74]. The test-retest reliability across 3 months was .69 for both strategies [74].

Anxiety Sensitivity Index-3

Anxiety Sensitivity Index-3 is an 18-item scale with 3 factors (physical, cognitive, and social concerns) on a 5-point Likert scale [76]. The German version was first published in 2009. The internal consistency is between .86 and .89 [77]. Satisfactory measurement accuracy and good validity can be seen in comparison with the English version [77].

Self-compassion Scale (German Version)

The Self-compassion Scale (SCS) contains 26 items with originally 3 basic components: (1) self-kindness, (2) common humanity, and (3) mindfulness, which are answered on a 5-level scale (1=very rarely and 5=very often) [78]. The German version of the SCS (SCS-D) was first checked for reliability and validity in 2011 [79]. In comparison with the original, a 6-factorial structure (self-kindness, self-condemnation, common humanity, isolation, overidentification, and mindfulness) was found and as expected, correlates with subjective well-being and psychological strain. With the German version of the SCS, an economic, reliable, and valid assessment of self-compassion is available.

Perceived Stress Scale-10

The Perceived Stress Scale (PSS-14) contains 14 items, which are answered on a 5-point response scale (0=never and 4=very often) [80]. On the basis of principal component analysis, a low factor loading of 4 items was determined and then dropped. The shortened PSS-10 shows a slightly increased reliability (Cronbach α=.78 vs Cronbach α=.75) and a similar validity [81]. The German version of the PSS-10 shows good internal consistency (Cronbach α=.84) and construct validity between perceived stress and depression, anxiety, fatigue, procrastination, and quality of life [82,83]. PSS-10 is an economic, reliable, and valid assessment tool for assessing perceived stress.

Trier Inventory for the Assessment of Chronic Stress–Screening Scale for Chronic Stress

The TICS-SSCS (Trier Inventory for the assessment of Chronic Stress–Screening Scale for Chronic Stress) comprises 12 items [84]. The TICS-SSCS measures the frequency of self-perceived overall stress in 5 different stress domains in the past 3 months: chronic worrying, work-related overload, social overload, excessive demands, and lack of social recognition. The

frequency of stress in the 5 stress domains is recorded with the values *never* (0 points), *rarely* (1 point), *sometimes* (2 points), *frequently* (3 points), and *very frequently* (4 points), and in the end, an average score can be calculated. The internal consistency for the TICS-SSCS is rated as very good, with Cronbach α=.91 [84,85].

The Stress Reactivity Scale

The 29-item Stress Reactivity Scale measures the duration and magnitude of an effective response that a person displays in various stress situations. Each item consists mainly of 2 parts: (1) a typical stress situation and (2) 3 response items. From this, the total score can be calculated. A satisfying Cronbach α between .71 and .82 for the various subscales and good retest reliability coefficients over 7 months between .63 and .84 could be shown [86].

General Self-efficacy Scale

The General Self-efficacy Scale is a 10-item psychometric scale that assesses general optimistic self-conviction [87]. The items are answered on a 4-level scale (1=not correct; 2=hardly correct; 3=rather correct; and 4=exactly correct). At the end, all points are summed up, and the result is a score between 10 and 40. The internal consistency of Cronbach α is between .75 and .91. Confirmatory factor analysis could confirm the single-factor structure of the scale. The scale shows a good retest reliability of .67 [88].

Multidimensional Mood State Questionnaire

To assess psychological responses to acute laboratory stress induction, we will use the Multidimensional Mood State Questionnaire (German translation: *Mehrdimensionaler Befindlichkeitsfragebogen* [MDBF]) [89]. The MDBF consists of 24 adjectives that reflect positive or negative emotional states. Participants' ratings on a 5-point Likert scale could be summed up to a total score of subjective well-being, where higher scores reflect a more positive emotional state. Sufficient reliability (Cronbach α=.80-.92) and validity of the MDBF have been confirmed in several studies [90-92]. As in previous studies by our group [50,93], we will use the MDBF at multiple time points before and after the stress tasks at T0 and T2 to assess variations in psychological well-being in response to stress (–2 minutes, +15 minutes, and +60 minutes relative to stress onset).

Sports Medicine Questionnaires

Habitual Physical Activity Questionnaire

The Habitual Physical Activity Questionnaire is divided into 3 indices evaluating (1) occupational physical activity, (2) sports, and (3) leisure time, and it originally included 16 items [94]. The German version of the Habitual Physical Activity Questionnaire was compared with the original version in 2001 and was reduced by 2 items after item-analytical analysis [95]. The test-retest reliability of the indices of physical activity over 3 months is .80 and .90 for (1) and (2) and .74 for (3) [94].

International Physical Activity Questionnaire (Long Version)

The long version of the International Physical Activity Questionnaire contains 27 items and collects physical activity values in different domains (occupational, transport, yard or garden, household, leisure, and sitting) and different intensities (moderate and vigorous) within the past 7 days [96]. The German long version was validated on German adolescents [97]. It is an acceptable, valid, and reliable questionnaire for assessing physical activity in many countries [96].

Short-Form Health Survey

The 36-item Short-Form Health Survey is a cross-disease assessment instrument for measuring the health-related quality of life of the general population and patients [98]. It consists of 8 dimensions of subjective health: physical functioning (10 questions), social functioning (2 questions), role limitations (physical problems, 4 questions; emotional problems, 3 questions), general mental health (psychological distress and well-being; 5 questions), vitality (energy and fatigue; 4 questions), bodily pain (2 questions), and general health perception (5 questions). In addition to the 8 dimensions, one question is used to request health changes [99]. These dimensions can be assigned to the functional status and well-being of the basic dimensions. The version of the Short-Form Health Survey-36 used here refers to the past 4 weeks. Except for social functioning (Cronbach α=.73), the 7 other dimensions showed acceptable internal consistency, with a Cronbach α≥.85. The test-retest reliability is excellent within 2 weeks [99].

Physical Activity Readiness Questionnaire

The Physical Activity Readiness Questionnaire is an internationally renowned preparticipation screening tool that was based on expert opinion (British Columbia Ministry of Health and the Multidisciplinary Board on Exercise) [100]. It intends to find whether the test participant should see a physician before beginning physical activity or a sport. Here, cardiovascular, balance, medical, emotional, and joint issues, which could hinder physical activity or sports activity, should be excluded. All questions should be answered with *no*. This questionnaire is used as an exclusion criterion in this study and is used in the telephone survey. If a question is answered with *yes*, the person is not included in the study.

Psychological Stress Tests (T0 and T2)

Stress Induction Paradigms

As the study design aims to investigate acute stress effects at several time points (T0 and T2) by focusing on the change in saliva cortisol levels as a primary end point, 2 alternative paradigms for stress induction are required, which are described below. Thus, habituation and expectation effects can be reduced based on the first stress induction paradigm. These psychological stress tests will be conducted between 1:30 PM and 4 PM to control the circadian cortisol level. To eliminate possible contaminations of saliva, participants will be instructed to refrain from eating or drinking for 1 hour before the stress tests. In addition, participants will watch a relaxing movie for approximately 20 minutes to minimize baseline differences in cortisol concentrations.

Socially Evaluated Cold Pressure Test (T0)

Stress induction at T0 will be performed by means of the SECPT [49]. The participant will be asked to immerse their nondominant hand in a pool of cold water (0-4 °C) and to keep it there if

possible. During this time, the participant will be observed by an experimenter, who will keep a neutral facial expression while taking notes on a clipboard. To further enhance the social evaluation, the face of the participant will be recorded with a mock camera. The participants will be encouraged to keep their hands immersed for a maximum of 3 minutes.

Psychosocial Stress Task for Scanner Environments (T2)

Stress induction at T2 will be performed using the compact version of the psychosocial stress task for scanner environments (ScanSTRESS) paradigm [50,52]. First, the participants will go through a control phase and then a stress phase (6 minutes each). During the stress phase, 2 types of cognitively challenging tasks will be processed with computer assistance (Neurobs Presentation software, Neurobehavioral Systems): mental rotation and arithmetic subtraction tasks. A preprogrammed algorithm adapts the task difficulty and speed to the participant´s performance, thus creating time pressure and forcing errors. The social-evaluative component is a jury (consisting of 2 test supervisors in white lab coats) that is transmitted via a live video stream to the screen of the participant during the task processing and thus continuously providing negative disapproving feedback. In case of too slow processing, as well as in the case of an erroneous answer, the jury can also project negative written feedback onto the respondent's screen via a buzzer (“Work faster!” and “Error!”). To further increase the stress level, the stress phase will be interrupted halfway through for verbal feedback. Here, the participant will be reminded that the data can only be used if maximum performance is achieved. Accordingly, the highest possible concentration is requested. During the control phase, the participants will only perform simple assignment tasks without time pressure and negative feedback.

Saliva Cortisol

To validate the effectiveness of the stress tests performed, 6 saliva samples will be collected throughout the experiment to detect the stress hormone cortisol. Commercially available Salivettes (Sarstedt) will be used for this purpose. All saliva samples will be stored at –20 °C and sent to the Institute of Biopsychology at the Technical University Dresden, Germany, for analysis. Salivary concentrations will be measured using commercially available chemiluminescence immunoassays with high sensitivity (IBL International).

Emotion Induction and Regulation (T0 and T2)

To detect differences in the ability to regulate emotions, 2 different tests will be used in parallel to the stress tests.

Cognitive Emotion Regulation Task (T0)

The Cognitive Emotion Regulation Task (CERT) [101,102] comprises 3 task conditions and 2 image categories. In the first task condition, the participants are instructed to merely watch the presented stimuli and react naturally to them (*view condition*). In the second task condition, the participants are asked to cognitively modify the content of the presented image by assigning it a positive content (*cognitive reappraisal*) and thereby regulating their emotions. In the third task condition, participants are asked to indicate as fast as possible if the given mathematical equation is correct or incorrect via a button press (*distraction*). For this purpose, the participants are presented with both negative (first image category) and neutral images (second image category). The images are taken from the internationally standardized and evaluated databases *International Affective Picture System*) [103] and *Emotional Picture Set* [104]. After 1000 ms of stimulus presentation, the task instructions are presented for 1000 ms (transparent overlay). The image stimulus is then on display for another 5000 ms, followed by a 4000-ms rating phase where participants indicate their current affective state using the *Self-Assessment Manikin* scale for valence [105]. The interstimulus interval is 3000-5025 ms. In our study, the CERT comprises 75 trials of approximately 14.5 seconds each, 15 trials each for the following conditions: view_negative, view_neutral, distract_negative, distract_neutral, and reappraise_negative. In total, the CERT lasts approximately 19 minutes.

Script-Based Reappraisal Test (T2)

The Script-Based Reappraisal Test [106] is a computer-based behavioral experiment that assesses an individual’s ability to regulate emotions. In this experiment, text-based scripts will be presented that describe everyday situations and induce negative emotions (anger toward others, anger toward oneself, and fear). In this experiment, participants will work through several passages in which a script is first presented (20 seconds). Subsequently, participants will be instructed, depending on the passage, to reduce the emerging negative emotions within 1 minute by cognitive reassessment (reassessment passages) or to allow them to arise (control passages). At the end of each session, the participants will use *Self-Assessment Manikin* scales [105] to indicate their affective state in terms of valence and arousal (6 seconds) and type in their revaluation thoughts or negative thoughts (90 seconds). The Script-Based Reappraisal Test contains 12 revaluation sessions and 12 control sessions. At the beginning of the experiment, 2 sample runs will be performed, and the participants' questions on understanding will be answered.

Peak Oxygen Uptake Determination (T1 and T3)

To determine the individual VO_2peak as the primary end point and the training areas, participants will complete a stepwise incremental running test on a treadmill (Saturn, HP-Cosmos) until subjective exhaustion is reached or general indications for stopping an exercise test according to the American College of Sports Medicine guidelines are fulfilled [59]. Maximal oxygen uptake is reached if a plateau of VO_2 is observed within the final 2 work rates of the stepwise incremental running test [59]. Here, we have untrained participants who may not be able to reach a plateau in VO_2 uptake. Therefore, we will use VO_2peak and take the highest value of VO_2. To avoid outliers, there should be no high variance around this VO_2 value within the 4 previously taken breaths. The exercise test includes a starting velocity of 4 km/hour, a duration of each step of 3 minutes, a pause time between 30 seconds and 60 seconds, and an increase in velocity by 1.5 km/hour from step to step. To determine the lactate threshold, 20 µL of whole blood will be collected from the fingertip with an end-to-end capillary (Sodium-Heparin, EKF-Diagnostics GmbH) at rest and between the stages. Heart

rate (electrocardiogram), as well as oxygen uptake and carbon dioxide release (spiroergometry), will be continuously recorded. The latter will be used to estimate VO_2peak for IG and CG at T1 and T3. VO_2peak at T1 will be considered as innate aerobic capacity, and VO_2peak of the IG at T3 will be considered as acquired aerobic capacity. Absolute and relative contraindications will be defined according to the American College of Sports Medicine guidelines [59].

Infrared Thermography (T1 and T3)

Infrared thermography is a noninvasive, contact-free, nonradiating tool used to measure surface radiation temperature and patterns [107]. In this study, a high-resolution infrared camera (Jenoptik VarioCam; 480×640 pixels; focal plane array; spectral range 7.5-14 micrometers; accuracy ± 0.05 K; and set emissivity: 0.98) will be applied for the measurement of mean surface radiation temperature (T_{sr} [°C]) of the calves (CT_{sr}). The infrared camera will be placed on a tripod behind the participant at the height of 85 cm. The distance between the camera and participant will be 2.30 m. The focus will be set perpendicular to the backside of the calves to capture the area from the popliteal space to the ankle. To stabilize the running position on the treadmill, a horizontal barrier made of elastic-plastic will be fixed behind the participant, and the foot position will be marked on the treadmill with adhesive tape. The infrared camera temperature scale will be set from 25 °C to 35 °C. An acclimatization period of 10 minutes will be implemented before the exercise test. The participants will only be allowed to wear ankle socks and shorts; should sleep and fast for 8 hours; should drink not more than 1.5 L of water; should be physically inactive; and should avoid cosmetics, showering, and sunbathing for at least 8 hours before the test.

We will perform 3 steps for thermogram analysis: (1) thermogram selection, (2) thermogram processing, and (3) analysis of the region of interest. We will process the image by coloring everything in black, except for the relevant area in the thermogram. This analysis procedure is in line with that of Ludwig et al [108]. The final regions of interests analysis will be performed with the software *Analysis of thermal images–TDM V2.0* (Optoprecision GmbH). The report of the entire infrared thermography procedure is in accordance with that of Moreira et al [109].

Measurements of Blood Parameters (T1 and T3)

Before, immediately after, and 30 minutes and 60 minutes after the exercise testing, the median cubital vein will be punctured for venous blood sampling. In total, 100 mL of whole blood will be taken and further processed for the preparation of blood serum and plasma aliquots, depending on the subsequent analysis. Blood counts and physiological parameters will be assessed from the venous plasma or serum, respectively, at the defined time points. The following parameters will be included: creatine kinase, lactate dehydrogenase, hydroxybutyrate dehydrogenase, calcium, cholesterol, triglycerides, high-density lipoprotein-associated cholesterol, low-density lipoprotein-associated cholesterol, total leukocytes, erythrocytes, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, platelets, neutrophils, eosinophils, basophils, monocytes, lymphocytes, and total protein. Blood plasma samples for molecular marker analysis will be aliquoted and stored at –80 °C before further processing. Venous blood will be used to determine and analyze venous cell-free DNA (concentration using quantitative real-time polymerase chain reaction [110,111]); non–disease-specific epigenetic patterns and sequence analysis using targeted next-generation sequencing [112]; endocannabinoids, catecholamines, and inflammatory lipids using mass spectrometry [113,114]; and further circulating signal transducers (extracellular vesicles and cytokines using multiplexed assays [115-117]). In parallel with venous blood sampling and additionally at each increment of the exercise test, capillary blood samples will be taken from the fingertip to determine capillary cell-free DNA concentrations.

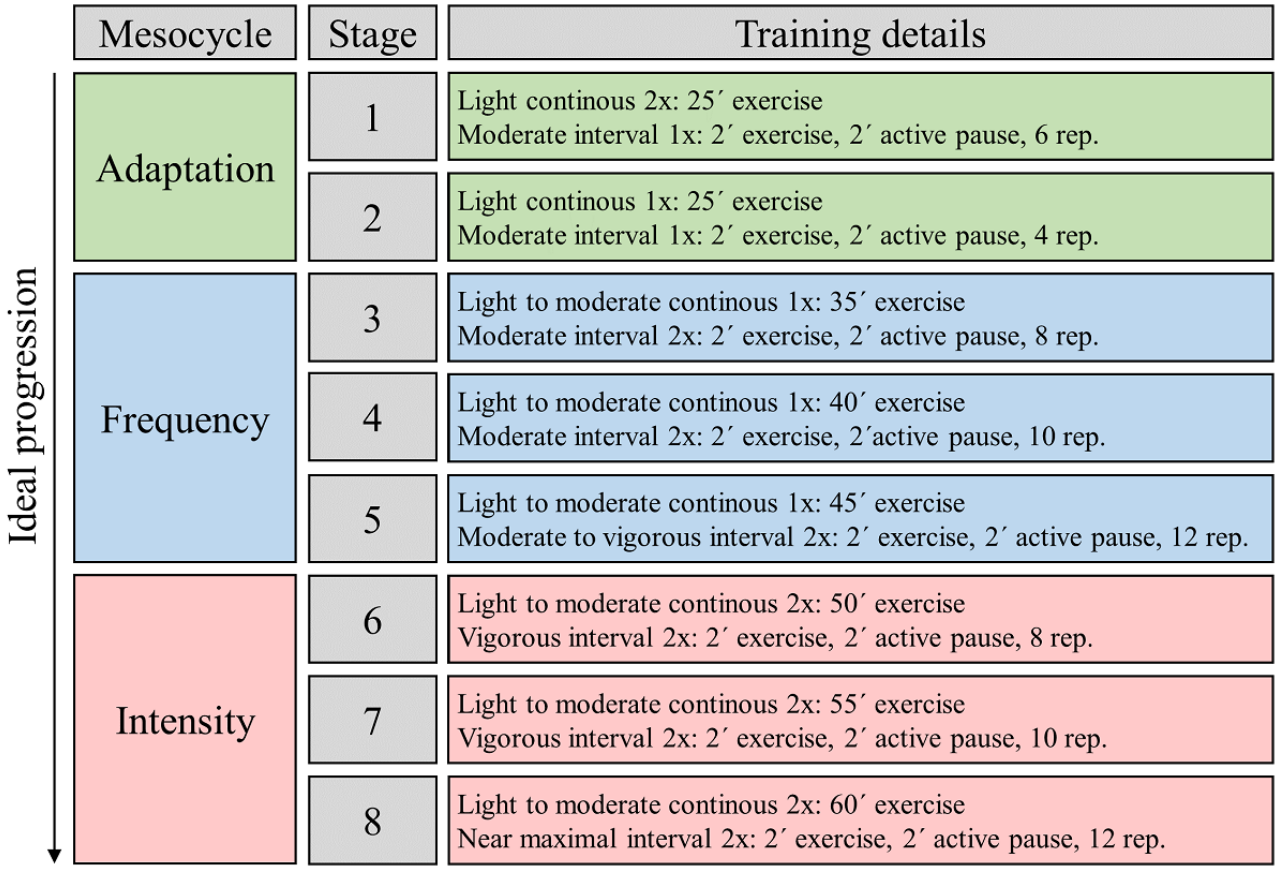
Lactate Threshold and Determination of the Training Ranges (T1 and T3)

On the basis of lactate kinetics during the incremental stepwise running tests, the individual anaerobic threshold (IAT) will be used to determine the intensity ranges (regeneration, light, moderate, and vigorous) for the training sessions. The IAT will be determined by means of minimum lactate equivalent +1.5 mmol/L [118,119]. Here, we will define 4 training intensities (regeneration: 50%-70%, light: 70%-85%, moderate: 85%-100%, and vigorous: 100%-110%), which are relatively related to the velocity at IAT (100%).

Training Intervention

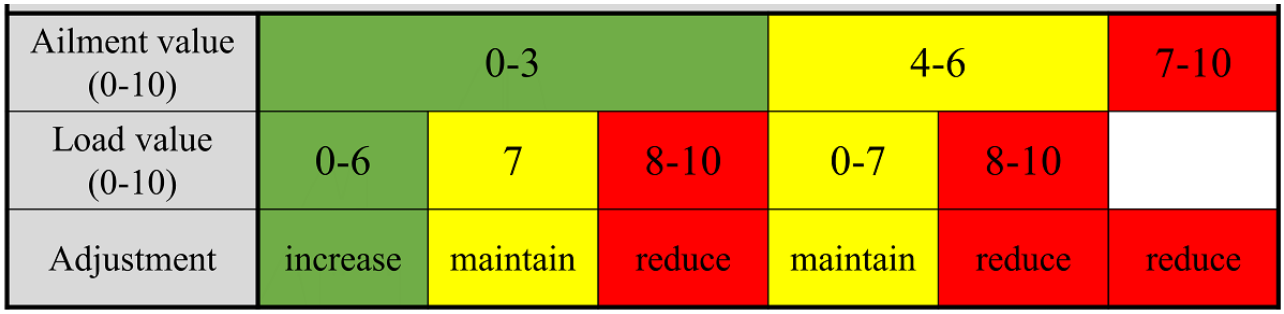
After the baseline examination (T0 and T1), an 8-week sports intervention will be carried out for the IG. The CG will not participate in any training interventions during this period. The training contents are interval- and continuous endurance–oriented. The external load can be individually controlled and adjusted with the help of the IAT and the related relative training intensities. The intervention is divided into 3 mesocycles and 8 microcycles (=1 week): adaptation (2 weeks), frequency (3 weeks), and intensity (3 weeks; Figure 3). One box (Training details) corresponds to a fixed training week from Monday to Sunday. 5 minutes warm up and 5 minutes cool down should be included in every training session. The numbers 1x and 2x are the weekly frequencies of the training session.

Figure 3. Ideal progression of training load from eight stages over the 8-week sport intervention period. Rep: repetitions.



Here, a comprehensible protocol is used to adjust the training load using the principle of periodizing and cyclizing (frequency, intensity, time, type, volume, pattern, and progression; Figure 4) [43,45,59]. The gradual progression of the training load is based on weekly feedback of the participant via the Foster scale (0-10) [120]. The value for ailments has a higher priority than the load value. An optimal training load increase over 8 weeks of the training intervention is shown in Figure 3. After 8 weeks, each participant in the IG can end the training intervention on another stage based on the weekly feedback. In addition to the exercise training, the participants can conduct relaxation exercises in the form of stretching and mobilization exercises.

Figure 4. Individual training adjustment using the modified Borg scale [120] and the FITT-VP principle [43,45,59]. FITT-VP: Frequency, Intensity, Time, Type, Volume, Pattern, and Progression.



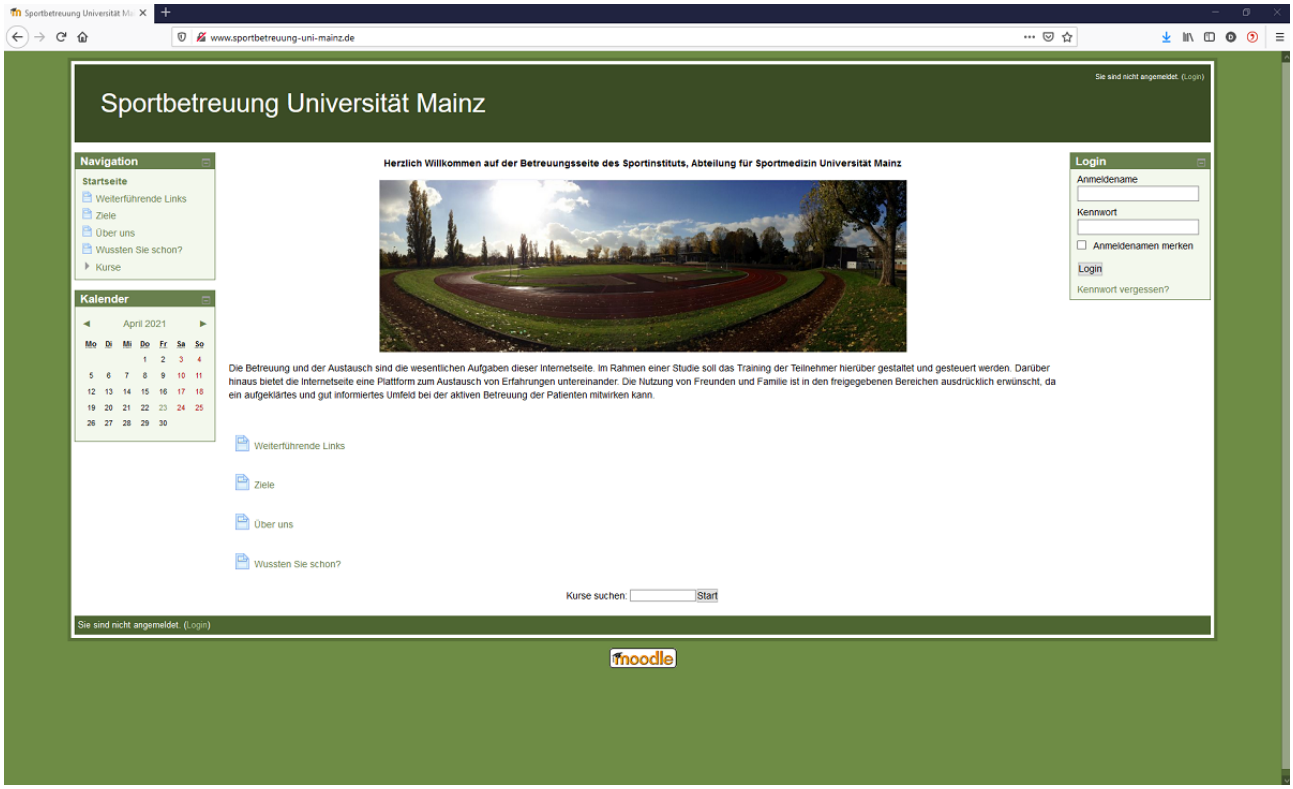
IG and CG participants will receive a smartwatch (M430, Polar Electro Oy) to record training times and monitor daily activities (eg, step count and sitting time). In addition, smartwatch data will be used to control for additional physical activity apart from the training intervention in the IG and physical activity, in general, in the CG. Furthermore, it will be used as a mechanism to control for the effect on primary outcomes by only receiving an intervention. The heart rate and distance of the training session will be recorded by the IG using the M430, which enables comparison of the data reported via the weekly feedback with smartwatch-recorded data. In the CG, the smartwatch is only used to record daily activity. To improve adherence of all participants, 15 smartwatches will be raffled among all participants who have completed the study.

Web-Based Supervision

The training intervention described above will be accompanied and remotely supervised with the help of a web-based physical exercise training support via a website (Figure 5) [121]. In a personal appointment after the incremental stepwise running test, the participants in the IG will be introduced to the website and will receive comprehensive information about the training.

External access to the website is not possible as only study participants can register. Both the introduction and the remote training supervision will be done by 1 person, which enables the coach to supervise several participants in their training process without any time constraints. Although there is no face-to-face supervision, based on the objective training session heart rate data and GPS data as well as the subjective feedback, adequate supervision can be guaranteed remotely. Participants have the possibility to get in direct contact with the coach via a message function, for example, in case of problems or uncertainties. The weekly training schedule is also transmitted in this manner. If a participant misses the feedback, a reminder is sent via email at the beginning of the following week. In a table that participants can download from the website, they will enter various medical and sports values that are therapeutically relevant after each training session. These data will be used for evaluation and for the training adjustment of the following week, as described in Figure 4. A follow-up is planned at 12 weeks (T4) and 24 weeks (T5) after completion of T3, and participants will be asked via email to complete the web-based questionnaires used at T2.

Figure 5. The home screen of the used website [121].



Data Management and Security

All data will be recorded and stored in the Department of Sports Medicine, Prevention, and Rehabilitation (Mainz, Germany), and access will be restricted to authorized personnel. Confidential information will be stored safely in the trial files and will not be shared with any other third institution or entity except in response to a legal requirement. Electronic data will be stored on password-protected computers in a restricted-access building. All data will be pseudonymized and submitted to the evaluation team for analysis. A data manager from each department is nominated, who will be responsible for data management and processing. The data and safety management team will be formed by the members of the project. Only the data manager will have access to all personal data. Trial documentation and data will be archived for 10 years after completion of the trial. All dropouts and the reason for dropping out of the study will be reported. Any harm or unintended events during the examinations will be recorded and reported to the Landesärztekammer (State Medical Association) Rhineland-Palatinate. The results will be publicly available in open-access journals and presented via contributions at conferences and congresses according to good scientific practice.

Statistical Methods

The power calculation was based on the analyses of the primary outcomes, that is, aerobic capacity (VO_2peak) and experimental stress reactivity (saliva cortisol). On the basis of the results of Bacon et al [122], the sample size was determined a priori via power analysis (G*Power V5), yielding a minimum sample size of 67 for a medium-to-large effect size of $f(V)$=0.35. An alpha error set to .05 and statistical power of 0.80 were assumed for a multivariate analysis of variance (MANOVA) with 2 repeated measurements, 2 groups, and interaction effects. Descriptive statistics will be used for all outcome measures at each time point to give an overview of all results. First, MANOVA will be performed with the main primary outcomes as dependent variables, that is, aerobic capacity (VO_2peak) and experimental stress reactivity (saliva cortisol) to maximize the power of the analyses and to be able to investigate the main and interaction effects of time (baseline [T0, T1] vs post [T2, T3]) and group (IG vs CG). Groups should be equal at preintervention (T0 and

T1). A time effect should be observed for the IG. Furthermore, we expect a significant time×group interaction as the IG should react differently over time, with a higher increase in aerobic capacity (VO_2peak). Significant effects of the MANOVA will be followed up by posthoc analyses of variance. As a secondary aim of our study, we aim to identify variables (eg, emotion regulation and biological metrics) that mediate the relationship between physical exercise and resilience outcomes. To that end, we plan to calculate multiple regression analyses that include potential mediators. Principal component analyses regarding potential mediating variables will precede the mediator analyses to avoid redundancy in our regression models. This will be statistically detailed with posthoc tests and corrections for multiple comparisons (Bonferroni-Holm correction [123]). Missing data will be omitted from the data set.

Results

The study was registered in October 2019 (DRKS00018078). Enrollment began in September 2019 and was paused from April 2020 until submission of this study protocol because of the COVID-19 pandemic. Of the 161 interested people who have contacted us so far, 26.7% (43/161) fulfilled the inclusion criteria. Among the 55% (17/31) participants in the IG and 45% (14/31) participants in the CG, who completed the study (N=31), no serious adverse incidents were reported. Within the program, 9% (4/43) of participants (2/17, 12% in the IG and 2/14, 14% in the CG) withdrew because of individual reasons (dropout rate 11.4%). Approximately 19% (8/43) have not yet participated in the program because of the COVID-19 pandemic. Although the COVID-19 pandemic does not affect the web-based exercise training approach, the study had to be paused in April 2020, as it was not possible to determine the primary and secondary end points (VO_2peak and cortisol levels) because of the lockdown of the laboratory facilities. Further study recruitment will resume when COVID-19 restrictions are completely lifted. On the basis of the experiences from the first recruitment period, the study is expected to continue for another 6 months to complete the intended sample size.

Discussion

Benefits of the Study

Evidence that exercise can lead to various benefits in mental health and resilience is increasing [16,124-129]. This positive impact was achieved in supervised as well as unsupervised exercise programs. Here, we implement a study design that addresses the link between aerobic capacity and resilience from a multifactorial perspective to understand why some people are more resilient to stress than others. To follow this question, we will investigate the association between innate and trained aerobic capacities in the form of VO_2peak of healthy, physically inactive adults and their resilience expressed primarily by salivary cortisol level changes and emotion regulation ability in response to different stress paradigms. We hypothesize that (1) participants with a high innate aerobic capacity will show a higher resilience to stress compared with participants with low aerobic capacity. Furthermore, we hypothesize that (2) 8 weeks of individually structured interval-type and continuous endurance exercise training remotely supervised by a web-based approach will improve the aerobic capacity of healthy inactive adults and that (3) the change from sedentary to an active lifestyle will improve resilience. In this study setting, we will be able to exploratively examine the molecular link between the effects of acute and chronic physical exercise and improved resilience to stress.

Strengths and Limitations

The strengths of our web-based, supervised physical exercise training approach with a focus on increasing VO_2peak in healthy, physically inactive adults are as follows: (1) participants are not location dependent for the training sessions; (2) individualized, gradual, and timely adjustment of training content based on the individual's feedback reduces the risk of injury, avoids overtraining, and avoids ineffective training; and (3) only 1 sports therapist or trainer is needed for training management of several training groups or trainees, which obviously has economic advantages and reduces bias from different sports therapists. However, web-based training support also has disadvantages compared with presence (face-to-face) interventions. Notably, it requires access to the internet, which limits the study population. Furthermore, we are dependent on the correct and complete documentation of the training sessions by the participants. For an objective way to control reports on the training and to remotely supervise the participants in the IG, we included a smartwatch (Polar M430) that records the heart rate and distance of the individual training sessions. These are given to both the IG and CG participants to exclude an effect on the study outcome only by wearing the smartwatch. Furthermore, group or partner training can bring motivational and social benefits [130-132], which is not directly provided in our web-based physical exercise training support. This may reduce adherence of the participants to the study and, additionally, exclude the social aspect of the effect of an active lifestyle on resilience. Therefore, communication via the web-based platform is intended to be frequent and without any restraints toward the trainer. Finally, inexperience, fear, and the risk of injury can occur during an unaccustomed and intensive training load, which could be reduced or not arise at all through presence support. To counteract this, we have implemented a 2-week adaptation phase in our training intervention that will offer an easy training start and reduce the indicated risks. In addition, we address the individual needs of the participants based on their weekly feedback, so overload is unlikely to occur during the intervention. Adhering to the described improvements in web-based physical exercise interventions will offer the most individual and effective training support with a simultaneously reduced workload for the coach. With this, our research group has already successfully conducted similar studies using the internet for training interventions in patients with Barrett carcinoma, nonalcoholic fatty liver disease, depression, cystic fibrosis, and systemic lupus erythematosus [40-45].

Here, we selected an exercise intervention period of 8 weeks using a combination of interval-type training and continuous endurance exercise to efficiently enhance aerobic capacity in a short period. Interval training improves VO_2peak more strongly in comparison with continuous exercise training [8]. Moreover,

psychological benefits in attention, complex attention, and executive function were shown in high-intensity interval training compared with those in low-intensity training [133-135]. However, to counteract overtraining and risk of injury and to promote adherence, we complement interval-type training with endurance exercise sessions. A number of high-intensity interval training and moderate-intensity intervention studies with physically inactive participants decided for a comparable exercise intervention time leading to significant increases in VO_2peak of 3%-19% [9-11]. Although a longer intervention period generally leads to higher increases in maximal oxygen uptake [122], it has been reported that enjoyment of interval training decreases with time [10]. Therefore, we considered a study design that used mixed model exercise sessions with a short intervention time of 8 weeks as efficient to enhance aerobic capacity in physically inactive adults and as suitable to analyze the impact on resilience.

Repeated stress induction and the estimation of resilience factors in a test-retest setting, as chosen in our study, are obstacles to resilience research. It was shown that for psychological stress tests, a test-retest design could lead to a learning effect, resulting in lower stress response [136,137]. Here, we use 2 different stress tests for T0 and T2 to reduce habituation to the applied stressor. By randomly assigning participants to the 2 groups, we intend to obtain the best estimate of the intervention effect on stress responses. However, differences in stress parameters at T2 might not exclusively be attributed to the intervention, as possible placebo effects (ie, simply receiving an intervention) or mediators may need to be considered. Previous studies analyzed similar between-subject comparisons, with less stress reactivity during the Trier Social Stress Test in trained men compared with untrained men [138]. In addition, we account for preintervention differences in stress reactivity and recovery by applying the SECPT at T0. However, as measures from both stress tests are not directly comparable, the experimental design does not permit within-subject analyses. To assess differences in individual changes within the IG, future studies may construct and apply parallel versions of a stress test pre and postintervention.

Several psychological interventions have been similarly used to increase resilience [139], and it might have been interesting to have a sport exercise group; a psychological exercise group that uses a psychoeducational element, such as cognitive restructuring; a mixed model group (sport and psychological); and a CG to obtain the influence of different types of interventions and their combinations on resilience to stress exposure. In our study, we focus on the physiological aspects of increasing VO_2peak and its effect on resilience only. However, the identified relationships between molecular markers and exercise-induced resilience parameters in our setting may be further elucidated in mixed model interventions in follow-up studies.

We cannot exclude a selection bias so that persons who are generally interested in (1) psychological questions, (2) physical exercise, or (3) web-based services are rather addressed by the study announcement. Furthermore, because of a high time commitment for presence tests (2 measurement time points before and after the intervention), (4) people who live close to the survey site are more likely to participate and complete the study. On the basis of the World Health Organization guidelines on physical activity and sedentary behavior, we included individuals who were physically active for <150 minutes/week [140]. These individuals are described as insufficiently active, although this definition is very strict. Possibly, a cutoff point of physical activity <90 minutes/week would obtain a greater effect on the primary outcomes. Here, we decided in favor of the adherence to the study considering the training times that had to be completed.

Resilience is a dynamic and variable state that can be represented in a multifactorial manner. So far, individual instruments have failed to fully capture the variance of resilience [17,141,142]. For this reason, our study uses a wide variety of methods (physiological [blood markers, saliva markers, and hair] and psychological [questionnaires, stress tests, and emotion regulation]) to have a large number of independent predictors to clarify the variance in resilience to the greatest degree of accuracy. Owing to the high number of methods and the collected variables, spurious correlations or pseudoassociations may occur [143], especially when exploratory analysis is performed beyond hypothesis testing. The validity of these findings may be estimated in future studies.

Conclusions

This study will allow us to investigate whether an increase in physical activity with a simultaneous improvement in aerobic capacity is associated with an increase in resilience and whether this effect is reflected in circulating molecular marker levels. These findings will help to reveal novel characteristics of human resilience and may offer novel approaches for the prevention and therapy of mental disorders by exercise prescription.

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The data sets used and analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

PS, BL, MW, and KL conceived the original ideas. DTO, AB, KFAP, BH, EN, and PS conceived and planned physical exercise testing and intervention. AB, EN, DTO, IRA, PS, and BL conceived and planned the molecular marker analysis. PZ, MS, and MW conceived and planned psychological testing. DTO and AB wrote the manuscript in consultation with KFAP, PZ, MS, BH, EN, IRA, KL, MW, BL, and PS.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 12772 KB - resprot_v10i11e29712_app1.pdf]

Multimedia Appendix 2
Flyer announcement for the study.
[PDF File (Adobe PDF File), 503 KB - resprot_v10i11e29712_app2.pdf]

References

1. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. Can Med Asso J 2006 Mar;174(6):801-809 [FREE Full text] [doi: 10.1503/cmaj.051351] [Medline: 16534088]
2. Pedersen BK, Saltin B. Exercise as medicine - evidence for prescribing exercise as therapy in 26 different chronic diseases. Scand J Med Sci Sports 2015 Dec;25 Suppl 3:1-72. [doi: 10.1111/sms.12581] [Medline: 26606383]
3. Rovio S, Spulber G, Nieminen LJ, Niskanen E, Winblad B, Tuomilehto J, et al. The effect of midlife physical activity on structural brain changes in the elderly. Neurobiol Aging 2010 Nov;31(11):1927-1936 [FREE Full text] [doi: 10.1016/j.neurobiolaging.2008.10.007] [Medline: 19062136]
4. Firth J, Stubbs B, Vancampfort D, Schuch F, Lagopoulos J, Rosenbaum S, et al. Effect of aerobic exercise on hippocampal volume in humans: a systematic review and meta-analysis. Neuroimage 2018 Feb 01;166:230-238 [FREE Full text] [doi: 10.1016/j.neuroimage.2017.11.007] [Medline: 29113943]
5. Małkiewicz MA, Szarmach A, Sabisz A, Cubała WJ, Szurowska E, Winklewski PJ. Blood-brain barrier permeability and physical exercise. J Neuroinflammation 2019 Jan 24;16(1):15 [FREE Full text] [doi: 10.1186/s12974-019-1403-x] [Medline: 30678702]
6. Paillard T, Rolland Y, de Souto Barreto P. Protective effects of physical exercise in Alzheimer's disease and Parkinson's disease: a narrative review. J Clin Neurol 2015 Jul;11(3):212-219 [FREE Full text] [doi: 10.3988/jcn.2015.11.3.212] [Medline: 26174783]
7. Chekroud S, Gueorguieva R, Zheutlin A, Paulus M, Krumholz HM, Krystal JH, et al. Association between physical exercise and mental health in 1·2 million individuals in the USA between 2011 and 2015: a cross-sectional study. Lancet Psychiatry 2018 Sep;5(9):739-746 [FREE Full text] [doi: 10.1016/S2215-0366(18)30227-X]
8. Helgerud J, Høydal K, Wang E, Karlsen T, Berg P, Bjerkaas M, et al. Aerobic high-intensity intervals improve VO2max more than moderate training. Med Sci Sports Exerc 2007 Apr;39(4):665-671. [doi: 10.1249/mss.0b013e3180304570] [Medline: 17414804]
9. Fisher G, Brown AW, Brown MM, Alcorn A, Noles C, Winwood L, et al. High intensity interval- vs moderate intensity-training for improving cardiometabolic health in overweight or obese males: a randomized controlled trial. PLoS One 2015;10(10):e0138853 [FREE Full text] [doi: 10.1371/journal.pone.0138853] [Medline: 26489022]
10. Foster C, Farland CV, Guidotti F, Harbin M, Roberts B, Schuette J, et al. The effects of high intensity interval training vs steady state training on aerobic and anaerobic capacity. J Sports Sci Med 2015 Dec;14(4):747-755 [FREE Full text] [Medline: 26664271]
11. Vella CA, Taylor K, Drummer D. High-intensity interval and moderate-intensity continuous training elicit similar enjoyment and adherence levels in overweight and obese adults. Eur J Sport Sci 2017 Oct;17(9):1203-1211 [FREE Full text] [doi: 10.1080/17461391.2017.1359679] [Medline: 28792851]
12. Jackson EM, Dishman RK. Cardiorespiratory fitness and laboratory stress: a meta-regression analysis. Psychophysiology 2006 Jan;43(1):57-72 [FREE Full text] [doi: 10.1111/j.1469-8986.2006.00373.x] [Medline: 16629686]
13. Dishman R, Jackson E. Exercise, fitness, and stress. Int J Sport Psychol 2000;31(2):175-203 [FREE Full text]
14. Åberg MA, Waern M, Nyberg J, Pedersen NL, Bergh Y, Åberg ND, et al. Cardiovascular fitness in males at age 18 and risk of serious depression in adulthood: Swedish prospective population-based study. Br J Psychiatry 2012 Nov;201(5):352-359 [FREE Full text] [doi: 10.1192/bjp.bp.111.103416] [Medline: 22700083]
15. Blumenthal JA, Babyak MA, Doraiswamy PM, Watkins L, Hoffman BM, Barbour KA, et al. Exercise and pharmacotherapy in the treatment of major depressive disorder. Psychosom Med 2007;69(7):587-596 [FREE Full text] [doi: 10.1097/PSY.0b013e318148c19a] [Medline: 17846259]

16. Silverman MN, Deuster PA. Biological mechanisms underlying the role of physical fitness in health and resilience. Interface Focus 2014 Oct 06;4(5):20140040 [FREE Full text] [doi: 10.1098/rsfs.2014.0040] [Medline: 25285199]
17. Kalisch R, Müller MB, Tüscher O. A conceptual framework for the neurobiological study of resilience. Behav Brain Sci 2015;38:e92. [doi: 10.1017/S0140525X1400082X] [Medline: 25158686]
18. Bonanno GA, Diminich ED. Annual research review: positive adjustment to adversity—trajectories of minimal-impact resilience and emergent resilience. J Child Psychol Psychiatry 2013 Apr;54(4):378-401 [FREE Full text] [doi: 10.1111/jcpp.12021] [Medline: 23215790]
19. Kalisch R, Müller MB, Tüscher O. Advancing empirical resilience research. Behav Brain Sci 2015;38:e128 [FREE Full text] [doi: 10.1017/S0140525X15000023] [Medline: 26815844]
20. Feder A, Nestler EJ, Charney DS. Psychobiology and molecular genetics of resilience. Nat Rev Neurosci 2009 Jun;10(6):446-457 [FREE Full text] [doi: 10.1038/nrn2649] [Medline: 19455174]
21. Crane MF, Searle BJ, Kangas M, Nwiran Y. How resilience is strengthened by exposure to stressors: the systematic self-reflection model of resilience strengthening. Anxiety Stress Coping 2019 Jan;32(1):1-17 [FREE Full text] [doi: 10.1080/10615806.2018.1506640] [Medline: 30067067]
22. Bernstein EE, McNally RJ. Exercise as a buffer against difficulties with emotion regulation: a pathway to emotional wellbeing. Behav Res Ther 2018 Oct;109:29-36 [FREE Full text] [doi: 10.1016/j.brat.2018.07.010] [Medline: 30081242]
23. Giles GE, Eddy MD, Brunyé TT, Urry HL, Graber HL, Barbour RL, et al. Endurance exercise enhances emotional valence and emotion regulation. Front Hum Neurosci 2018;12:398 [FREE Full text] [doi: 10.3389/fnhum.2018.00398] [Medline: 30459576]
24. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev 2000 Mar;21(1):55-89 [FREE Full text] [doi: 10.1210/edrv.21.1.0389] [Medline: 10696570]
25. Straub RH, Cutolo M, Buttgereit F, Pongratz G. Energy regulation and neuroendocrine-immune control in chronic inflammatory diseases. J Intern Med 2010 Jun;267(6):543-560 [FREE Full text] [doi: 10.1111/j.1365-2796.2010.02218.x] [Medline: 20210843]
26. Walker BR. Glucocorticoids and cardiovascular disease. Eur J Endocrinol 2007 Nov;157(5):545-559 [FREE Full text] [doi: 10.1530/EJE-07-0455] [Medline: 17984234]
27. Chrousos GP, Kino T. Glucocorticoid action networks and complex psychiatric and/or somatic disorders. Stress 2007 Jun;10(2):213-219 [FREE Full text] [doi: 10.1080/10253890701292119] [Medline: 17514590]
28. Luger A, Deuster PA, Kyle SB, Gallucci WT, Montgomery LC, Gold PW, et al. Acute hypothalamic-pituitary-adrenal responses to the stress of treadmill exercise. Physiologic adaptations to physical training. N Engl J Med 1987 May 21;316(21):1309-1315 [FREE Full text] [doi: 10.1056/NEJM198705213162105] [Medline: 3033504]
29. Sothmann MS, Hart BA, Horn TS. Plasma catecholamine response to acute psychological stress in humans: relation to aerobic fitness and exercise training. Med Sci Sports Exerc 1991 Jul;23(7):860-867. [Medline: 1921680]
30. Webb HE, Rosalky DS, Tangsilsat SE, McLeod KA, Acevedo EO, Wax B. Aerobic fitness affects cortisol responses to concurrent challenges. Med Sci Sports Exerc 2013 Mar;45(2):379-386 [FREE Full text] [doi: 10.1249/MSS.0b013e318270b381] [Medline: 22935740]
31. Knaepen K, Goekint M, Heyman EM, Meeusen R. Neuroplasticity - exercise-induced response of peripheral brain-derived neurotrophic factor: a systematic review of experimental studies in human subjects. Sports Med 2010 Sep 01;40(9):765-801 [FREE Full text] [doi: 10.2165/11534530-000000000-00000] [Medline: 20726622]
32. Hamer M. The relative influences of fitness and fatness on inflammatory factors. Prev Med 2007 Jan;44(1):3-11 [FREE Full text] [doi: 10.1016/j.ypmed.2006.09.005] [Medline: 17064760]
33. Agudelo LZ, Femenía T, Orhan F, Porsmyr-Palmertz M, Goiny M, Martinez-Redondo V, et al. Skeletal muscle PGC-1α1 modulates kynurenine metabolism and mediates resilience to stress-induced depression. Cell 2014 Sep 25;159(1):33-45 [FREE Full text] [doi: 10.1016/j.cell.2014.07.051] [Medline: 25259918]
34. Joisten N, Kummerhoff F, Koliamitra C, Schenk A, Walzik D, Hardt L, et al. Exercise and the Kynurenine pathway: current state of knowledge and results from a randomized cross-over study comparing acute effects of endurance and resistance training. Exerc Immunol Rev 2020;26:24-42 [FREE Full text] [Medline: 32139353]
35. Ferreira-Vieira TH, Bastos CP, Pereira GS, Moreira FA, Massensini AR. A role for the endocannabinoid system in exercise-induced spatial memory enhancement in mice. Hippocampus 2014 Jan;24(1):79-88 [FREE Full text] [doi: 10.1002/hipo.22206] [Medline: 24115292]
36. Heyman E, Gamelin F, Goekint M, Piscitelli F, Roelands B, Leclair E, et al. Intense exercise increases circulating endocannabinoid and BDNF levels in humans--possible implications for reward and depression. Psychoneuroendocrinology 2012 Jun;37(6):844-851 [FREE Full text] [doi: 10.1016/j.psyneuen.2011.09.017] [Medline: 22029953]
37. Sparling PB, Giuffrida A, Piomelli D, Rosskopf L, Dietrich A. Exercise activates the endocannabinoid system. Neuroreport 2003 Dec 02;14(17):2209-2211 [FREE Full text] [doi: 10.1097/00001756-200312020-00015] [Medline: 14625449]
38. Coelho FG, Andrade LP, Pedroso RV, Santos-Galduroz RF, Gobbi S, Costa JL, et al. Multimodal exercise intervention improves frontal cognitive functions and gait in Alzheimer's disease: a controlled trial. Geriatr Gerontol Int 2013 Jan;13(1):198-203 [FREE Full text] [doi: 10.1111/j.1447-0594.2012.00887.x] [Medline: 22686565]

39. Baatile J, Langbein WE, Weaver F, Maloney C, Jost MB. Effect of exercise on perceived quality of life of individuals with Parkinson's disease. J Rehabil Res Dev 2000;37(5):529-534 [FREE Full text] [Medline: 11322151]
40. Huber Y, Pfirrmann D, Gebhardt I, Labenz C, Gehrke N, Straub BK, et al. Improvement of non-invasive markers of NAFLD from an individualised, web-based exercise program. Aliment Pharmacol Ther 2019 Oct;50(8):930-939. [doi: 10.1111/apt.15427] [Medline: 31342533]
41. Pfirrmann D, Huber Y, Schattenberg JM, Simon P. Web-based exercise as an effective complementary treatment for patients with nonalcoholic fatty liver disease: intervention study. J Med Internet Res 2019 Jan 02;21(1):e11250 [FREE Full text] [doi: 10.2196/11250] [Medline: 30602434]
42. Pfirrmann D, Haller N, Huber Y, Jung P, Lieb K, Gockel I, et al. Applicability of a web-based, individualized exercise intervention in patients with liver disease, cystic fibrosis, esophageal cancer, and psychiatric disorders: process evaluation of 4 ongoing clinical trials. JMIR Res Protoc 2018 May 22;7(5):e106 [FREE Full text] [doi: 10.2196/resprot.8607] [Medline: 29789277]
43. Pfirrmann D, Tug S, Brosteanu O, Mehdorn M, Busse M, Grimminger PP, et al. Internet-based perioperative exercise program in patients with Barrett's carcinoma scheduled for esophagectomy [iPEP - study] a prospective randomized-controlled trial. BMC Cancer 2017 Jun 14;17(1):413 [FREE Full text] [doi: 10.1186/s12885-017-3400-8] [Medline: 28615010]
44. Haller N, Lorenz S, Pfirrmann D, Koch C, Lieb K, Dettweiler U, et al. Individualized web-based exercise for the treatment of depression: randomized controlled trial. JMIR Ment Health 2018 Oct 12;5(4):e10698 [FREE Full text] [doi: 10.2196/10698] [Medline: 30314962]
45. Boedecker SC, Philippi KF, Neuberger E, Schmidt S, Pfirrmann D, Haller N, et al. Twelve-week internet-based individualized exercise program in adults with systemic lupus erythematosus: protocol for a randomized controlled trial. JMIR Res Protoc 2020 Nov 03;9(11):e18291 [FREE Full text] [doi: 10.2196/18291] [Medline: 33141101]
46. Huang C, Webb HE, Zourdos MC, Acevedo EO. Cardiovascular reactivity, stress, and physical activity. Front Physiol 2013 Nov 07;4:314 [FREE Full text] [doi: 10.3389/fphys.2013.00314] [Medline: 24223557]
47. Rimmele U, Seiler R, Marti B, Wirtz PH, Ehlert U, Heinrichs M. The level of physical activity affects adrenal and cardiovascular reactivity to psychosocial stress. Psychoneuroendocrinology 2009 Mar;34(2):190-198 [FREE Full text] [doi: 10.1016/j.psyneuen.2008.08.023] [Medline: 18922645]
48. Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. Psychol Bull 2004 May;130(3):355-391. [doi: 10.1037/0033-2909.130.3.355] [Medline: 15122924]
49. Schwabe L, Haddad L, Schachinger H. HPA axis activation by a socially evaluated cold-pressor test. Psychoneuroendocrinology 2008 Jul;33(6):890-895 [FREE Full text] [doi: 10.1016/j.psyneuen.2008.03.001] [Medline: 18403130]
50. Sandner M, Lois G, Streit F, Zeier P, Kirsch P, Wüst S, et al. Investigating individual stress reactivity: high hair cortisol predicts lower acute stress responses. Psychoneuroendocrinology 2020 Aug;118:104660 [FREE Full text] [doi: 10.1016/j.psyneuen.2020.104660] [Medline: 32485341]
51. Schwabe L, Schächinger H. Ten years of research with the socially evaluated cold pressor test: data from the past and guidelines for the future. Psychoneuroendocrinology 2018 Jun;92:155-161 [FREE Full text] [doi: 10.1016/j.psyneuen.2018.03.010] [Medline: 29573884]
52. Streit F, Haddad L, Paul T, Frank J, Schäfer A, Nikitopoulos J, et al. A functional variant in the neuropeptide S receptor 1 gene moderates the influence of urban upbringing on stress processing in the amygdala. Stress 2014 Jul;17(4):352-361 [FREE Full text] [doi: 10.3109/10253890.2014.921903] [Medline: 24800784]
53. Chan A, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. Br Med J 2013 Jan 08;346:e7586 [FREE Full text] [doi: 10.1136/bmj.e7586] [Medline: 23303884]
54. Eysenbach G, CONSORT-EHEALTH Group. CONSORT-EHEALTH: improving and standardizing evaluation reports of Web-based and mobile health interventions. J Med Internet Res 2011;13(4):e126 [FREE Full text] [doi: 10.2196/jmir.1923] [Medline: 22209829]
55. Stetler C, Miller GE. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. Psychosom Med 2011;73(2):114-126 [FREE Full text] [doi: 10.1097/PSY.0b013e31820ad12b] [Medline: 21257974]
56. Steudte-Schmiedgen S, Wichmann S, Stalder T, Hilbert K, Muehlhan M, Lueken U, et al. Hair cortisol concentrations and cortisol stress reactivity in generalized anxiety disorder, major depression and their comorbidity. J Psychiatr Res 2017 Jan;84:184-190 [FREE Full text] [doi: 10.1016/j.jpsychires.2016.09.024] [Medline: 27744230]
57. Nielsen SE, Segal SK, Worden IV, Yim IS, Cahill L. Hormonal contraception use alters stress responses and emotional memory. Biol Psychol 2013 Feb;92(2):257-266 [FREE Full text] [doi: 10.1016/j.biopsycho.2012.10.007] [Medline: 23131613]
58. Cooper J. Diagnostic and statistical manual of mental disorders (4th edn, text revision) (DSM–IV–TR) Washington, DC: American Psychiatric Association 2000. 943 pp. £39.99 (hb). ISBN 0 89042 025 4. Br J Psychiatry 2018 Jan 02;179(1):85 [FREE Full text] [doi: 10.1192/bjp.179.1.85-a]

59. American College of Sports Medicine. Acsm's Guidelines for Exercise Testing and Prescription, 10th Edition. Philadelphia: Lippincott Williams & Wilkins; 2017.
60. Wester VL, van Rossum EF. Clinical applications of cortisol measurements in hair. Eur J Endocrinol 2015 Oct;173(4):1-10 [FREE Full text] [doi: 10.1530/EJE-15-0313] [Medline: 25924811]
61. Smith BW, Dalen J, Wiggins K, Tooley E, Christopher P, Bernard J. The brief resilience scale: assessing the ability to bounce back. Int J Behav Med 2008;15(3):194-200. [doi: 10.1080/10705500802222972] [Medline: 18696313]
62. Chmitorz A, Wenzel M, Stieglitz R, Kunzler A, Bagusat C, Helmreich I, et al. Population-based validation of a German version of the Brief Resilience Scale. PLoS One 2018;13(2):e0192761 [FREE Full text] [doi: 10.1371/journal.pone.0192761] [Medline: 29438435]
63. Grabe HJ, Schulz A, Schmidt CO, Appel K, Driessen M, Wingenfeld K, et al. [A brief instrument for the assessment of childhood abuse and neglect: the childhood trauma screener (CTS)]. Psychiatr Prax 2012 Apr;39(3):109-115 [FREE Full text] [doi: 10.1055/s-0031-1298984] [Medline: 22422160]
64. Bernstein DP, Ahluvalia T, Pogge D, Handelsman L. Validity of the Childhood Trauma Questionnaire in an adolescent psychiatric population. J Am Acad Child Adolesc Psychiatry 1997 Mar;36(3):340-348 [FREE Full text] [doi: 10.1097/00004583-199703000-00012] [Medline: 9055514]
65. Bernstein D, Stein J, Newcomb M, Walker E, Pogge D, Ahluvalia T, et al. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. Child Abuse Neglect 2003 Feb;27(2):169-190 [FREE Full text] [doi: 10.1016/s0145-2134(02)00541-0]
66. Derogatis L. The Brief Symptom Inventory-18 (BSI-18): Administration, Scoring, and Procedures Manual. Nat Comput Syst Pearson 2000:A. [doi: 10.1037/t07502-000]
67. Spitzer C, Hammer S, Löwe B, Grabe HJ, Barnow S, Rose M, et al. [The short version of the Brief Symptom Inventory (BSI -18): preliminary psychometric properties of the German translation]. Fortschr Neurol Psychiatr 2011 Sep;79(9):517-523. [doi: 10.1055/s-0031-1281602] [Medline: 21870312]
68. Radloff L. The CES-D Scale: a self-report depression scale for research in the general population. Appl Psychol Measure 1977 Jun 01;1(3):385-401 [FREE Full text] [doi: 10.1177/014662167700100306]
69. Hautzinger M, Bailer M. Allgemeine Depressionsskala (ADS). Psychiat Prax 2012 Aug 31;39(06):302-304. [doi: 10.1055/s-0032-1326702]
70. Hautzinger M, Bailer M, Hofmeister D, Keller F. Allgemeine Depressionsskala (ADS). Göttingen, Germany: Hogrefe; 2012.
71. Garnefski N, Kraaij V, Spinhoven P. Negative life events, cognitive emotion regulation and emotional problems. Personal Individ Diff 2001 Jun;30(8):1311-1327 [FREE Full text] [doi: 10.1016/s0191-8869(00)00113-6]
72. Görgen S, Loch N, Hiller W, Witthöft M. Kognitive Emotionsregulation und Psychopathologie: Erste teststatistische Untersuchung des deutschen Cognitive Emotion Regulation Questionnaire (CERQ) in einer klinischen Stichprobe. Zeitschrift für Psychiatrie, Psychologie und Psychotherapie 2015 Dec;63(4):255-265 [FREE Full text] [doi: 10.1024/1661-4747/a000248]
73. Loch N, Hiller W, Witthöft M. Der Cognitive Emotion Regulation Questionnaire (CERQ). Zeitschrift für Klinische Psychologie und Psychotherapie 2011 Apr;40(2):94-106 [FREE Full text] [doi: 10.1026/1616-3443/a000079]
74. Gross JJ, John OP. Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. J Pers Soc Psychol 2003 Aug;85(2):348-362. [doi: 10.1037/0022-3514.85.2.348] [Medline: 12916575]
75. Abler B, Kessler H. Emotion Regulation Questionnaire – Eine deutschsprachige Fassung des ERQ von Gross und John. Diagnostica 2009 Jul;55(3):144-152 [FREE Full text] [doi: 10.1026/0012-1924.55.3.144]
76. Taylor S, Zvolensky MJ, Cox BJ, Deacon B, Heimberg RG, Ledley DR, et al. Robust dimensions of anxiety sensitivity: development and initial validation of the Anxiety Sensitivity Index-3. Psychol Assess 2007 Jun;19(2):176-188 [FREE Full text] [doi: 10.1037/1040-3590.19.2.176] [Medline: 17563199]
77. Kemper C, Ziegler M, Taylor S. Überprüfung der psychometrischen Qualität der deutschen Version des Angstsensitivitätsindex-3. Diagnostica 2009 Oct;55(4):223-233 [FREE Full text] [doi: 10.1026/0012-1924.55.4.223]
78. Neff KD. The development and validation of a scale to measure self-compassion. Self Identity 2003 Jul;2(3):223-250 [FREE Full text] [doi: 10.1080/15298860309027]
79. Hupfeld J, Ruffieux N. Validierung einer deutschen Version der Self-Compassion Scale (SCS-D). Zeitschrift für Klinische Psychologie und Psychotherapie 2011 Apr;40(2):115-123 [FREE Full text] [doi: 10.1026/1616-3443/a000088]
80. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983 Dec;24(4):385 [FREE Full text] [doi: 10.2307/2136404]
81. Cohen S, Williamson GM. Perceived stress in a probability sample of the United States. In: Spacapan S, Oskamp S, editors. The Social Psychology of Health: The Claremont Symposium on Applied Social Psychology. Thousand Oaks, California, United States: SAGE Publications Ltd; 1988:31-67.
82. Klein EM, Brähler E, Dreier M, Reinecke L, Müller KW, Schmutzer G, et al. The German version of the Perceived Stress Scale - psychometric characteristics in a representative German community sample. BMC Psychiatry 2016 Dec 23;16:159 [FREE Full text] [doi: 10.1186/s12888-016-0875-9] [Medline: 27216151]

83. Schneider EE, Schönfelder S, Domke-Wolf M, Wessa M. Measuring stress in clinical and nonclinical subjects using a German adaptation of the Perceived Stress Scale. Int J Clin Health Psychol 2020;20(2):173-181 [FREE Full text] [doi: 10.1016/j.ijchp.2020.03.004] [Medline: 32550857]
84. Schulz P, Schlotz W, Becker P. Trierer Inventar zum Chronischen Stress (TICS) [Trier Inventory for Chronic Stress (TICS)]. Gottingen, Germany: Hogrefe; 2004:1-61.
85. Schulz P, Schlotz W. Trierer Inventar zur Erfassung von chronischem Streß (TICS): Skalenkonstruktion, teststatistische Überprüfung und Validierung der Skala Arbeitsüberlastung. Diagnostica 1999 Jan;45(1):8-19 [FREE Full text] [doi: 10.1026//0012-1924.45.1.8]
86. Schulz P, Jansen L, Schlotz W. Stressreaktivität: Theoretisches Konzept und Messung. Diagnostica 2005 Jul;51(3):124-133 [FREE Full text] [doi: 10.1026/0012-1924.51.3.124]
87. Jerusalem M, Schwarzer R. Selbstwirksamkeit. In: Schwarzer R, editor. Skalen zur Befindlichkeit und Persönlichkeit. Berlin: Freie Universität, Institut für Psychologie; 1986:15-28.
88. Schmitz G. Entwicklung der Selbstwirksamkeitserwartungen von Lehrern [Development of teachers' self-efficacy beliefs]. Unterrichtswissenschaft 1998;2:140-157. [doi: 10.25656/01:7770]
89. Steyer R, Eid M, Schwenkmezger P. Modeling true intraindividual change: true change as a latent variable. Methods Psychol Res 1997;2:21-33 [FREE Full text]
90. Buckert M, Schwieren C, Kudielka BM, Fiebach CJ. Acute stress affects risk taking but not ambiguity aversion. Front Neurosci 2014;8:82 [FREE Full text] [doi: 10.3389/fnins.2014.00082] [Medline: 24834024]
91. Klinkenberg IAG, Rehbein MA, Steinberg C, Klahn AL, Zwanzger P, Zwitserlood P, et al. Healthy individuals maintain adaptive stimulus evaluation under predictable and unpredictable threat. Neuroimage 2016 Aug 01;136:174-185 [FREE Full text] [doi: 10.1016/j.neuroimage.2016.05.041] [Medline: 27208859]
92. Plessow F, Fischer R, Kirschbaum C, Goschke T. Inflexibly focused under stress: acute psychosocial stress increases shielding of action goals at the expense of reduced cognitive flexibility with increasing time lag to the stressor. J Cogn Neurosci 2011 Nov;23(11):3218-3227 [FREE Full text] [doi: 10.1162/jocn_a_00024] [Medline: 21452940]
93. Sandner M, Zeier P, Lois G, Wessa M. Cognitive emotion regulation withstands the stress test: an fMRI study on the effect of acute stress on distraction and reappraisal. Neuropsychologia 2021 Jul;157:107876 [FREE Full text] [doi: 10.1016/j.neuropsychologia.2021.107876] [Medline: 33930388]
94. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr 1982 Nov;36(5):936-942. [doi: 10.1093/ajcn/36.5.936] [Medline: 7137077]
95. Singer R, Wagner P. Überprüfung eines (Kurz-) Fragebogens zur Erfassung der habituellen körperlichen Aktivität. In: Meck S, Klussmann PG, editors. Festschrift für Dieter Voigt. Münster, Germany: LIT Verlag; 2001:364-370.
96. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003 Aug;35(8):1381-1395. [doi: 10.1249/01.MSS.0000078924.61453.FB] [Medline: 12900694]
97. Hagströmer M, Bergman P, De Bourdeaudhuij I, Ortega FB, Ruiz JR, Manios Y, HELENA Study Group. Concurrent validity of a modified version of the International Physical Activity Questionnaire (IPAQ-A) in European adolescents: The HELENA Study. Int J Obes (Lond) 2008 Nov;32 Suppl 5:42-48 [FREE Full text] [doi: 10.1038/ijo.2008.182] [Medline: 19011653]
98. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992 Jun;30(6):473-483. [Medline: 1593914]
99. Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. Br Med J 1992 Jul 18;305(6846):160-164 [FREE Full text] [doi: 10.1136/bmj.305.6846.160] [Medline: 1285753]
100. Warburton DE, Jamnik VK, Bredin SS, McKenzie DC, Stone J, Shephard RJ, et al. Evidence-based risk assessment and recommendations for physical activity clearance: an introduction. Appl Physiol Nutr Metab 2011 Jul;36 Suppl 1:1-2 [FREE Full text] [doi: 10.1139/h11-060] [Medline: 21800937]
101. Kanske P, Heissler J, Schönfelder S, Bongers A, Wessa M. How to regulate emotion? Neural networks for reappraisal and distraction. Cereb Cortex 2011 Jun;21(6):1379-1388 [FREE Full text] [doi: 10.1093/cercor/bhq216] [Medline: 21041200]
102. Schönfelder S, Kanske P, Heissler J, Wessa M. Time course of emotion-related responding during distraction and reappraisal. Soc Cogn Affect Neurosci 2014 Sep;9(9):1310-1319 [FREE Full text] [doi: 10.1093/scan/nst116] [Medline: 23988760]
103. Lang P, Bradley M, Cuthbert B. International Affective Picture System (IAPS): technical manual and affective ratings. NIMH Center for the Study of Emotion and Attention. 1997. URL: https://www2.unifesp.br/dpsicobio/adap/instructions.pdf [accessed 2021-09-18]
104. Wessa M, Kanske P, Bode K, Heissler J, Schönfelder S. EmoPics: Subjektive und psychophysiologische Evaluationen neuen Bildmaterials für die klinisch-bio-psychologische Forschung. Zeitschrift für Klinische Psychologie und Psychotherapie. 2010. URL: https://www.klinische-psychologie-und-neuropsychologie.uni-mainz.de/forschung/emopics/ [accessed 2021-09-18]
105. Bradley M, Lang P. Measuring emotion: the self-assessment manikin and the semantic differential. J Behav Ther Experiment Psychiat 1994 Mar;25(1):49-59 [FREE Full text] [doi: 10.1016/0005-7916(94)90063-9]

106. Zeier P, Sandner M, Wessa M. Script-based reappraisal test introducing a new paradigm to investigate the effect of reappraisal inventiveness on reappraisal effectiveness. Cogn Emot 2020 Jun;34(4):793-799 [FREE Full text] [doi: 10.1080/02699931.2019.1663153] [Medline: 31496356]
107. Hillen B, Pfirrmann D, Nägele M, Simon P. Infrared thermography in exercise physiology: the dawning of exercise radiomics. Sports Med 2020 Mar;50(2):263-282 [FREE Full text] [doi: 10.1007/s40279-019-01210-w] [Medline: 31734882]
108. Ludwig N, Formenti D, Gargano M, Alberti G. Skin temperature evaluation by infrared thermography: comparison of image analysis methods. Infrared Physics Technol 2014 Jan;62:1-6 [FREE Full text] [doi: 10.1016/j.infrared.2013.09.011]
109. Moreira DG, Costello JT, Brito CJ, Adamczyk JG, Ammer K, Bach AJ, et al. Thermographic imaging in sports and exercise medicine: a Delphi study and consensus statement on the measurement of human skin temperature. J Therm Biol 2017 Oct;69:155-162 [FREE Full text] [doi: 10.1016/j.jtherbio.2017.07.006] [Medline: 29037377]
110. Breitbach S, Tug S, Helmig S, Zahn D, Kubiak T, Michal M, et al. Direct quantification of cell-free, circulating DNA from unpurified plasma. PLoS One 2014;9(3):e87838 [FREE Full text] [doi: 10.1371/journal.pone.0087838] [Medline: 24595313]
111. Neuberger E, Brahmer A, Ehlert T, Kluge K, Philippi K, Boedecker S, et al. Validating quantitative PCR assays for cell-free DNA detection without DNA extractionxercise induced kinetics in systemic lupus erythematosus patients. medRxiv 2021:A Preprint posted online January 20, 2021. [FREE Full text] [doi: 10.1101/2021.01.17.21249972]
112. Caggiano C, Celona B, Garton F, Mefford J, Black B, Lomen-Hoerth H, et al. Estimating the rate of cell type degeneration from epigenetic sequencing of cell-free DNA. bioRxiv. 2020. Preprint posted online January 16, 2020. URL: https://www.biorxiv.org/content/10.1101/2020.01.15.907022v1 [accessed 2021-09-18]
113. Bindila L, Lutz B. Extraction and simultaneous quantification of endocannabinoids and endocannabinoid-like lipids in biological tissues. Methods Mol Biol 2016;1412:9-18 [FREE Full text] [doi: 10.1007/978-1-4939-3539-0_2] [Medline: 27245887]
114. Kranaster L, Hoyer C, Aksay SS, Bumb JM, Leweke FM, Janke C, et al. Electroconvulsive therapy enhances endocannabinoids in the cerebrospinal fluid of patients with major depression: a preliminary prospective study. Eur Arch Psychiatry Clin Neurosci 2017 Dec;267(8):781-786 [FREE Full text] [doi: 10.1007/s00406-017-0789-7] [Medline: 28342110]
115. Brahmer A, Neuberger E, Esch-Heisser L, Haller N, Jorgensen MM, Baek R, et al. Platelets, endothelial cells and leukocytes contribute to the exercise-triggered release of extracellular vesicles into the circulation. J Extracell Vesicles 2019;8(1):1615820 [FREE Full text] [doi: 10.1080/20013078.2019.1615820] [Medline: 31191831]
116. Bæk R, Jørgensen MM. Multiplexed phenotyping of small extracellular vesicles using protein microarray (EV Array). Methods Mol Biol 2017;1545:117-127 [FREE Full text] [doi: 10.1007/978-1-4939-6728-5_8] [Medline: 27943210]
117. Lehmann JS, Rughwani P, Kolenovic M, Ji S, Sun B. LEGENDplex™: Bead-assisted multiplex cytokine profiling by flow cytometry. Methods Enzymol 2019;629:151-176 [FREE Full text] [doi: 10.1016/bs.mie.2019.06.001] [Medline: 31727238]
118. Dickhuth H, Huonker M, Münzel T, Drexler H, Berg A, Keul J. Individual anaerobic threshold for evaluation of competitive athletes and patients with left ventricular dysfunction. In: Bachl N, Graham TE, Löllgen H, editors. Advances in Ergometry. Berlin: Springer; 1991:173-179.
119. Dickhuth HH, Yin L, Niess A, Röcker K, Mayer F, Heitkamp HC, et al. Ventilatory, lactate-derived and catecholamine thresholds during incremental treadmill running: relationship and reproducibility. Int J Sports Med 1999 Mar;20(2):122-127 [FREE Full text] [doi: 10.1055/s-2007-971105] [Medline: 10190774]
120. Foster C, Florhaug JA, Franklin J, Gottschall L, Hrovatin LA, Parker S, et al. A new approach to monitoring exercise training. J Strength Cond Res 2001 Feb;15(1):109-115. [Medline: 11708692]
121. Sportbetreuung Universität Mainz. URL: http://www.sportbetreuung-uni-mainz.de/ [accessed 2021-04-23]
122. Bacon AP, Carter RE, Ogle EA, Joyner MJ. VO2max trainability and high intensity interval training in humans: a meta-analysis. PLoS One 2013;8(9):e73182 [FREE Full text] [doi: 10.1371/journal.pone.0073182] [Medline: 24066036]
123. Holm S. A simple sequentially rejective multiple test procedure. Scandinavian J Statistics 1979;6:65-70 [FREE Full text]
124. Ludyga S, Gerber M, Pühse U, Looser VN, Kamijo K. Systematic review and meta-analysis investigating moderators of long-term effects of exercise on cognition in healthy individuals. Nat Hum Behav 2020 Jun;4(6):603-612 [FREE Full text] [doi: 10.1038/s41562-020-0851-8] [Medline: 32231280]
125. Tyson P, Wilson K, Crone D, Brailsford R, Laws K. Physical activity and mental health in a student population. J Ment Health 2010 Dec;19(6):492-499. [doi: 10.3109/09638230902968308] [Medline: 20812852]
126. Deuster PA, Silverman MN. Physical fitness: a pathway to health and resilience. US Army Med Dep J 2013:24-35. [Medline: 24146240]
127. Zschucke E, Renneberg B, Dimeo F, Wüstenberg T, Ströhle A. The stress-buffering effect of acute exercise: evidence for HPA axis negative feedback. Psychoneuroendocrinology 2015 Jan;51:414-425. [doi: 10.1016/j.psyneuen.2014.10.019] [Medline: 25462913]
128. Wyss T, Boesch M, Roos L, Tschopp C, Frei KM, Annen H, et al. Aerobic fitness level affects cardiovascular and salivary alpha amylase responses to acute psychosocial stress. Sports Med Open 2016 Dec;2(1):33 [FREE Full text] [doi: 10.1186/s40798-016-0057-9] [Medline: 27747788]
129. Bergh C, Udumyan R, Fall K, Almroth H, Montgomery S. Stress resilience and physical fitness in adolescence and risk of coronary heart disease in middle age. Heart 2015 Apr;101(8):623-629 [FREE Full text] [doi: 10.1136/heartjnl-2014-306703] [Medline: 25740818]

130. Lindström M, Hanson B, Östergren P. Socioeconomic differences in leisure-time physical activity: the role of social participation and social capital in shaping health related behaviour. Soc Sci Med 2001 Feb;52(3):441-451 [FREE Full text] [doi: 10.1016/s0277-9536(00)00153-2]
131. Wijndaele K, Matton L, Duvigneaud N, Lefevre J, De Bourdeaudhuij I, Duquet W, et al. Association between leisure time physical activity and stress, social support and coping: a cluster-analytical approach. Psychol Sport Exercise 2007 Jul;8(4):425-440 [FREE Full text] [doi: 10.1016/j.psychsport.2006.08.001]
132. Alexandris K, Tsorbatzoudis C, Grouios G. Perceived constraints on recreational sport participation: investigating their relationship with intrinsic motivation, extrinsic motivation and amotivation. J Leisure Res 2017 Dec 13;34(3):233-252 [FREE Full text] [doi: 10.1080/00222216.2002.11949970]
133. Ardoy DN, Fernández-Rodríguez JM, Jiménez-Pavón D, Castillo R, Ruiz JR, Ortega FB. A physical education trial improves adolescents' cognitive performance and academic achievement: the EDUFIT study. Scand J Med Sci Sports 2014 Mar;24(1):52-61 [FREE Full text] [doi: 10.1111/sms.12093] [Medline: 23826633]
134. Cassilhas RC, Viana VA, Grassmann V, Santos RT, Santos RF, Tufik S, et al. The impact of resistance exercise on the cognitive function of the elderly. Med Sci Sports Exerc 2007 Aug;39(8):1401-1407 [FREE Full text] [doi: 10.1249/mss.0b013e318060111f] [Medline: 17762374]
135. Jeon YK, Ha CH. The effect of exercise intensity on brain derived neurotrophic factor and memory in adolescents. Environ Health Prev Med 2017 Apr;22(1):27 [FREE Full text] [doi: 10.1186/s12199-017-0643-6] [Medline: 29165142]
136. Boesch M, Sefidan S, Ehlert U, Annen H, Wyss T, Steptoe A, et al. Mood and autonomic responses to repeated exposure to the Trier Social Stress Test for Groups (TSST-G). Psychoneuroendocrinology 2014 May;43:41-51 [FREE Full text] [doi: 10.1016/j.psyneuen.2014.02.003] [Medline: 24703169]
137. Minkley N, Schröder TP, Wolf OT, Kirchner WH. The socially evaluated cold-pressor test (SECPT) for groups: effects of repeated administration of a combined physiological and psychological stressor. Psychoneuroendocrinology 2014 Jul;45:119-127 [FREE Full text] [doi: 10.1016/j.psyneuen.2014.03.022] [Medline: 24845183]
138. Gröpel P, Urner M, Pruessner JC, Quirin M. Endurance- and resistance-trained men exhibit lower cardiovascular responses to psychosocial stress than untrained men. Front Psychol 2018;9:852 [FREE Full text] [doi: 10.3389/fpsyg.2018.00852] [Medline: 29910757]
139. Chmitorz A, Kunzler A, Helmreich I, Tüscher O, Kalisch R, Kubiak T, et al. Intervention studies to foster resilience - a systematic review and proposal for a resilience framework in future intervention studies. Clin Psychol Rev 2018 Feb;59:78-100 [FREE Full text] [doi: 10.1016/j.cpr.2017.11.002] [Medline: 29167029]
140. World Health Organization. Who Guidelines on Physical Activity and Sedentary Behaviour. Geneva: World Health Organization; 2020.
141. Bonanno GA, Westphal M, Mancini AD. Resilience to loss and potential trauma. Annu Rev Clin Psychol 2011;7:511-535. [doi: 10.1146/annurev-clinpsy-032210-104526] [Medline: 21091190]
142. Bonanno G, Romero S, Klein S. The temporal elements of psychological resilience: an integrative framework for the study of individuals, families, and communities. Psychol Inq 2015 Jun 11;26(2):139-169 [FREE Full text] [doi: 10.1080/1047840x.2015.992677]
143. Kunzler AM, Gilan DA, Kalisch R, Tüscher O, Lieb K. [Current concepts of resilience research]. Nervenarzt 2018 Jul;89(7):747-753 [FREE Full text] [doi: 10.1007/s00115-018-0529-x] [Medline: 29796896]

Abbreviations

ADS: Allgemeine Depressionsskala
ADS-L: Allgemeine Depressionsskala–Long Version
CERT: Cognitive Emotion Regulation Task
CG: control group
CTS: Childhood Trauma Screener
HPA: hypothalamic-pituitary-adrenal
IAT: individual anaerobe threshold
IG: intervention group
MANOVA: multivariate analysis of variance
MDBF: Mehrdimensionaler Befindlichkeitsfragebogen
PSS: Perceived Stress Scale
SCS: Self-compassion Scale
SECPT: socially evaluated cold pressor test
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TICS-SSCS: Trier Inventory for the assessment of Chronic Stress–Screening Scale for Chronic Stress
VO_2peak: peak oxygen uptake

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Protocol

The Effects of Workplace-Based HIV Self-testing on Uptake of Testing and Linkage to HIV Care or Prevention by Men in Uganda (WISe-Men): Protocol for a Cluster Randomized Trial

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Abstract

Background: HIV testing uptake remains low among men in sub-Saharan Africa. HIV self-testing (HIVST) at the workplace is a novel approach to increase the availability of, and access to, testing among men. However, both access and linkage to posttest services remain a challenge.

Objective: The aim of this protocol is to describe a cluster randomized trial (CRT)—Workplace-Based HIV Self-testing Among Men (WISe-Men)—to evaluate the effect of HIVST in workplace settings on the uptake of HIV testing services (HTS) and linkage to treatment and prevention services among men employed in private security services in Uganda.

Methods: This is a two-arm CRT involving men employed in private security services in two Ugandan districts. The participants in the intervention clusters will undergo workplace-based HIVST using OraQuick test kits. Those in the control clusters will receive routine HTS at their work premises. In addition to HTS, participants in both the intervention and control arms will undergo other tests and assessments, which include blood pressure assessment, blood glucose and BMI measurement, and rapid diagnostic testing for syphilis. The primary outcome is the uptake of HIV testing. The secondary outcomes include HIV status reporting, linkage into HIV care and confirmatory testing following HIVST, initiation of antiretroviral therapy following a confirmatory HIV test, the uptake of voluntary medical male circumcision, consistent condom use, and the uptake of pre-exposure prophylaxis by the most at-risk populations.

Results: Participant enrollment commenced in February 2020, and the trial is still recruiting study participants. Follow-up for currently enrolled participants is ongoing. Data collection and analysis is expected to be completed in December 2021.

Conclusions: The WISe-Men trial will provide information regarding whether self-testing at worksites increases the uptake of HIV testing as well as the linkage to care and prevention services at male-dominated workplaces in Uganda. Additionally, the findings will help us propose strategies for improving men's engagement in HTS and ways to improve linkage to further care following a reactive or nonreactive HIVST result.

Trial Registration: ClinicalTrials.gov NCT04164433; https://clinicaltrials.gov/ct2/show/NCT04164433

International Registered Report Identifier (IRRID): DERR1-10.2196/25099

(JMIR Res Protoc 2021;10(11):e25099) doi:10.2196/25099

KEYWORDS

Africa; workplace HIV testing; HIV self-testing; linkage to care; linkage to prevention

Introduction

Background

Global estimates report that 81% of people living with HIV (PLHIV) knew their HIV status at the end of 2019, and 67% were on antiretroviral therapy (ART) [1]. Over the past several years, there has been a significant decrease in new HIV infections and an increase in the proportion of people accessing ART, with a consequent decline in AIDS-related deaths [2]. The decline in HIV/AIDS-related deaths is attributable, at least in part, to early initiation of HIV care and improved adherence to ART [2]. While numerous efforts and advances in the fight to end the HIV/AIDS epidemic have resulted in substantial gains, the HIV prevalence of 6.3% in Uganda is still quite high [3]. In 2019, there were approximately 1.4 million PLHIV, and approximately 23,000 died of AIDS-related illnesses in Uganda [4].

The failure to reach greater numbers of men with HIV testing and treatment appears to be driving ongoing cycles of HIV transmission in different settings [5]. Not surprisingly, in Uganda, more women (86%) than men (78%) know their HIV status [6]. This may be partly because, unlike women who attend regular maternity and reproductive health services, men do not have similar touch points within the health care system [7]. Furthermore, there are overlooked gender norms and societal beliefs around masculinity and health testing behaviors [8,9] as well as increasing homophobia and transphobia at health facilities [10,11]. When men living with HIV are not diagnosed in a timely fashion, do not start treatment, or fail to remain on treatment, it endangers not only their own health but also the well-being of their families and communities [12]. The current level of new infections in Uganda is still remarkably high, with an estimated 53,000 newly infected people in 2019 [4]. This may be an indication that the country will continue to register high numbers of people with HIV unless innovative measures are put in place to reach and test hard-to-reach populations such as men and youths [13]. Recognizing the importance of closing this gap, various efforts are being directed at developing innovative strategies to increase men's engagement in HIV prevention and care.

The Joint United Nations Programme on HIV/AIDS (UNAIDS) campaign "Blind spot: Reaching out to men and boys" encourages HIV programs to design campaigns that promote men's engagement in HIV services [12]. In line with HIV testing, men in different parts of Uganda have expressed concern with getting tested at a health facility because of the long queues, poor attitudes of health workers, fear of being labeled an HIV "victim," and stigma [14,15]. Additionally, some men have declined an HIV test for fear of imminent death following a positive result, fear that a positive result would stop them from acquiring new sexual partners, fear of a divorce, and a lack of confidentiality for the test results [16-18]. In that regard, the Uganda National HIV Testing Services Policy and Implementation Guidelines [19] proposed that men be targeted at their workplaces, because that is where they spend most of their time. The goal of workplace HIV testing services (HTS) is to increase access to HIV testing by men and women. This approach has demonstrated success in increasing the uptake of HTS at several male-dominated worksites [6].

We propose the use of HIV self-testing (HIVST) to increase the uptake of HTS at the workplace. HIVST overcomes some of the barriers for standard HTS, such as stigma, long lines at health facilities, lack of time to take a test, and the perceived lack of confidentiality of test results [20,21]. During HIVST, an individual collects his or her own oral fluids or blood, performs the test either in private or with someone he or she trusts, and then interprets the results [22]. According to the World Health Organization (WHO), several studies have demonstrated the feasibility and acceptability of HIVST in diverse populations, including men [23]. In a study conducted in South Africa, Van Dyk observed that participants who preferred HIVST were predominantly men [24]. In Malawi, Zambia, and Zimbabwe, Hatzold and colleagues used several HIVST distribution models among men, young people, and index HIV testers [25]. Current trends indicate that HIVST is gaining traction, and many countries have developed policies and guidelines for large-scale implementation [26]. Therefore, this study aims to assess the effectiveness of HIVST in increasing the uptake of HIV testing among wen in work settings in Uganda. However, even as evidence of the high feasibility, acceptability, and accuracy of HIVST continues to accumulate across many delivery models, there is a need for randomized trials to evaluate the outcomes and cost-effectiveness of different HIVST delivery models. More importantly, trials that focus on the linkage to HIV prevention and treatment remain a necessity.

Objective

We present the protocol for the Workplace-Based HIV Self-testing Among Men (WISe-Men) study, which is a cluster randomized trial (CRT) to assess the effectiveness of workplace-based HIVST in Uganda. The aim of this trial is to evaluate the effect of HIVST in work settings on the uptake of HTS and linkage to further HIV services among men employed in private security services in Uganda.

Hypothesis

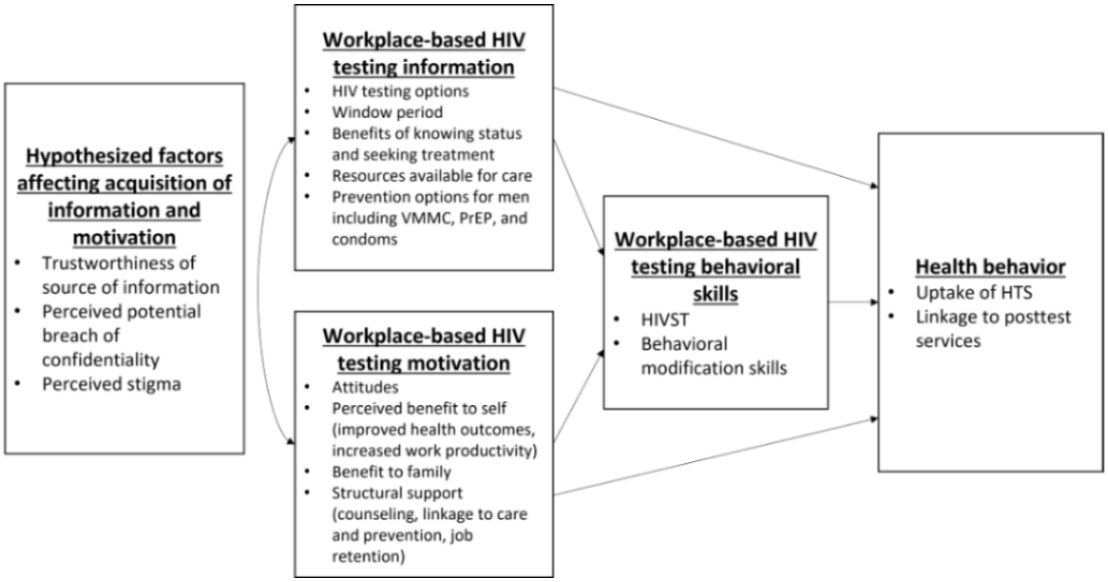
We hypothesize that workplace-based HIVST will increase the proportion of men who take an HIV test, the proportion of men who initiate ART following a positive result, and the proportion of men who are linked to prevention services following a negative result.

Methods

Conceptual Model

This trial is guided by the information-motivation-behavioral skills (IMB) model [27]. The model suggests that health-related sensitization, incentives, and behavioral skills are key determinants for health behaviors. It asserts that if individuals are well informed, receive the appropriate motivation, and have the right behavioral skills, they are more likely to initiate and sustain behaviors that lead to positive health outcomes [28,29]. We use a modified version of the IMB model proposed by a study for HIV testing in the emergency department [28,30] (Figure 1).

Figure 1. Conceptual model adapted from the information-motivation-behavioral skills model. HIVST: HIV self-testing; HTS: HIV testing services; PrEP: pre-exposure prophylaxis; VMMC: voluntary medical male circumcision.



Study Setting

This study will be conducted in two Ugandan districts, namely Kampala, the capital city, which houses headquarters for most companies offering security services in Uganda, and Hoima, an oil and natural gas base that has several security companies. Additionally, the social and relational dynamics created by the work demands of men working in private security services have an influence on their vulnerability to HIV risk. Many of the workers migrate from their homes to work in cities, which places them at high risk of HIV, especially if they remain away from home and/or away from their regular partners for long periods [31].

Study Participants

Permission will be sought from the management of each company to allow the research team to meet with the employees at the company premises. The team will meet the employees during the morning meeting to introduce the study and provide information leaflets. The team will then return on another agreed-upon day to enroll participants, collect baseline data, and carry out the workplace HIV testing. On each data collection day, all eligible employees will receive an equal opportunity to participate in the study activities. Initially, the men will receive study information as a group, followed by one-on-one eligibility assessment and subsequent recruitment.

Study Design

This is a two-arm CRT involving men employed in private security companies. Clusters were private security companies employing 50 or more men in two districts in Uganda. This CRT was informed partly by findings from a previous exploratory qualitative study exploring the perceptions and preferences of employers and employees in private security companies regarding workplace-based HIVST and linkage to further services [32]. The study proposed several strategies to optimize linkage to posttest services following workplace-based HIV testing. These strategies included the use of referral and linkage documentation, paid time off from employers to attend health facilities, assurance of the confidentiality of the test results, peer support from PLHIV, health education and sensitization, expanded clinic hours, the reduction of stigma, and the mitigation of any potential harm. Furthermore, both the employers and employees in the security companies proposed the inclusion of further assessments in addition to HIV testing. This approach would allow them to understand their health status and reduce the stigma associated with taking an HIV test more fully. The additional health assessments include measuring blood pressure and blood glucose, assessing BMI, and screening for syphilis. Participation will be discontinued in response to harm or participant request.

Site Selection and Allocation

Through randomization, Kampala District was allocated to the intervention arm and Hoima District was allocated to the control arm. The clusters in the intervention arm will receive HIVST while those in the control arm will receive standard HTS.

Eligibility Criteria

Eligible private security companies, each employing at least 50 male personnel, were identified and listed per district. The eligibility criteria for participants are as follows [33]:

- Men 18 to 60 years old
- Employed more than 6 months within the security industry
- Men who have either never taken an HIV test or who tested negative for HIV more than 1 year ago.

Ethics Approval, Trial Registration, and Informed Consent

Both the Makerere University School of Health Sciences Research Ethics Committee (reference No. 2018-054) and the Uganda National Council of Science and Technology (UNCST; reference No. HS 2672) granted ethics approval. The trial was registered at ClinicalTrials.gov (NCT04164433). Any important protocol deviations or adverse events (AEs) will immediately be communicated to the Research Ethics Committee, the UNCST, and ClinicalTrials.gov. Additionally, we will seek permission from the responsible personnel officer at every site.

Each participant will provide written consent prior to recruitment into the CRT and will receive a copy of the signed form. They will also be informed that their participation is voluntary and that they may withdraw from the study at any time. Furthermore, permission will be sought to audio-record and take notes during the interviews.

All disclosed HIV status results will remain confidential. The employers will be made aware that the results will remain confidential and that the workers are not under any obligation to disclose their results, especially in the event that this may lead to a loss of jobs for those who are found to be HIV positive. All original documents will be deposited in a secure locked cabinet and accessed only by the three investigators. The trial data set will not have any participant identifiers and will be stored in electronic password-protected files.

Sample Size Determination

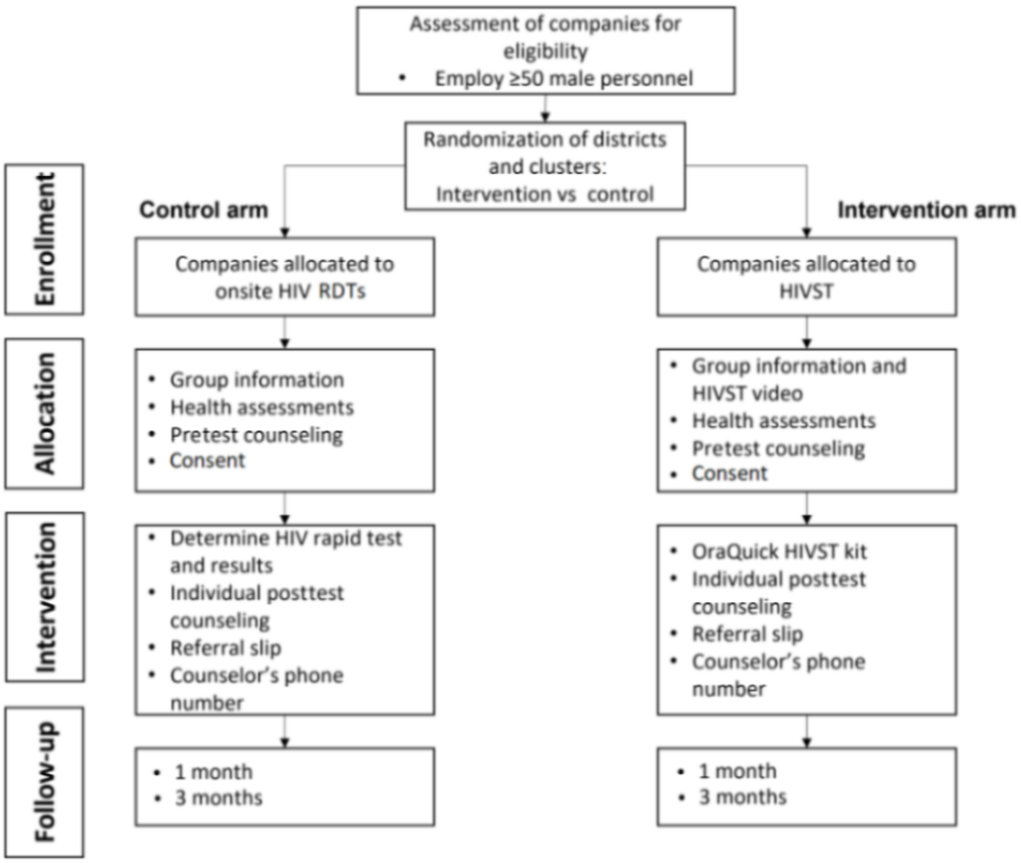
Sample size estimation is based on the primary outcome: proportion of men who take an HIV test. The main outcomes were at the participant level. Currently, approximately 55% of males in Uganda have taken an HIV test [34]. We hypothesize a 15% increase in HIV testing in the workplace HIVST group in comparison to the control group. We considered a two-sided α of .05 with a power of 80% to detect a significant change between both groups, a 1:1 allocation ratio between the intervention and control arms, a response rate of 90%, and a design effect of 1.399. We estimate a minimum total sample size of 548 participants, with 274 per arm. The proxy for design effect was picked from the proxy variable “Had taken an HIV test and obtained results in the past year” [35].

Data Collection

Cluster Randomized Trial Flow

All participants will be provided with a list of nearby health facilities that are accredited to provide ART. Participants will be asked to propose three facilities that they would like to visit for a confirmatory test if found to be HIV positive (Figure 2).

Figure 2. Cluster randomized trial flow diagram. HIVST: HIV self-testing; RDT: rapid diagnostic test.

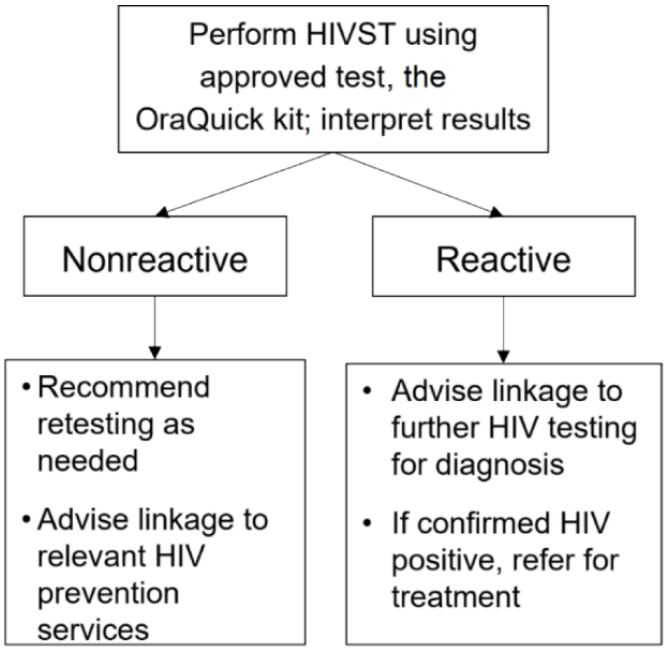


Intervention Arm

Since 2014, the WHO has encouraged countries to implement pilot HIVST programs to evaluate this approach. We will, therefore, follow the WHO strategy on self-testing to pilot HIVST in the workplace [22] (Figure 3). The strategy steps are as follows:

1. Explain the HIVST procedure and how to interpret the self-test results.
2. Demonstrate the HIVST procedure and the interpretation of the results.
3. Provide any additional instructional materials using an HIVST video.
4. Answer any questions raised by the potential participant.
5. Issue the OraQuick HIVST kits for collection of a mouth swab; participants will test at home or at a venue of their choice.
6. Participants will return the results to the trial team in one of the following ways that will be agreed upon when they receive the kit:
   a. A phone call to the study toll-free line.
   b. A picture of the test results sent via email, WhatsApp, Facebook, or another preferred social media app.
   c. Presentation of the test kit at the health facility.
   d. Participant self-reporting the results at the health facility.
7. Provide a referral slip and further information on linking to further services for those who receive a reactive self-test result. Those who test negative will receive further information and a referral to HIV prevention services.
8. Provide participants with a counselor's phone number. They will be offered the option of a call-back to return the results within 3 days of testing. Participants will also be told to use this number if they have any difficulty and need support during and after testing. This is in line with a recommendation from a study in Nigeria [36], where more than half of the participants who tested HIV positive used the helpline for support.
9. Each participant will receive a code and instructions on what to write in case he is positive and can send these results as a text message. For example, 2018-7TR9-122-S is the code for a positive reactive test, and 2018-7TR9-122-T is the code for the nonreactive test. These codes will be randomly generated for each participant to avoid coworkers being able to accidentally interpret another person's results.
10. Participants who do not return the HIVST results within 3 days shall be phoned. This is in line with the Ugandan Ministry of Health test-and-treat strategy [6]. They will have given prior consent to be contacted.

Figure 3. HIV self-testing (HIVST) pathway.



Control Arm

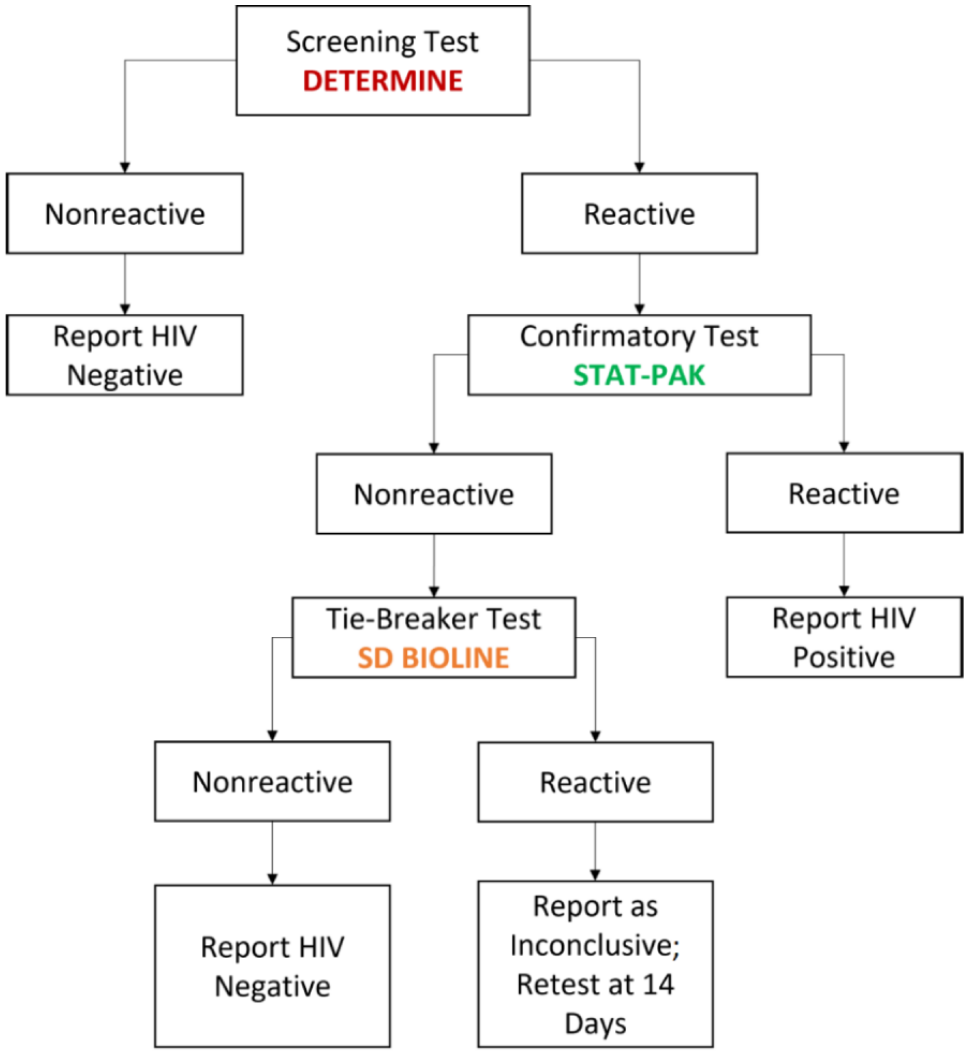
Security personnel allocated to the control arm will receive standard-of-care HIV counseling and testing based on the Ugandan Ministry of Health guidelines [6], as follows:

1. The control arm of this study will be offered standard facility-based care using antibody-based rapid diagnostic tests (RDTs), which follow the approved serial testing algorithm in Uganda for people above 18 months of age [6] (Figure 4).
2. Whole blood will be collected via finger stick and capillary sampling by a trained HIV nurse or counselor who will use a lancet and transfer the blood to the screening test kit using a capillary tube. The specimen will be tested immediately.
3. The nationally approved algorithm for HIV testing is as follows:
   a. All participants will undergo the screening test using the Alere Determine HIV-1/2 test (Abbott).

b. All participants who receive a reactive result will undertake a confirmatory test using the HIV 1/2 STAT-PAK test (Chembio Diagnostic Systems).
c. All participants with a nonreactive confirmatory test result will undertake a tie-breaker test using the SD BIOLINE HIV-1/2 test (Abbott).

4. Participants whose samples react using the tie-breaker test shall be retested after 14 days.
5. Participants who test positive will receive a referral slip to nearby public and private health facilities to expedite linkage to treatment, care, and support services.
6. Participants who test negative will receive a referral slip for HIV prevention services. The participants will be referred to one of five public health facilities within the district.
7. Each participant will be provided with a counselor's contact number for continued consultation.

Figure 4. Serial HIV testing algorithm for testing persons over 18 months of age in Uganda.



Linkage to Care or Prevention Services

The participants will be followed up at 1 month and 3 months to determine their linkage into prevention, treatment, or care.

Referral of Clients With a Confirmed HIV Diagnosis

Following confirmatory HIV testing, clients diagnosed with HIV will be referred to local HIV treatment facilities using a paper referral slip provided by the research team. Once a client presents to a health facility with a referral slip, they will receive a confirmatory test prior to ART initiation. This approach reduces the risk of misdiagnosing their HIV status and unnecessarily treating HIV-negative persons, which has ethical and health system implications and causes individuals to suffer needless psychological effects [6,37]. A copy of the referral slip will be retained by the research team for use during follow-up. Participants who test positive for HIV will be encouraged to take their referral slip to the referral facility where staff will have been trained to keep the referral documentation and mark the source of the referral during patient registration. The unit of evaluation (ie, the indicator for the outcome of linkage to care) will be defined by the facility's HIV testing registration records and clinic records of ART initiation.

Referral of Clients Confirmed as HIV Negative

Following confirmation of an HIV-negative result, clients will be offered information about voluntary medical male circumcision (VMMC). Pre-exposure prophylaxis (PrEP), condom use, and partner notification will be offered as an option for those who are sexually active. They will also receive a

referral slip for these services to refer them to the nearest public health facility of their choice from their company offices. As mentioned above, the clients who present at the health facility will also receive a confirmatory test. The unit of evaluation will be defined by HIV testing by the facility, VMMC, partner services, and PrEP records.

Permitted Concomitant Interventions

In addition to HTS, security personnel in both the intervention and control arms will receive identical additional services. These services were identified through a needs assessment that was conducted earlier [32]. The findings from that study reported that both employers and employees were more willing to undergo HIV testing at the workplace if this was provided in combination with other health promotion interventions as a way of mitigating stigma. The additional package will, therefore, include the following: a blood pressure assessment, blood glucose and BMI measurements, and an RDT for syphilis. The additional package will be offered to both the intervention and control groups prior to enrollment in the study. We do not expect these concomitant interventions to affect the results of the trial.

Study Outcomes

Overview

The primary outcome will be uptake of HIV testing. Secondary outcomes will include testing yield, proportion of participants initiating ART during the first 3 months following HIV test results, and proportion of participants linked to prevention services (ie, consistent condom use, VMMC, PrEP, and retesting for HIV).

Primary Outcome Assessment

We are operationally defining uptake of HIV testing as accepting to take an HIV test from the standard-of-care services that will be offered to the control group or receiving and returning a used HIVST kit for the intervention group. The proportion of security personnel in the control group who take an HIV test will be computed by dividing the number of participants in the standard-of-care cluster who agree to take an HIV test by the total number of those enrolled in the control arm. For the participants in the intervention cluster, uptake of HIV testing will be computed by dividing the number of participants who return the used HIVST kit within 1 month from the time of the test kit distribution by the total number who enrolled in the intervention arm.

Secondary Outcome Assessment

The following outcomes will be reported in the clinical trial record [33]:

1. HIV status reporting—the proportion of participants who self-report HIV test results. This will be assessed via telephone call by participants to the trial toll-free line or via picture of the self-test result sent through any of the following electronic channels: study email, WhatsApp, or the study Facebook account. Further assessment will include the presentation of either the trial participant or the self-test at a health facility.
2. Linkage into HIV care—the proportion of participants with positive results who link to a health facility for HIV care. This will be assessed by checking the clinic records from the selected HIV care and treatment facilities at 1 and 3 months.
3. Initiation of ART—the proportion of participants who initiate ART. This will be assessed by checking clinic records or possession of an ART card. Data will be collected using a questionnaire at 1 and 3 months.
4. Uptake of VMMC following HIVST—the proportion of previously uncircumcised participants who self-report VMMC at 1 and 3 months.
5. Consistent condom use following HIVST—the proportion of participants who use a condom for each sexual encounter for 1 month. Condom use will be assessed through verbal reports from the participants. Participants will be followed up at 1 and 3 months.
6. Uptake of PrEP by men who have sex with men (MSM)—the proportion of MSM who initiate PrEP at 1 and 3 months. In this study, MSM will indicate the behaviors that transmit HIV infection, rather than how individuals self-identify in terms of their sexuality [38].

Data Monitoring, Potential Harms, and Audit Process

HIV testing and HIVST at the workplace in Uganda are still novel and may result in unexpected harms and AEs. We set up a data safety and monitoring committee to oversee the progress of the trial. The committee is charged with ensuring that the trial protocol is adhered to and that the trial data are correctly recorded, analyzed, and reported. The trial quality-management officer, together with the research team, will monitor the participants for harm and AEs, such as physical violence, stigma, and discrimination at the workplace, as well as personal and social harm related to receiving HIV test results. AEs will be classified as mild, moderate, or severe. AEs such as suicide threats, self-harm threats, hospitalization, or death up to 28 days after a reactive HIVST result will be classified as severe [39]. The trial quality-management officer will report all events and withdrawals from the trial due to AEs using an open-ended AE reporting form. These data will be collected fortnightly. Severe events will be reported to the principal investigator and the Research Ethics Committee, while mild and moderate AEs will be recorded and reported to the trial counseling team. In the event of severe AEs, the data monitoring committee will evaluate the benefits and harms separately, followed by an overall measure that considers the balance between benefits and harms [40]. At the end of the trial, two independent officials will evaluate the trial-related activities and documents to ensure that they were carried out according to the protocol and Good Clinical Practices.

Statistical Analysis

We will use the intention-to-treat principle for all analyses. Participants' sociodemographic characteristics will be summarized using frequencies and proportions and will be compared across the study arms. We will employ chi-square and Fisher exact tests for categorical variables as well as means and *t* tests or analyses of variance for continuous variables [41]. To avoid unit-of-analysis errors, we shall conduct analyses by allocation unit via hierarchical logistic regression models that compare the outcome between the two arms and account for

clustering among the respondents. The analysis will also adjust for individual-level covariates to elicit associations between the outcomes and the covariates. This method of analysis has been selected over other methods of analyzing cluster data to avoid any ecological fallacy [42]. For the primary outcome, we will compare the proportion of participants taking an HIV test between the two arms. Secondary analyses will be conducted to compare the proportion of HIV-positive participants who become linked to care between the two arms as well as the proportion of HIV-negative participants who take up prevention services between the two arms. The statistical analysis will be performed using Stata software (version 14; StataCorp LP). Trial findings will be published following the CONSORT (Consolidated Standards of Reporting Trials) guidelines [43].

Results

Participant enrollment for the WISe-Men trial commenced in February 2020 and was still recruiting study participants at the time of this submission. Follow-up for currently enrolled participants is ongoing. Data collection and analysis is expected to be completed in December 2021.

Discussion

This research project aims to evaluate the effects of HIVST on HIV care-seeking among men. One anticipated challenge of the HIVST intervention is how the researchers will confirm the participants' HIVST results, as these will be self-reported. We propose the use of mobile phone apps, such as WhatsApp, that participants can use to send their results back for verification, but this may be a challenge for those without smartphones. Another anticipated challenge revolves around participants' work schedules. The field employees in the private security companies may not be available for HTS on the days scheduled for data collection, which may delay recruitment and hinder achieving the desired sample size.

With 88% of PLHIV identified in Uganda, it is difficult to identify the remaining undiagnosed PLHIV with general population approaches. This project uses one of the recommended approaches called targeted testing, which focuses on an individual or group of individuals who are at high risk of HIV acquisition [6]. Men employed in private security companies represent an ideal population for targeted testing. They are considered among the priority populations with limited access to HTS due to the nature of their work, and their social migration puts them at risk of HIV [34]. Additionally, the WISe-Men trial will provide information regarding whether testing at worksites increases men's engagement in HIV testing and linkage to post-HTS in Uganda. The trial results will be communicated to the participants, health care professionals, and the public through workshops and meetings and to other relevant groups through publications in peer-reviewed journals and conferences. The findings from this study will contribute to policy development regarding HIVST and will inform the future regional, national, and international implementation of HTS.

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Authors' Contributions

PAM, DN, NKS, and NK made substantial contributions to the conception of the project; in addition, PAM, NKS, and NK are investigators on the WISe-Men trial. TDN and PAM drafted the paper and made substantial contributions to the cluster randomized trial design. PAM, DN, NKS, NK, LEN, EMN, and CPO critically revised the manuscript for important intellectual content. All authors gave final approval for the work to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

None declared.

References

1. Global AIDS Update 2020. Seizing the Moment: Tackling Entrenched Inequalities to End Epidemics. Geneva, Switzerland: UNAIDS; 2020. URL: https://www.unaids.org/en/resources/documents/2020/global-aids-report [accessed 2020-06-28]
2. Global AIDS Update 2019. Communities at the Centre. Geneva, Switzerland: UNAIDS; 2019. URL: https://www.unaids.org/en/resources/documents/2019/2019-global-AIDS-update [accessed 2020-06-11]
3. Ministry of Health, Uganda. Uganda Population-Based HIV Impact Assessment (UPHIA) 2016-2017: Final Report. Kampala, Uganda: Ministry of Health; 2019 Jul. URL: https://phia.icap.columbia.edu/wp-content/uploads/2019/07/UPHIA_Final_Report_Revise_07.11.2019_Final_for-web.pdf [accessed 2020-06-11]
4. Country fact sheets: Uganda. AIDSInfo. Geneva, Switzerland: UNAIDS; 2020. URL: https://aidsinfo.unaids.org/ [accessed 2020-08-10]

5. Brenner B, Ibanescu R, Hardy I, Stephens D, Otis J, Moodie E, Montreal PHI, SPOT cohorts. Large cluster outbreaks sustain the HIV epidemic among MSM in Quebec. AIDS 2017;31(5):707-717 [FREE Full text] [doi: 10.1097/qad.0000000000001383]
6. Ministry of Health, Uganda. Consolidated Guidelines for the Prevention and Treatment of HIV and AIDS in Uganda. Kampala, Uganda: Ministry of Health; 2020 Feb. URL: https://tinyurl.com/shrarsud [accessed 2020-03-22]
7. Adeyeye AO, Stirratt MJ, Burns DN. Engaging men in HIV treatment and prevention. Lancet 2018 Dec 01;392(10162):2334-2335. [doi: 10.1016/S0140-6736(18)32994-5] [Medline: 30527600]
8. Sileo KM, Fielding-Miller R, Dworkin SL, Fleming PJ. What role do masculine norms play in men's HIV testing in sub-Saharan Africa?: A scoping review. AIDS Behav 2018 Aug;22(8):2468-2479 [FREE Full text] [doi: 10.1007/s10461-018-2160-z] [Medline: 29777420]
9. Siu GE, Wight D, Seeley JA. Masculinity, social context and HIV testing: An ethnographic study of men in Busia district, rural eastern Uganda. BMC Public Health 2014 Jan 13;14:33 [FREE Full text] [doi: 10.1186/1471-2458-14-33] [Medline: 24417763]
10. King R, Sebyala Z, Ogwal M, Aluzimbi G, Apondi R, Reynolds S, et al. How men who have sex with men experience HIV health services in Kampala, Uganda. BMJ Glob Health 2020 Apr 19;5(4):1-8 [FREE Full text] [doi: 10.1136/bmjgh-2019-001901]
11. Müller A. Scrambling for access: Availability, accessibility, acceptability and quality of healthcare for lesbian, gay, bisexual and transgender people in South Africa. BMC Int Health Hum Rights 2017 May 30;17(1):16 [FREE Full text] [doi: 10.1186/s12914-017-0124-4] [Medline: 28558693]
12. Blind Spot. Reaching Out to Men and Boys: Addressing a Blind Spot in the Response to HIV. Geneva, Switzerland: UNAIDS; 2017. URL: https://www.unaids.org/sites/default/files/media_asset/blind_spot_en.pdf [accessed 2020-07-13]
13. Government of Uganda. Uganda AIDS Country Progress Report July 2017-June 2018. Kampala, Uganda: Government of Uganda; 2018 Sep. URL: https://www.unaids.org/sites/default/files/country/documents/UGA_2019_countryreport.pdf [accessed 2021-10-12]
14. Buregyeya E, Naigino R, Mukose A, Makumbi F, Esiru G, Arinaitwe J, et al. Facilitators and barriers to uptake and adherence to lifelong antiretroviral therapy among HIV infected pregnant women in Uganda: A qualitative study. BMC Pregnancy Childbirth 2017 Mar 21;17(1):94 [FREE Full text] [doi: 10.1186/s12884-017-1276-x] [Medline: 28320347]
15. Bwambale FM, Ssali SN, Byaruhanga S, Kalyango JN, Karamagi CA. Voluntary HIV counselling and testing among men in rural western Uganda: Implications for HIV prevention. BMC Public Health 2008 Jul 30;8:263 [FREE Full text] [doi: 10.1186/1471-2458-8-263] [Medline: 18664301]
16. Byamugisha R, Tumwine JK, Semiyaga N, Tylleskär T. Determinants of male involvement in the prevention of mother-to-child transmission of HIV programme in Eastern Uganda: A cross-sectional survey. Reprod Health 2010 Jun 23;7:12 [FREE Full text] [doi: 10.1186/1742-4755-7-12] [Medline: 20573250]
17. Ramirez-Ferrero E. Male Involvement in the Prevention of Mother-to-Child Transmission of HIV. Geneva, Switzerland: World Health Organization; 2012. URL: http://apps.who.int/iris/bitstream/handle/10665/70917/9789241503679_eng.pdf?sequence=3 [accessed 2021-10-12]
18. Aarnio P, Chipeta E, Kulmala T. Men's perceptions of delivery care in rural Malawi: Exploring community level barriers to improving maternal health. Health Care Women Int 2013;34(6):419-439. [doi: 10.1080/07399332.2012.755982] [Medline: 23641896]
19. Ministry of Health, Uganda. National HIV Testing Services Policy and Implementation Guidelines: Uganda. 4th edition. Kampala, Uganda: Ministry of Health; 2016 Oct. URL: https://www.health.go.ug/cause/national-hiv-testing-services-policy-and-implementation-guidelines/ [accessed 2021-10-12]
20. Figueroa C, Johnson C, Ford N, Sands A, Dalal S, Meurant R, et al. Reliability of HIV rapid diagnostic tests for self-testing compared with testing by health-care workers: A systematic review and meta-analysis. Lancet HIV 2018 Jun;5(6):e277-e290 [FREE Full text] [doi: 10.1016/S2352-3018(18)30044-4] [Medline: 29703707]
21. Jennings L, Conserve DF, Merrill J, Kajula L, Iwelunmor J, Linnemayr S, et al. Perceived cost advantages and disadvantages of purchasing HIV self-testing kits among urban Tanzanian men: An inductive content analysis. J AIDS Clin Res 2017 Aug;8(8):1-21 [FREE Full text] [doi: 10.4172/2155-6113.1000725] [Medline: 29051841]
22. Guidelines on HIV Self-Testing and Partner Notification: Supplement to Consolidated Guidelines on HIV Testing Services. Geneva, Switzerland: World Health Organization; Dec 2016.
23. Figueroa C, Johnson C, Verster A, Baggaley R. Attitudes and acceptability on HIV self-testing among key populations: A literature review. AIDS Behav 2015 Nov;19(11):1949-1965 [FREE Full text] [doi: 10.1007/s10461-015-1097-8] [Medline: 26054390]
24. van Dyk AC. Self-testing as strategy to increase the uptake of HIV testing in South Africa. Afr J AIDS Res 2013 Mar;12(1):41-48. [doi: 10.2989/16085906.2013.815413] [Medline: 25871310]
25. Hatzold K, Gudukeya S, Mutseta MN, Chilongosi R, Nalubamba M, Nkhoma C, et al. HIV self-testing: Breaking the barriers to uptake of testing among men and adolescents in sub-Saharan Africa, experiences from STAR demonstration projects in Malawi, Zambia and Zimbabwe. J Int AIDS Soc 2019 Mar;22 Suppl 1:e25244 [FREE Full text] [doi: 10.1002/jia2.25244] [Medline: 30907505]

26. Indravudh PP, Choko AT, Corbett EL. Scaling up HIV self-testing in sub-Saharan Africa. Curr Opin Infect Dis 2018;31(1):14-24. [doi: 10.1097/qco.0000000000000426]
27. Fisher JD, Fisher WA. Changing AIDS-risk behavior. Psychol Bull 1992 May;111(3):455-474. [doi: 10.1037/0033-2909.111.3.455] [Medline: 1594721]
28. Fisher JD, Fisher WA. The information-motivation-behavioral skills model. In: DiClemente RJ, Crosby RA, Kegler MC, editors. Emerging Theories in Health Promotion Practice and Research. San Francisco, CA: Jossey-Bass; 2002:40-70.
29. Sasaki Y, Arifin A, Ali M, Kakimoto K. Willingness to undergo HIV testing among factory workers in Surabaya, Indonesia. AIDS Care 2011 Oct;23(10):1305-1313. [doi: 10.1080/09540121.2011.555745] [Medline: 21547754]
30. Merchant RC, Liu T, Clark MA, Carey MP. Facilitating HIV/AIDS and HIV testing literacy for emergency department patients: A randomized, controlled, trial. BMC Emerg Med 2018 Jul 09;18(1):21 [FREE Full text] [doi: 10.1186/s12873-018-0172-7] [Medline: 29986662]
31. HIV Self-Testing at the Workplace. Geneva, Switzerland: World Health Organization; 2018 Nov. URL: https://www.who.int/publications/i/item/hiv-self-testing-at-the-workplace [accessed 2021-10-12]
32. Muwanguzi PA, Nasuuna EM, Osingada CP, Seruwagi GK, Nuwagira E, Kiwanuka N, et al. Employers' and employees' perspectives of HIV self-testing at male-dominated work sites and linkage to posttest services in Uganda. J Assoc Nurses AIDS Care 2020 Jun 24;31(6):632-645. [doi: 10.1097/jnc.0000000000000188]
33. Muwanguzi PA. Workplace-based HIV Self-testing Among Men in Uganda (WISe-Men). ClinicalTrials.gov. 2020. URL: https://ClinicalTrials.gov/show/NCT04164433 [accessed 2020-09-16]
34. Government of Uganda. The Uganda HIV and AIDS Country Progress Report July 2015-June 2016. Kampala, Uganda: Government of Uganda; 2016 Aug 26. URL: https://www.unaids.org/sites/default/files/country/documents/UGA_2017_countryreport.pdf [accessed 2021-10-12]
35. Uganda Bureau of Statistcs and ICF. Uganda Demographic and Health Survey 2016: Key Indicators Report. Kampala, Uganda, and Rockville, MD: Uganda Bureau of Statistics and ICF; 2017 Mar. URL: https://www.healthynewbornnetwork.org/hnn-content/uploads/PR80.pdf [accessed 2021-10-12]
36. Tun W, Vu L, Dirisu O, Sekoni A, Shoyemi E, Njab J, et al. Uptake of HIV self-testing and linkage to treatment among men who have sex with men (MSM) in Nigeria: A pilot programme using key opinion leaders to reach MSM. J Int AIDS Soc 2018 Jul;21 Suppl 5:e25124 [FREE Full text] [doi: 10.1002/jia2.25124] [Medline: 30033680]
37. Eaton JW, Johnson CC, Gregson S. The cost of not retesting: Human immunodeficiency virus misdiagnosis in the antiretroviral therapy "test-and-offer" era. Clin Infect Dis 2017 Aug 01;65(3):522-525 [FREE Full text] [doi: 10.1093/cid/cix341] [Medline: 28444206]
38. HIV and gay and bisexual men. Centers for Disease Control and Prevention. URL: https://www.cdc.gov/hiv/group/msm/index.html [accessed 2020-09-20]
39. Neuman M, Indravudh P, Chilongosi R, d'Elbée M, Desmond N, Fielding K, et al. The effectiveness and cost-effectiveness of community-based lay distribution of HIV self-tests in increasing uptake of HIV testing among adults in rural Malawi and rural and peri-urban Zambia: Protocol for STAR (self-testing for Africa) cluster randomized evaluations. BMC Public Health 2018 Nov 06;18(1):1234 [FREE Full text] [doi: 10.1186/s12889-018-6120-3] [Medline: 30400959]
40. Ioannidis JP, Evans SJW, Gøtzsche PC, O'Neill RT, Altman DG, Schulz K, CONSORT Group. Better reporting of harms in randomized trials: An extension of the CONSORT statement. Ann Intern Med 2004 Nov 16;141(10):781-788 [FREE Full text] [doi: 10.7326/0003-4819-141-10-200411160-00009] [Medline: 15545678]
41. Saitz R, Friedmann PD, Sullivan LM, Winter MR, Lloyd-Travaglini C, Moskowitz MA, et al. Professional satisfaction experienced when caring for substance-abusing patients. Faculty and resident physician perspectives. J Gen Intern Med 2002 May;17(5):373-376. [doi: 10.1046/j.1525-1497.2002.10520.x]
42. Wears RL. Advanced statistics: Statistical methods for analyzing cluster and cluster‐randomized data. Acad Emerg Med 2002;9(4):330-341 [FREE Full text] [doi: 10.1197/aemj.9.4.330]
43. Campbell MK, Piaggio G, Elbourne DR, Altman DG, CONSORT Group. CONSORT 2010 statement: Extension to cluster randomised trials. BMJ 2012 Sep 04;345:e5661. [doi: 10.1136/bmj.e5661] [Medline: 22951546]

Abbreviations

AE: adverse event
ART: antiretroviral therapy
CONSORT: Consolidated Standards of Reporting Trials
CRT: cluster randomized trial
HIVST: HIV self-testing
HTS: HIV testing services
IMB: information-motivation-behavioral skills
MSM: men who have sex with men
PLHIV: people living with HIV
PrEP: pre-exposure prophylaxis

RDT: rapid diagnostic test
UNAIDS: Joint United Nations Programme on HIV/AIDS
UNCST: Uganda National Council of Science and Technology
VMMC: voluntary medical male circumcision
WHO: World Health Organization
WISe-Men: Workplace-Based HIV Self-testing Among Men

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Protocol

Effectiveness of a Walking Football Program for Middle-Aged and Older Men With Type 2 Diabetes: Protocol for a Randomized Controlled Trial

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Abstract

Background: Studies on walking football have found positive effects on health; however, there are still several research gaps when applying walking football programs for patients with type 2 diabetes.

Objective: This study aims to test the effectiveness of a walking football exercise program on glycemic control and cardiovascular risk factors in middle-aged and older men with type 2 diabetes.

Methods: The study will be run as a randomized controlled trial with a 6-month duration in Portugal. Eligible participants will be randomized using a 1:1 ratio for intervention or control groups and compared using an intention-to-treat analysis. The intervention will consist of a walking football exercise program. The control group will continue with usual care in primary health care units. The primary outcome will be the mean difference in glycated hemoglobin between intervention and control groups after 6 months. Secondary outcomes include the mean differences in fasting blood glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, systolic and diastolic blood pressure, body mass index, waist circumference, fat-free mass, and fat mass. Additionally, secondary outcomes include the incidence of exercise-related injuries and adverse events and the walking football exercise program's cost-utility.

Results: The study protocol is being prepared to be submitted to the Health Ethics Committee of the Northern Regional Health Administration, Portugal. After approval, participant recruitment will start in primary health care units in Porto's metropolitan area by family medicine doctors.

Conclusions: Walking football might have the potential to be effective in improving glycemic control and cardiovascular risk factors, with a low rate of exercise-related injuries and adverse events and a good cost-utility ratio. Therefore, walking football may be a sustainable intervention strategy for type 2 diabetes management.

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KEYWORDS

type 2 diabetes; cardiovascular risk factors; physical activity; exercise; football; soccer; walking; randomized controlled trial

Introduction

Background and Rationale

Type 2 diabetes (T2D) is a global public health concern considering its morbidity, mortality, and health expenditure [1]. In 2019, it was estimated that 463 million adults (20-79 years old) worldwide were diagnosed with diabetes, corresponding to 9.0% of all adults in this age group [1] and representing nearly 90% of T2D cases. Increased exposure to environmental factors, such as obesity and physical inactivity, has been associated with the alarming increase in the prevalence of diabetes [1]. Portugal is one of the European countries with the highest prevalence of diabetes. In 2015, the prevalence of diabetes in the adult population (25-74 years old) was 9.9% [2]. The prevalence was higher in men than in women (12.1% vs 7.8%), and higher in individuals aged 65-74 years (23.8%) compared with younger individuals [2].

The benefits of physical activity in the prevention and control of T2D have long been documented [3-6]; however, a considerable proportion of individuals with T2D do not adhere to the recommendations proposed by international organizations (eg, American Diabetes Association, American College of Sports Medicine) [7,8]. Data from Portugal revealed that about 60% of individuals with T2D reported not practicing any type of exercise [9], demanding interventions to increase physical activity levels in this population.

Recreational football is conducted as small-sided games, from 3 vs 3 to 7 vs 7, practiced 2-3 times per week, in sessions of 45-60 minutes. The practice of recreational football is an intermittent activity, with participants moving at slow speed, but with consecutive changes in direction, accelerations, and decelerations, leading to periods of moderate-to-vigorous intensity. This intermittent activity has shown cardiovascular, metabolic, and neuromuscular benefits across different populations [10-14]. This can contribute to increased physical activity levels and, therefore, to the control of several noncommunicable diseases, including T2D [10-14].

Exercise-related injuries and the high exercise intensities observed in recreational football led some football clubs to develop walking football strategies for their older players [15]. Walking football follows football's general rules, but it does not allow players to run or have physical contact, and the ball must always be played below the players' average waist height [16]. Available studies on walking football have reported engagement and satisfaction with the modality, the pattern of exercise intensity (from light to vigorous), and health benefits (namely on body composition, aerobic fitness, blood pressure, cognitive function, psychologic well-being, and quality of life) [17-22].

Only 3 studies provided details regarding the participants' medical conditions [17,20,22]. Participants were mainly middle-aged and older men with overweight, obesity, hypertension, or T2D. Characterization of medical conditions and cardiovascular risk factors seems particularly important when extrapolating exercise effects for some populations. Patients with T2D have an increased risk of injuries and acute adverse events associated with exercise training compared with healthy subjects [23]. Indeed, efforts for safety are fundamental in exercise programs and may compromise participants' adherence.

A 12-week study that tested the feasibility and safety of a walking football program in middle-aged and older men with T2D in a quasiexperimental design found that the most common adverse events were falls and musculoskeletal injuries, and no acute metabolic or hemodynamic adverse events were observed. No registered injuries or adverse events were reported, mainly due to the safety protocols applied before, during, and after each exercise session [22].

Studies on walking football showed positive effects on health. However, there are still several research gaps regarding walking football in patients with T2D. It includes limitations in study designs, sample sizes, length of the programs, assessment of variables that may influence adherence to the programs (such as the enjoyment), and impact on glycemic control and cardiovascular risk factors.

Objectives

This study aims to test the effectiveness of a 6-month walking football exercise program on glycemic control and cardiovascular risk factors in middle-aged and older men with T2D.

This study will be accomplished through the following specific objectives: (1) evaluate the effects of a walking football exercise program on glycemic control, blood lipid profile, blood pressure, anthropometric profile, and body composition; (2) assess exercise-related injuries and adverse events of a walking football exercise program; (3) assess the cost-utility of a walking football exercise program.

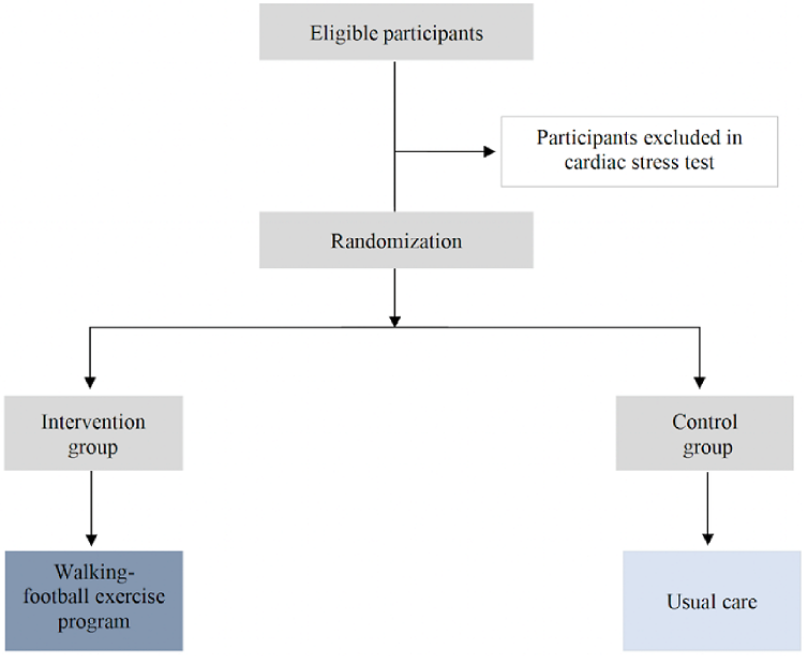
Methods

This protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement [24]. The SPIRIT checklist is available in Multimedia Appendix 1, and the trial for this protocol will be registered at ClinicalTrials.gov.

Design

This study is based on a parallel-group, randomized controlled trial with a 6-month duration. Eligible participants will be randomized using a 1:1 ratio within each primary health care unit (PHCU) to intervention or control groups. The intervention will consist of a 60-minute walking football exercise program, 3 times per week (nonconsecutive days), for 24 weeks. The control group will maintain daily life routines and continue with usual care. The study design is represented in Figure 1.

Figure 1. Flow diagram of the randomized controlled trial.



Setting

The study will be conducted in PHCU of Porto's metropolitan area, in the northern region of Portugal. A PHCU consists of multiprofessional teams, with a mean of 7 family medicine doctors, an equal number of family nurses, and administrative professionals. Family medicine doctors have a patient list that ranges from 1500 to 2000 patients, handling preventive activities and most of the acute and chronic health problems of the individuals. In these units, patients with chronic conditions, such as T2D, have regular consultations and close contact with their family medicine doctor.

Participants

Participants will be recruited from 5 PHCUs. Family medicine doctors at these PHCUs will extract a list of potential participants from the information system and contact them by telephone. Each PHCU is expected to enroll 40 patients, corresponding to a total of 200 participants.

Inclusion Criteria

The participants will be selected according to the following criteria: diagnosis of T2D for at least 12 months; male; aged 55-70 years; glycated hemoglobin between 6.0% and 10.0%; not having started insulin therapy in the previous 6 months and/or sulfonylureas therapy in the previous 3 months; major complications of diabetes screened and controlled (diabetic retinopathy, diabetic nephropathy, and diabetic foot); no cardiovascular, respiratory, nor musculoskeletal contraindications to exercise; without symptoms of coronary artery disease; without limitations in gait or balance; nonsmokers at least for 6 months; not practicing supervised exercise for at least 6 months; independent living in the community; and availability for the exercise session schedule. Participants who fulfil the inclusion criteria will be invited to participate in the study and perform a treadmill cardiac stress test.

Exclusion Criteria

Individuals with issues identified in the cardiac stress test, namely asymptomatic cardiac or hemodynamic problems, will be excluded from the study.

Intervention and Control Groups

Participants assigned to the intervention group will enroll in a walking football exercise program and receive basic sports material (eg, sports bag, t-shirt, and sports shoes). The participants will be organized into 5 groups of 20 players in different time schedules. Each group will have 60-minute walking football exercise sessions, 3 times per week (nonconsecutive days), for 24 weeks (72 sessions).

Walking football sessions will be conducted on a football field and supervised by a football coach certified by the Union of European Football Associations and by a nurse.

The sessions will consist of strength and conditioning exercises, technical skill drills, and small-sided and conditioned walking football games, including warm-up and cool-down periods.

The participants from the intervention and control groups will be asked to maintain daily life routines (lifestyle-related physical activity and dietary pattern) and continue with usual care (diabetes consultations and pharmacological regimen). In Portugal, the usual care at a PHCU already includes brief counseling for physical activity and sedentary behavior [25].

Participants from the control group will also receive basic sports material (eg, sports bag, t-shirt, and sports shoes).

All activities, participation rules, project team members, and the sports facilities will be presented to participants and their families before starting the intervention.

Outcomes

The primary outcome is the difference in the change in glycated hemoglobin level between intervention and control groups after 6 months. Secondary outcomes include changes between groups in fasting blood glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, systolic and diastolic blood pressure, body mass index, waist circumference, fat-free mass, and fat mass.

Secondary outcomes also include the incidence of exercise-related injuries and adverse events, as well as the cost-utility of the walking football exercise program.

Assignment of Interventions

The principal investigator will use a computerized random number generator to randomize participants.

Each patient will have a unique patient study number, which will be given immediately by the randomization software (the latest version of Excel Office 365).

Family medicine doctors at each PHCU will invite patients for an appointment; then, family medicine doctors will provide information about the study, assess the availability for participation, and collect informed written consent. After consent, the participants will be invited to perform a treadmill cardiac stress test.

If still eligible after the stress test, the participants will be enrolled in the study by the research team, who will provide an opaque envelope with the codification previously generated for each participant; the participant will then open the envelope and check his allocation for the intervention or control group.

Blinding of the participants, health care professionals, and research team members will not be possible.

Data Collection

Data collection will have 3 main time points: baseline (before starting the study), 6 months (after the study ends), and every walking football exercise session. The descriptions of the variables assessed at baseline and the 6-month evaluation are presented in Table 1.

Table 1. Variables assessed at baseline and at the end of the study.

Variable	Method
Glycemic control	
Glycated hemoglobin	Venous blood analysis
Fasting blood glucose	Venous blood analysis
Blood lipid profile	
Total cholesterol	Venous blood analysis
LDL[a] cholesterol	Venous blood analysis
HDL[b] cholesterol	Venous blood analysis
Triglycerides	Venous blood analysis
Blood pressure	
Systolic blood pressure	Automatic digital sphygmomanometer
Diastolic blood pressure	Automatic digital sphygmomanometer
Anthropometric profile	
Body mass index	Formula
Waist circumference	Anthropometric tape
Body composition	
Fat mass	Bioelectrical impedance analysis
Fat-free mass	Bioelectrical impedance analysis
Habitual physical activity	Global Physical Activity Questionnaire score [26]
Dietary intake	3-day food record, 24-hour dietary recall analysis
Health-related quality of life	EQ-5D questionnaire [27]
Medication (number, type, and dosage)	Form

[a]LDL: low-density lipoprotein.

[b]HDL: high-density lipoprotein.

Before and after the study, habitual physical activity, dietary intake, health-related quality of life, and regular medication will be collected to be used as control variables. We will also collect sociodemographic characteristics at baseline.

At every exercise session, objective and subjective exercise intensity and enjoyment will be recorded for control purposes.

The descriptions of the variables to be assessed before, during, and after each exercise session are detailed in Table 2. Capillary blood glucose, blood pressure, and feet wounds will be assessed before the exercise session; objective exercise intensity will be recorded during the exercise session; subjective exercise intensity and enjoyment will be assessed at the end of the exercise session; and exercise-related injuries and adverse events will be evaluated during and after the exercise session if participants report symptoms or the nurse notices any issue.

Table 2. Variables assessed in each exercise session.

Variable	Method
Pre-exercise capillary blood glucose	Glucometer
Pre-exercise blood pressure	Automatic digital sphygmomanometer
Pre-exercise feet wounds	Self-observation
Exercise intensity	
Subjective	OMNI perceived exertion scale [28]
Objective	Heart rate and time-motion tracking
Exercise sessions enjoyment	Physical Activity Enjoyment Scale [29]
Exercise-related injuries and adverse events	Observational/clinical/self-reported

All personnel involved in the study — nurses, nutritionists, medical doctors, football coaches, and sports scientists — will receive training before baseline assessments. This aims to standardize procedures.

Specifically, the principal investigator will provide training to the other research team members regarding the clinical assessments and forms.

The Portugal Football School of the Portuguese Football Federation will provide training to football coaches to ensure the walking football program is administered in a similar way in the different centers and according to a predefined manual.

A sports scientist will monitor, in real time, internal (heart rate [HR]) and external (eg, distance covered, number of actions) workload and apply the OMNI perceived exertion scale in all sessions.

The nurse must have training in emergency procedures, be responsible for measurements at exercise sessions, manage and record exercise-related injuries and adverse events, follow-up with participants, and refer to health care facilities if necessary.

Procedures

Before each walking football session, the nurse present at the local sports facility will evaluate capillary blood glucose (Contour XT, Ascencia Diabetes Care, Basel, Switzerland) and blood pressure (M6 Comfort, Omron, Kyoto, Japan) for all participants. Furthermore, participants will self-observe the presence of feet wounds and report any to the nurse. These measurements aim to evaluate the baseline safety conditions before the exercise session.

The participants will be allowed to start the session only under the following conditions: (1) capillary blood glucose ≥100 and ≤300 mg/dL, (2) systolic blood pressure ≤200 mm Hg, (3) diastolic blood pressure ≤100 mm Hg, and (4) no foot wounds.

During and after sessions, capillary blood glucose, blood pressure, and feet will be evaluated if participants report related symptoms. An adverse event is considered if there are any of the following after reporting symptoms: capillary blood glucose <72 mg/dL (symptomatic hypoglycemia) or >300 mg/dL (symptomatic hyperglycemia), systolic blood pressure <100 mm Hg (symptomatic hypotension) or >160 mm Hg (symptomatic hypertension response), or foot wounds are observed [3,23]. Participants in these conditions will not return to the exercise session, and corrective measures will be applied when necessary (ie, hydration, glucose intake, rest).

Strains, sprains, and contusions will be considered musculoskeletal injuries. Falls, seizures, myalgias, headache, malaise, chest pain and discomfort, and other relevant events will be considered adverse events [22].

During the walking football program, exercise intensity will be monitored systematically in every session through HR and rating of perceived exertion (RPE). From the estimated HR reserve (HRR) [30], we will classify the exercise intensity using the method by Karvonen and Vuorimaa [31]: light intensity (30%-39% HRR), moderate intensity (40%-59% HRR), vigorous intensity (60%-89% HRR), and near-maximal to maximal intensity (≥90% HHR) [32]. During training sessions, all participants will use adjustable chest strap HR monitors, and HR will be recorded at 5-second intervals using short-range radio telemetry (Firstbeat Sports, Jyväskylä, Finland). Participants will classify subjective exercise intensity through RPE using the 11-point OMNI scale (from extremely easy [0 points] to extremely hard [10 points]) at the end of the session [28]. With this RPE scale, light intensity is considered as 3-4 points, moderate intensity as 5-6 points, vigorous intensity as 7-8 points, and near-maximal to maximal intensity as 9-10 points.

Data Analysis and Sample Size

The number of participants to be involved was defined to test the superiority of walking football compared with usual care, using intention-to-treat analysis. For a 1:1 ratio of the intervention and control groups, significance level of 5%, and

statistical power of 80%, a total of 162 participants will be needed to detect a mean difference of at least 0.35% in the primary outcome (glycated hemoglobin), based on previous meta-analyses [33,34]. Assuming the complete follow-up of at least 80% of the participants, a total of 200 participants will be enrolled.

We will use a 2-way (group*time) analysis of variance with repeated measures to compare the mean differences between intervention and control groups.

For the cost-utility analysis, we will calculate the walking football implementation costs compared with the usual care. Costs include technical training for the professionals involved, patients' medical assessments, material for capillary blood glucose and blood pressure evaluations, football equipment, sports facility rental, sports insurance, and payment to nurses and football coaches. The costs of the intervention and reported gains in quality of life (based on quality-adjusted life years) [27] will be used to calculate the incremental cost-utility ratio (ICUR). ICUR will be compared with the World Health Organization thresholds for health interventions based on per capita gross domestic product.

The amount of missing data is expected to be low considering the training of all the staff and the use of standardized procedures for data collection. No imputation is being planned.

Ethics and Dissemination

This study will follow the General Data Protection Regulation and be submitted to the Health Ethics Committee of the Northern Regional Health Administration, Portugal. All procedures will comply with the Declaration of Helsinki. Any protocol deviation will be reported.

All participants will provide informed consent after receiving a detailed explanation of the potential risks and benefits. They will also have research insurance to cover the risks associated with exercise practice and evaluations before and after the exercise program. All participants will have a codification number to be used in the evaluations (questionnaires and blood samples). All the data collected will be treated as confidential and strictly used for this project. Data storage will be anonymized. Only the principal investigator will have access to the data.

Participants can withdraw from the study at any time, without any prejudice to the care provided at their PHCU, and have the right to access personal data collected in person from the researchers.

Findings from this study will be submitted for publication in international peer-reviewed journals. The results will also be disseminated at national and international scientific meetings and in mass media press releases.

Results

The study protocol is being prepared to be submitted to the Health Ethics Committee of the Northern Regional Health Administration, Portugal. After approval, participant recruitment will start by family medical doctors in PHCUs in Porto's metropolitan area.

Discussion

Overview

The main goal of this study is to test the effectiveness of a walking football program for glycemic control and cardiovascular risk factors in middle-aged and older male patients with T2D.

To the best of our knowledge, this is the first study testing the effects of a walking football exercise program for these outcomes in this specific population. Also, the investigation proposed relies on robust methodology, with a large study sample.

We expect that the walking football program will be effective in improving diabetes control and cardiovascular risk factors. We also expect a low rate of exercise-related injuries and adverse events and a good cost-utility ratio, as observed in other studies testing the effect of physical activity on diabetes control [35-38].

Developing an effective program with a good cost-utility ratio may contribute to making walking football a sustainable intervention strategy for T2D control. In addition, it can be used by football clubs to offer these programs as a service to their communities, ultimately contributing to the sustainability of the intervention and scaling up the offer to population coverage.

Limitations

Some limitations need to be addressed: First, the lack of participant, health care professional, and elements of the research team's blinding may introduce bias that may affect the outcome assessment. Nevertheless, our primary outcome is an objective measure — glycated hemoglobin, measured by blood clinical analysis — which may reduce the impact on the lack of blinding.

Second, contamination may occur since randomization units are individuals and not PHCUs, and there is proximity in the geographical area for participants from each PHCU. However, education of all research members and participants towards contamination and clear information about the purposes of the trial may minimize its occurrence.

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Authors' Contributions

AB, RM, and JB conceived and designed the study. AB wrote the first version of the manuscript. JB, AS, PF, and RM critically revised the manuscript for relevant intellectual content. All authors approved the final version for submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The Standard Protocol Items: Recommendations for Interventional Trials checklist.
[DOC File , 124 KB - resprot_v10i11e28554_app1.doc]

References

1. IDF Diabetes Atlas 2019. International Diabetes Federation. URL: https://www.diabetesatlas.org/en/resources/ [accessed 2021-09-26]
2. Barreto M, Kislaya I, Gaio V, Rodrigues AP, Santos AJ, Namorado S, INSEF Research Group. Prevalence, awareness, treatment and control of diabetes in Portugal: Results from the first National Health examination Survey (INSEF 2015). Diabetes Res Clin Pract 2018 Jun;140:271-278. [doi: 10.1016/j.diabres.2018.03.052] [Medline: 29626582]
3. Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, et al. Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. Diabetes Care 2016 Nov 25;39(11):2065-2079 [FREE Full text] [doi: 10.2337/dc16-1728] [Medline: 27926890]
4. American Diabetes Association. 5. Facilitating Behavior Change and Well-being to Improve Health Outcomes: Standards of Medical Care in Diabetes-2021. Diabetes Care 2021 Jan;44(Suppl 1):S53-S72. [doi: 10.2337/dc21-S005] [Medline: 33298416]
5. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med 2020 Dec 25;54(24):1451-1462 [FREE Full text] [doi: 10.1136/bjsports-2020-102955] [Medline: 33239350]
6. Dempsey PC, Friedenreich CM, Leitzmann MF, Buman MP, Lambert E, Willumsen J, et al. Global Public Health Guidelines on Physical Activity and Sedentary Behavior for People Living With Chronic Conditions: A Call to Action. J Phys Act Health 2020 Dec 04;18(1):76-85. [doi: 10.1123/jpah.2020-0525] [Medline: 33276323]
7. Jarvie JL, Pandey A, Ayers CR, McGavock JM, Sénéchal M, Berry JD, et al. Aerobic Fitness and Adherence to Guideline-Recommended Minimum Physical Activity Among Ambulatory Patients With Type 2 Diabetes Mellitus. Diabetes Care 2019 Jul 21;42(7):1333-1339 [FREE Full text] [doi: 10.2337/dc18-2634] [Medline: 31221698]
8. Zhao G, Ford ES, Li C, Balluz LS. Physical activity in U.S. older adults with diabetes mellitus: prevalence and correlates of meeting physical activity recommendations. J Am Geriatr Soc 2011 Jan;59(1):132-137. [doi: 10.1111/j.1532-5415.2010.03236.x] [Medline: 21226683]
9. Mendes R, Dias E, Gama A, Castelo-Branco M, Themudo-Barata JL. Prática de exercício físico e níveis de atividade física habitual em doentes com diabetes tipo 2 – estudo piloto em Portugal. Revista Portuguesa de Endocrinologia, Diabetes e Metabolismo 2013 Jan;8(1):9-15. [doi: 10.1016/j.rpedm.2012.05.001]
10. Milanović Z, Pantelić S, Čović N, Sporiš G, Mohr M, Krustrup P. Broad-spectrum physical fitness benefits of recreational football: a systematic review and meta-analysis. Br J Sports Med 2019 Aug 25;53(15):926-939 [FREE Full text] [doi: 10.1136/bjsports-2017-097885] [Medline: 29371223]
11. Luo H, Newton RU, Ma'ayah F, Galvão DA, Taaffe DR. Recreational soccer as sport medicine for middle-aged and older adults: a systematic review. BMJ Open Sport Exerc Med 2018 Aug 09;4(1):e000336 [FREE Full text] [doi: 10.1136/bmjsem-2017-000336] [Medline: 30112181]
12. Barbosa A, Brito J, Figueiredo P, Seabra A, Mendes R. Football can tackle type 2 diabetes: a systematic review of the health effects of recreational football practice in individuals with prediabetes and type 2 diabetes. Res Sports Med 2021 Jun 22;29(3):303-321. [doi: 10.1080/15438627.2020.1777417] [Medline: 32567951]
13. Schmidt JF, Andersen TR, Horton J, Brix J, Tarnow L, Krustrup P, et al. Soccer training improves cardiac function in men with type 2 diabetes. Med Sci Sports Exerc 2013 Dec;45(12):2223-2233. [doi: 10.1249/MSS.0b013e31829ab43c] [Medline: 23669882]
14. de Sousa MV, Fukui R, Krustrup P, Pereira RMR, Silva PRS, Rodrigues AC, et al. Positive effects of football on fitness, lipid profile, and insulin resistance in Brazilian patients with type 2 diabetes. Scand J Med Sci Sports 2014 Aug 19;24(Suppl 1):57-65. [doi: 10.1111/sms.12258] [Medline: 24944132]
15. Dönmez G, Korkusuz F, Özçakar L, Karanfil Y, Dursun E, Kudaş S, et al. Injuries Among Recreational Football Players: Results of a Prospective Cohort Study. Clin J Sport Med 2018 May;28(3):249-254. [doi: 10.1097/JSM.0000000000000425] [Medline: 28727642]
16. FA revises laws of the game for walking football. The Football Association. 2018. URL: http://www.thefa.com/news/2018/oct/08/walking-football-revised-laws-of-the-game-081018 [accessed 2021-02-16]

17. Arnold JT, Bruce-Low S, Sammut L. The impact of 12 weeks walking football on health and fitness in males over 50 years of age. BMJ Open Sport Exerc Med 2015 Oct 08;1(1):bmjsem-2015-000048 [FREE Full text] [doi: 10.1136/bmjsem-2015-000048] [Medline: 27900112]
18. Cholerton R, Breckon J, Butt J, Quirk H. Experiences Influencing Walking Football Initiation in 55- to 75-Year-Old Adults: A Qualitative Study. J Aging Phys Act 2019 Dec 10;10:1-13. [doi: 10.1123/japa.2019-0123] [Medline: 31825889]
19. Harper LD, Field A, Corr LD, Naughton RJ. The Physiological, Physical, and Biomechanical Demands of Walking Football: Implications for Exercise Prescription and Future Research in Older Adults. J Aging Phys Act 2019 Dec 10;10:1-11. [doi: 10.1123/japa.2019-0330] [Medline: 31825890]
20. McEwan G, Buchan D, Cowan D, Arthur R, Sanderson M, Macrae E. Recruiting Older Men to Walking Football: A Pilot Feasibility Study. Explore (NY) 2019 May;15(3):206-214. [doi: 10.1016/j.explore.2018.12.001] [Medline: 30639074]
21. Reddy P, Dias I, Holland C, Campbell N, Nagar I, Connolly L, et al. Walking football as sustainable exercise for older adults - A pilot investigation. Eur J Sport Sci 2017 Jun 19;17(5):638-645. [doi: 10.1080/17461391.2017.1298671] [Medline: 28316258]
22. Barbosa A, Brito J, Costa J, Figueiredo P, Seabra A, Mendes R. Feasibility and safety of a walking football program in middle-aged and older men with type 2 diabetes. Prog Cardiovasc Dis 2020 Nov;63(6):786-791. [doi: 10.1016/j.pcad.2020.06.014] [Medline: 32634461]
23. Mendes R, Sousa N, Reis VM, Themudo-Barata JL. Prevention of exercise-related injuries and adverse events in patients with type 2 diabetes. Postgrad Med J 2013 Dec;89(1058):715-721. [doi: 10.1136/postgradmedj-2013-132222] [Medline: 24194555]
24. Chan A, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013 Feb 05;158(3):200-207 [FREE Full text] [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
25. Mendes R, Nunes Silva M, Santos Silva C, Marques A, Godinho C, Tomás R, et al. Physical Activity Promotion Tools in the Portuguese Primary Health Care: An Implementation Research. Int J Environ Res Public Health 2020 Jan 28;17(3):815 [FREE Full text] [doi: 10.3390/ijerph17030815] [Medline: 32012974]
26. Bull F, Maslin TS, Armstrong T. Global physical activity questionnaire (GPAQ): nine country reliability and validity study. J Phys Act Health 2009 Nov;6(6):790-804. [doi: 10.1123/jpah.6.6.790] [Medline: 20101923]
27. Ferreira LN, Ferreira PL, Pereira LN, Oppe M. The valuation of the EQ-5D in Portugal. Qual Life Res 2014 Mar 8;23(2):413-423. [doi: 10.1007/s11136-013-0448-z] [Medline: 23748906]
28. Utter AC, Robertson RJ, Green JM, Suminski RR, McAnulty SR, Nieman DC. Validation of the Adult OMNI Scale of perceived exertion for walking/running exercise. Med Sci Sports Exerc 2004 Oct;36(10):1776-1780. [doi: 10.1249/01.mss.0000142310.97274.94] [Medline: 15595300]
29. Teques P, Calmeiro L, Silva C, Borrego C. Validation and adaptation of the Physical Activity Enjoyment Scale (PACES) in fitness group exercisers. J Sport Health Sci 2020 Jul;9(4):352-357 [FREE Full text] [doi: 10.1016/j.jshs.2017.09.010] [Medline: 32768128]
30. Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. Journal of the American College of Cardiology 2001 Jan;37(1):153-156. [doi: 10.1016/s0735-1097(00)01054-8]
31. Karvonen J, Vuorimaa T. Heart rate and exercise intensity during sports activities. Practical application. Sports Med 1988 May;5(5):303-311. [doi: 10.2165/00007256-198805050-00002] [Medline: 3387734]
32. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, American College of Sports Medicine. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011 Jul;43(7):1334-1359. [doi: 10.1249/MSS.0b013e318213fefb] [Medline: 21694556]
33. Snowling NJ, Hopkins WG. Effects of different modes of exercise training on glucose control and risk factors for complications in type 2 diabetic patients: a meta-analysis. Diabetes Care 2006 Nov 25;29(11):2518-2527. [doi: 10.2337/dc06-1317] [Medline: 17065697]
34. Boulé NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. JAMA 2001 Sep 12;286(10):1218-1227. [doi: 10.1001/jama.286.10.1218] [Medline: 11559268]
35. Kumar AS, Maiya AG, Shastry BA, Vaishali K, Ravishankar N, Hazari A, et al. Exercise and insulin resistance in type 2 diabetes mellitus: A systematic review and meta-analysis. Ann Phys Rehabil Med 2019 Mar;62(2):98-103 [FREE Full text] [doi: 10.1016/j.rehab.2018.11.001] [Medline: 30553010]
36. Munan M, Oliveira CLP, Marcotte-Chénard A, Rees JL, Prado CM, Riesco E, et al. Acute and Chronic Effects of Exercise on Continuous Glucose Monitoring Outcomes in Type 2 Diabetes: A Meta-Analysis. Front Endocrinol (Lausanne) 2020 Aug 4;11:495 [FREE Full text] [doi: 10.3389/fendo.2020.00495] [Medline: 32849285]
37. Leal J, Ahrabian D, Davies MJ, Gray LJ, Khunti K, Yates T, et al. Cost-effectiveness of a pragmatic structured education intervention for the prevention of type 2 diabetes: economic evaluation of data from the Let's Prevent Diabetes cluster-randomised controlled trial. BMJ Open 2017 Jan 09;7(1):e013592 [FREE Full text] [doi: 10.1136/bmjopen-2016-013592] [Medline: 28069625]

38. Coyle D, Coyle K, Kenny GP, Boulé NG, Wells GA, Fortier M, et al. Cost-Effectiveness of Exercise Programs in Type 2 Diabetes. Int J Technol Assess Health Care 2012 Jul;28(3):228-234. [doi: 10.1017/s0266462312000256]

Abbreviations

HR: heart rate
HRR: heart rate reserve
ICUR: incremental cost-utility ratio
PHCU: primary health care unit
RPE: rating of perceived exertion
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
T2D: type 2 diabetes

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Protocol

Effect of Door-to-Door Screening and Awareness Generation Activities in the Catchment Areas of Vision Centers on Service Use: Protocol for a Randomized Experimental Study

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Abstract

Background: A vision center (VC) is a significant eye care service model to strengthen primary eye care services. VCs have been set up at the block level, covering a population of 150,000-250,000 in rural areas in North India. Inadequate use by rural communities is a major challenge to sustainability of these VCs. This not only reduces the community's vision improvement potential but also impacts self-sustainability and limits expansion of services in rural areas. The current literature reports a lack of awareness regarding eye diseases and the need for care, social stigmas, low priority being given to eye problems, prevailing gender discrimination, cost, and dependence on caregivers as factors preventing the use of primary eye care.

Objective: Our organization is planning an awareness-cum-engagement intervention—door-to-door basic eye checkup and visual acuity screening in VCs coverage areas—to connect with the community and improve the rational use of VCs.

Methods: In this randomized, parallel-group experimental study, we will select 2 VCs each for the intervention arm and the control arm from among poor, low-performing VCs (ie, walk-in of ≤10 patients/day) in our 2 operational regions (Vrindavan, Mathura District, and Mohammadi, Kheri District) of Uttar Pradesh. Intervention will include door-to-door screening and awareness generation in 8-12 villages surrounding the VCs, and control VCs will follow existing practices of awareness generation through community activities and health talks. Data will be collected from each VC for 4 months of intervention. Primary outcomes will be an increase in the number of walk-in patients, spectacle advise and uptake, referral and uptake for cataract and specialty surgery, and operational expenses. Secondary outcomes will be uptake of refraction correction and referrals for cataract and other eye conditions. Differences in the number of walk-in patients, referrals, uptake of services, and cost involved will be analyzed.

Results: Background work involved planning of interventions and selection of VCs has been completed. Participant recruitment has begun and is currently in progress.

Conclusions: Through this study, we will analyze whether our door-to-door intervention is effective in increasing the number of visits to a VC and, thus, overall sustainability. We will also study the cost-effectiveness of this intervention to recommend its scalability.

Trial Registration: ClinicalTrials.gov NCT04800718; https://clinicaltrials.gov/ct2/show/NCT04800718

International Registered Report Identifier (IRRID): DERR1-10.2196/31951

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KEYWORDS

study protocol; randomized intervention study; vision centers; door-to-door screening; cost-effectiveness; sustainability; screening; awareness; vision; eye; utilization; usage; India; rural; intervention; engagement; scalability

Introduction

Primary care is the cornerstone of the global health system and is rooted in the 1978 Declaration of Alma Ata [1], encompassing disease prevention and the equitable distribution of health care [2]. Derivative to this, the Global Action Plan for Universal Eye Health [3] emphasizes the importance of providing basic eye care to all individuals, and the communities they constitute, at affordable rates [4]. An application of the bottom-up approach, primary eye care is an integral part of comprehensive eye care: promoting eye health, increasing accessibility, and linking individuals and the community to health care systems [5-8].

In India, primary eye care is delivered through two main mechanisms:

- Transient screening camp-scheduled, community-based activities that screen patients, provide glasses to those requiring them at the camp itself, and transport those needing surgery to the base hospital [9].
- Permanent facilities: Vision centers (VCs) with catchment areas of roughly 50,000 people, mostly located in rural areas and urban slums and accessible by public transport [10,11]. They refract, diagnose, and treat minor eye conditions and refer cases needing further care to their nearest base hospital [12].

Globally, awareness regarding eye health [13], need-based demand [13], financial issues and cost [13,14], and poor communication from providers [14] are the major barriers to primary eye care use. The literature on barriers to primary eye care in India is limited but points to a lack of knowledge about eye diseases, detrimental social stigmas, low priority being accorded to eye problems, gender discrimination, unaffordability, a lack of perceived need, and immobility and dependence on escorts [15-18]. These barriers to the access and use of services have the potential to affect the overall operational sustainability of the VCs, affected in large part by the number of walk-in patients [19].

Our organization is a network of eye care delivery mechanisms based on the pyramidal model [10] and spread across North India. Currently, 36 VCs (9 urban and 27 rural) are under operation, raising awareness; providing refraction, recognition, and referral services to their catchment population; and increasing contact of those in need of services with doctors through teleophthalmology. For the majority of people, these primary eye care centers are the first point of contact when accessing or attempting to access eye care services. Moreover, gender differences have been established in the use of VC services, with the proportion of women among the walk-in patients being higher compared to men in urban VCs and lower in rural ones [12].

Thus, generating awareness, developing trust, and improving access to these VCs, amongst the entire catchment population they service, is essential not only for the overall sustainability of these centers but also to bring more and more people under the ambit of primary care delivery. Previously, a door-to-door screening model was posited to eliminate avoidable blindness [15]. This research protocol aims to study the effect of an intervention combining door-to-door screening with regular awareness activities in the catchment population on service use at VCs. The overall cost-effectiveness of such an intervention will also be analyzed.

Methods

Study Design and Process

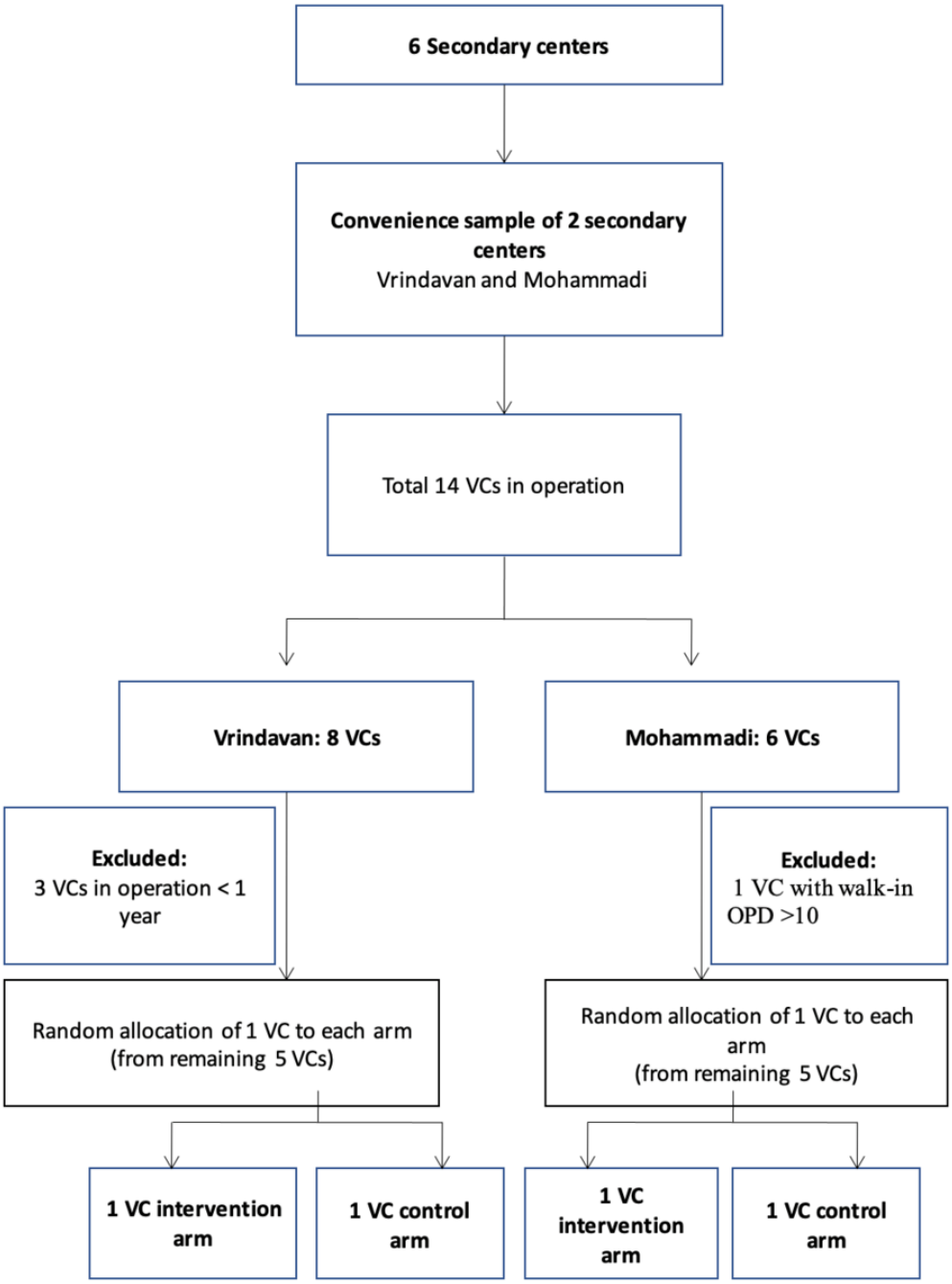
This study is a randomized, parallel-group experimental study in which we selected four VCs, two each in the intervention and control arms (one each from a particular operational area).

Our organization has six secondary centers, of which four are located in the state of Uttar Pradesh, namely Meerut, Mathura, Saharanpur, and Kheri. These regions have a total of 23 VCs operating in rural and semiurban areas, together serving around 1 million people. Of these four secondary centers, two were selected (Vrindavan in Mathura District and Mohammadi in Kheri District) for this study based on feasibility and the demographic profile of their catchment population.

The Vrindavan region has eight VCs delivering eye care services in its semiurban areas, while the Mohammadi region has six VCs (five rural and one semiurban). Most of these VCs have been operational for over 3 years. However, data from the previous year indicated that 80% of the VCs are suboptimal in their performance. The VCs performing suboptimally were listed. From a total of 10 VCs (5 in each region, meeting the inclusion/exclusion criteria), 2 were randomly selected from each region using the RAND function in Microsoft Excel (ie,

1 each for the control and the intervention arm). The process is illustrated in detail in Figure 1.

Figure 1. Selection process used to identify the study vision centers (VCs). OPD: outpatient department.



The VCs in the two blocks of Mathura District are located at Chhata and Raya, while the two VCs in the two blocks of Kheri District were located at Mitauli and Pashgaon. Due to the nature of the study, it was not possible to mask the field staff to the intervention.

Inclusion/Exclusion Criteria

The regional team gathered detailed information regarding all VCs operating in the Vrindavan and Mohammadi regions. VCs were included in the study based on the following inclusion criteria:

- Low performance (walk-in OPD ≤ 10 per day)
- Duration of operation > 1 year
- Presence of one VC in each arm from selected VCs

VCs with walk-in outpatient department (OPD) numbers greater than 10 per day and those in operation for less than 1 year were excluded.

Study Setting

Mathura District has a population of about 2.5 million, 70% of whom are resident in rural areas [20]. Kheri District has a population of around 4 million, of which 88% reside in rural areas [21].

Per our existing data, around 75% of the patients visiting our VCs in these 2 districts reside within 10 km of our VCs. The Chhata block, in Mathura, has 81 villages, with around 30 of

those being within 10 km of the VC. These 30 villages have a combined population of around 70,000. In contrast, the Raya block has 124 villages, with around 90 of these being within 10 km of the VC, having a combined population of around 130,000.

In Kheri District, the Mitauli block has 138 villages, of which 75 are within 10 km of the VC. The combined population of these villages is around 111,000. The Pashgaon block has 230 villages, with around 85 of these being within 10 km of the VC, having a combined population of around 110,000.

Sample Size

The average OPD attendance at the intervention centers is 7 per day at present. We expect to achieve 14 after the intervention, failing which, the intervention will not be considered a success. Therefore, the primary objective of the statistical analysis would be to estimate the average attendance, postintervention, with extreme precision, which will lead us to assess whether we have been able to achieve the target (14 per day, on average). We set the confidence interval (CI) to ±1 for the postintervention sample mean (the narrowest-possible CI in this case). To check whether at least 20 per day on average has been achieved, we expect a sample mean of at least 21 (ie, the CI will be 20-22). The number 20 has been determined based on a feasibility study conducted to project VC sustainability. We assume that the probability of the CI is 95% and the daily OPD attendance has a Poisson distribution. Thus, we expect that the postintervention daily attendance will have a Poisson distribution with a mean of at least 21. This implies that the variance of the distribution will also equal 21 (or more), and we want to estimate the mean with a 95% CI of ±1. This requires a minimum sample size of 81 days.

We used the following formula to calculate the sample size:

$$\text{Sample size} = (1.96^2/d^2) \times \text{Variance of the distribution}$$

where 1.96 is the 97.5 percentile point of the standard normal distribution and d is the length of the CI (on one side of the estimate). If d = 1 and variance = 21, we obtain sample size = 81. We set a target of 20 per day in the pre-CODIV-19 time, but due to the pandemic, we revised our desired target to 14 per day to consider the intervention a success. We persisted with the additional days in the sample size (instead of 58 days for a target of 14) to be able to estimate up to 14 per day OPD attendance with precision.

Intervention Arm

Our VC team includes a technical person (a trained vision technician) and a community health worker (a VC attendant). Although the vision technician is responsible for patient examination, the VC attendant assists the vision technician and carries out community engagement activities. In addition, each region has a VC coordinator to supervise all VCs in that region. The intervention will include door-to-door screening and awareness generation in 8-12 villages in the catchment area of the intervention VC. We will leave the villages adjacent to the VCs and instead approach a mix of near and distant villages within our catchment area. A list of surrounding villages (within 10 km) will be prepared by the VC coordinator and the VC attendant. The VC coordinator will meet each village leader to take permission for the door-to-door intervention survey to be carried out in the village. After having received the necessary permissions, a priority list of survey villages will be prepared to initiate the intervention.

The VC attendant will be trained to use the Peek acuity application [22] for measuring visual acuity and using the data collection software Taraka on Android platforms. They will also be trained to use the developed information, education, and communication (IEC) material. In the intervention villages, the VC attendant will go from door to door. During the screening, if any house is locked or family members are not available, the VC attendant will attempt to contact those missing at least three times. The VC attendant will explain the intervention and obtain verbal consent for participation in the survey. Household or family members who are unwilling or not interested to participate in the survey will also be recorded separately.

After obtaining verbal consent for the screening, the VC attendant will communicate regarding the need for eye care in general and share the IEC material. For each family member above 5 years of age, the visual acuity of each eye will be measured and recorded using the PEEK acuity application on a smartphone. Demographic data, ocular complaints, and information regarding any previous eye checkup will also be recorded in the Android application.

Any person with a visual acuity of <6/12 (cutoff) or other eye issues will be counseled and referred for a comprehensive examination to the VC. A referral slip will be provided to the patient when referred, mentioning the reason for referral. Referred patients' records will be accessible to the vision technician (optometrist) through the software. Patients reporting to the VC for a comprehensive checkup and treatment, due to the door-to-door intervention, will be recorded using vision center management software (VCMS). Any patient requiring surgical treatment or further care will be referred to the respective secondary center. Free cataract services will be provided to patients unable to afford the same. Follow-up of referred patients will be performed by the coordinators in the field.

Control Arm

The control arm VC will continue its routine awareness activities and health talk sessions in the community. The VC attendant will prepare a monthly activity plan and organize activities in the surrounding 8-10 villages. Persons with eye issues will be recorded and referred to the VC for further evaluation and treatment. Patients reporting to the VC will be registered in the VCMS. For surgical intervention or further care, patients will be referred to the respective secondary center. Follow-up of referred patients will be performed by the coordinators in the field.

A comparison of the activities of the community health workers in the two arms is summarized in Table 1. The activities will be the same in both the arms and will also be standardized in the same manner; only their mode and reach will be different.

Table 1. Comparison of activities of community health workers in the two study arms.

Serial number	Activity	Intervention arm	Control arm
1	• Meeting with key stakeholders	Yes	Yes
2	• Health talk sessions in community • Refer patients to VC	No	Yes
3	• Awareness activity through IEC distribution	Yes (door-to-door)	Yes (cluster meeting in village during visits)
4	• Permission for door-to-door survey intervention	Yes	No
5	• Door-to-door screening • Refer patients to VC	Yes	No

Project Timelines

The study period will be 12 months, of which 2 months will be spent preparing the study intervention and obtaining approvals, 3 months will be needed for preintervention work (ie, training the team, field preparation, finalizing the data collection format, and IEC development), and 4 months for the intervention and data collection; after data collection, the remaining 3 months will be used for data analysis and writing.

Data Collection, Management, and Analysis

Data Collection and Variables

We will collect both electronic and manual data for both study arms. In the intervention arm, field-level data (door-to-door surveys) will be captured through software, while field-level activity in the control arm will be manually recorded in the activity register. VC-level data will be extracted from the VCMS, which will contain data for both control and intervention VCs. In both arms, programmatic data will be collected, which will include data of the villages screened, door-to-door screening, walk-in OPD visits, those reporting after referrals from the field, and spectacles advised and their uptake, as well as referrals for cataract, specialty, and surgical follow-up (Figure 1 and Multimedia Appendix 1). Cost data will be collected for direct, indirect, and opportunity costs, such as rent, human resources, overheads, and community activities (Multimedia Appendix 2). We will also collect data for revenue from the OPD, spectacles, and surgeries done.

Most of the data for analysis will be directly extracted from the existing software at the VCs. The rest of the data pertaining to the cost will be entered, collected, and monitored as part of regular processes in the field. This will make the data collection process streamlined and integrated into the regular operations. Although the costs incurred in running any program may vary for different providers, we feel that the detailed checklists will help in disaggregating that data for use by different service providers.

Quality Assurance

There will be three sources of data in this research. The data from the door-to-door screening will be collected using a customized Android application, the data of patients visiting VCs will be captured through the VCMS, and the additional data pertaining to activities from the control VCs and the visits of various members of the staff will be collected in the registers.

Checks and balances have been built into the software to ensure completion of data collection. A comprehensive checklist has been prepared to standardize the manual data collection. Random visits will be made periodically to the field to monitor screening, awareness generation activities, and data collection. Data collected during the day will be uploaded to the cloud server at least once at the end of the day, and that would be available for review. Thus, the quality of data will be ensured by the clearly defined roles of the team members involved in the intervention, appropriate resource allocation, and regular meetings with the team members. A regular review process will be followed to maintain quality assurance of the collected data, and at least 10% of the collected data will be cross-checked/verified by field supervisors. Surgery-related data of the patients referred from VCs would be extracted from the electronic medical records of the secondary hospital. Data will be collated monthly as part of routine program monitoring and independently audited. The composition of the data-monitoring committee is provided as Multimedia Appendix 3.

No adverse events for the screener or the participants undergoing screening are anticipated, as services being provisioned are per standard hospital protocols and no experimental treatment is being given. Any complications in this scenario will be reported and dealt with per standard hospital policies.

Data Analysis

The collected data will further be tabulated and analyzed by each study arm: distance of the village, age, gender, eye issues, visual acuity, compliance with treatment (medicine, surgery, glasses), and revenue and expenditure of VCs. The difference from baseline in the number of walk-in patients, referrals, uptake of services, and costs involved in intervention will be analyzed. The Z test for proportions will be performed to compare the change in walk-in patients between the two arms. $P<0.05$ will be considered statistically significant. Subgroup analysis with respect to age and gender will also be carried out.

Cost-Effectiveness Analysis

Cost-effectiveness analysis and incremental cost-effectiveness analysis will be performed, and the incremental cost for every additional beneficiary attending the VC will be calculated. To calculate the increase in the number of patients, the average

number of patients visiting per day during the same months in the previous year will be subtracted from the average in the study period. A change in the control VCs, if any, will be further deducted from this before using this as the denominator for calculating cost-effectiveness.

Outcomes

The primary outcome for this study will be an increase in the number of walk-in patients at the VCs from baseline (7-8 walk-in patients to 14 per day after the intervention period of 4 months). The secondary outcomes will be uptake of spectacles and uptake of surgery among those advised. If the intervention proves effective in terms of the number of people visiting the VCs, cost-effectiveness will also be a secondary outcome.

Ethical Considerations

This study was approved by the institutional review board of Dr. Shroff's Charity Eye Hospital (IRB/2020/APR/54), has been registered as a clinical trial (NCT04800718) [23], and will follow the tenets laid out in the Declaration of Helsinki. Protocol amendments will be shared with all relevant parties via email, and approval will be sought again.

Data will be encrypted and kept confidential. These confidential data will be anonymized, and personal data will only be visible to those responsible for implementation. The final data set will only be accessible to the research team. Trial results will be disseminated via publication.

Results

Background work involved in planning the interventions and selecting VCs has been completed. Participant recruitment has begun and is currently in progress. We estimate the primary completion date (ie, the date on which participant enrollment ends) to be November 30, 2021, and the study completion date to be December 30, 2021.

Discussion

Importance of Principle Findings

To the best of our knowledge, there is no previous study assessing the impact of door-

to door intervention on the sustainability of VCs. VCs are evolving as an important model for primary eye care [7,10,19]. Any such model needs to be sustainable for it to be universally adopted. Uptake of glasses and uptake of surgery by patients are the major contributors to the sustainability of these VCs [24]. Both these parameters are dependent on the number of patients visiting the VC, and that will be assessed in our study.

Addressing the Barriers to Uptake of Services

In their study describing barriers to the uptake of eye care services among the rural population, Marmamula et al [17] reported a lack of felt need as the most important person-related barriers. Thus, when designing our intervention package, we have included awareness generation as one of the key components. Other barriers detected in that population are the absence of someone to accompany, lack of accessibility, and affordability. Taking the preliminary screening to people's doors in our intervention should manage, to some extent, the barriers to accessibility and the absence of an accompanist. We have also made the first examination at the VCs, free of cost for those reporting after a preliminary screening.

Cost-Effectiveness of the Model

In addition to evaluating the effect on the number of patients visiting the VCs, our study will provide evidence for the cost-effectiveness of such an intervention. Although community engagement has been established as an important element of primary care [1], the evidence for the cost-effectiveness of a door-to-door screening model will help in decision making regarding the scalability of such an intervention.

Generalizability of the Results

In India, like in many low-to-middle-income countries, the majority of the population resides in rural areas [25]. With an unequal distribution of doctors, including ophthalmologists, in rural locations [26], the need for primary care is greater there. All the VCs included in our study belong to such locations; thus, the learning can be used in other similar settings.

Limitations

Although we randomly selected the VCs from our two operational regions, the fact that we operate only in North India can be one limitation of our study. We had planned this study before the COVID-19 pandemic, and even after reasonable delay due to the unrelenting nature of the pandemic, we plan to start this study during the ongoing pandemic. Due to this, the target for the number of patients visiting the VCs has reduced. Although the conditions may not be near normal during data collection, we do not anticipate any difference in the way in which the intervention and control VCs would be affected by the prevalent conditions. Due to the nature of the intervention, it is not possible to mask the personnel on ground, and this may bring in some short-term behavior change, which may not be sustained. Another limitation of our study would be the short duration of data collection following the intervention. To analyze the long-term impact of the intervention, another study will be planned subsequently in case the results of this study show a positive impact.

Conclusion

We believe our results will provide evidence for the impact of the door-to-door screening model of community engagement, on VC sustainability. The cost-effectiveness analysis would help the community care organizations like us to decide the feasibility and scalability of such an intervention.

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Authors' Contributions

Conceptualization, methodology, project administration, supervision, writing—review and editing, SS; project administration, methodology, validation, writing—original draft, AC; methodology, writing—original draft, IS; data curation, formal analysis, validation, GG; data curation, validation, BS; conceptualization, writing—review and editing, PR; conceptualization, methodology, writing—review and editing, RS; supervision, validation, SG; supervision, validation, KB; conceptualization, supervision, validation, GM. All authors have read and approved the manuscript. No professional writers were used.
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Conflicts of Interest

None declared. The data-monitoring committee is independent of the funder and has no competing interests.

Multimedia Appendix 1
Data to be collected for the two study arms.
[DOCX File , 17 KB - resprot_v10i11e31951_app1.docx]

Multimedia Appendix 2
Data to be collected for calculating cost.
[DOCX File , 15 KB - resprot_v10i11e31951_app2.docx]

Multimedia Appendix 3
Data-monitoring committee.
[DOCX File , 24 KB - resprot_v10i11e31951_app3.docx]

References

1. World Health Organization. WHO Called to Return to the Declaration of Alma-Ata. URL: https://www.who.int/teams/social-determinants-of-health/declaration-of-alma-ata [accessed 2021-04-05]
2. Starfield B, Shi L, Macinko J. Contribution of primary care to health systems and health. Milbank Q 2005 Sep;83(3):457-502 [FREE Full text] [doi: 10.1111/j.1468-0009.2005.00409.x] [Medline: 16202000]
3. World Health Organization. Universal Eye Health: A Global Action Plan 2014?2019. URL: https://www.who.int/blindness/actionplan/en/ [accessed 2021-04-05]
4. Khan MA, Soni M, Khan MD. Development of primary eye care as an integrated part of comprehensive health care. Community Eye Health 1998;11(26):24-26 [FREE Full text] [Medline: 17492028]
5. Murthy G, Raman U. Perspectives on primary eye care. Community Eye Health 2009 Mar;22(69):10-11 [FREE Full text] [Medline: 19506714]
6. Gilbert C. The importance of primary eye care. Community Eye Health 1998;11(26):17-19 [FREE Full text] [Medline: 17492025]
7. Misra V, Vashist P, Malhotra S, Gupta SK. Models for primary eye care services in India. Indian J Community Med 2015;40(2):79-84 [FREE Full text] [doi: 10.4103/0970-0218.153868] [Medline: 25861167]
8. World Health Organization. Strategies for the Prevention of Blindness in National Programmes. 1997. URL: https://apps.who.int/iris/bitstream/handle/10665/41887/9241544929.pdf?sequence=1 [accessed 2021-04-05]
9. Community Outreach Initiatives for High Quality, Large Volume, Sustainable Cataract Surgery Programmes. Aravind Eye Hospitals, Postgraduate Institute of Ophthalmology Lions Aravind Institute of Community Ophthalmology and Seva Foundation.
10. Rao G, Khanna R, Athota S, Rajshekar V, Rani P. Integrated model of primary and secondary eye care for underserved rural areas: the L V Prasad Eye Institute experience. Indian J Ophthalmol 2012;60(5):396-400 [FREE Full text] [doi: 10.4103/0301-4738.100533] [Medline: 22944748]
11. World Health Organization. Blindness and Vision Impairment. URL: https://www.who.int/news-room/fact-sheets/detail/blindness-and-visual-impairment [accessed 2021-04-05]

12. Sabherwal S, Sood I, Garg G, DasGupta S, Nagappan S, Reddy P, et al. Gender-Inequity in Eyecare: Variation by Service Level and Location in North India. IndianJPublic HealthRes Dev. URL: https://doi.org/10.37506/ijphrd.v11i7.10183 [accessed 2021-05-21]
13. Hayden C, Trudinger D, Niblett V, Hurrell D, Donohoe S, Richardson I, et al. Access to Primary and Secondary Eye Care.: RNIB and Shared Intelligence URL: https://www.rnib.org.uk/knowledge-and-research-hub/research-reports/prevention-sight-loss/access-eye-care [accessed 2021-04-05]
14. Holley C, Lee P. Primary care provider views of the current referral-to-eye-care process: focus group results. Invest Ophthalmol Vis Sci 2010;51(4):1866-1872 [FREE Full text] [doi: 10.1167/iovs.09-4512]
15. Bhoosnurmath K. Hospital-based community eye health programme: a model for elimination of avoidable blindness on a sustainable basis. Community Eye Health 2017;30(98):S12-S15 [FREE Full text] [Medline: 30034112]
16. Kovai V, Krishnaiah S, Shamanna B, Thomas R, Rao G. Barriers to accessing eye care services among visually impaired populations in rural Andhra Pradesh, South India. Indian J Ophthalmol 2007;55(5):365-371 [FREE Full text] [doi: 10.4103/0301-4738.33823] [Medline: 17699946]
17. Marmamula S, Khanna RC, Shekhar K, Rao GN. A population-based cross-sectional study of barriers to uptake of eye care services in South India: the Rapid Assessment of Visual Impairment (RAVI) project. BMJ Open 2014 Jun 12;4(6):e005125-e005125 [FREE Full text] [doi: 10.1136/bmjopen-2014-005125] [Medline: 24928590]
18. Dandona R, Dandona L, Naduvilath T, McCarty C, Rao G. Utilisation of eyecare services in an urban population in southern India: the Andhra Pradesh eye disease study. Br J Ophthalmol 2000 Jan;84(1):22-27 [FREE Full text] [doi: 10.1136/bjo.84.1.22] [Medline: 10611094]
19. Khanna RC, Sabherwal S, Sil A, Gowth M, Dole K, Kuyyadiyil S, et al. Primary eye care in India: the vision center model. Indian J Ophthalmol 2020 Feb;68(2):333-339 [FREE Full text] [doi: 10.4103/ijo.IJO_118_19] [Medline: 31957722]
20. Census 2011. Mathura District. URL: https://www.census2011.co.in/census/district/516-mathura.html [accessed 2021-04-05]
21. Census 2011. Kheri District. URL: https://www.census2011.co.in/census/district/524-kheri.html [accessed 2021-04-06]
22. Bastawrous A, Rono HK, Livingstone IAT, Weiss HA, Jordan S, Kuper H, et al. Development and validation of a smartphone-based visual acuity test (Peek acuity) for clinical practice and community-based fieldwork. JAMA Ophthalmol 2015 Aug 01;133(8):930-937 [FREE Full text] [doi: 10.1001/jamaophthalmol.2015.1468] [Medline: 26022921]
23. National Library of Medicine (U.S.). Increasing Vision Center Service Utilization. Identifier NCT04800718. 2021. URL: https://www.clinicaltrials.gov/ct2/show/NCT04800718?term=NCT04800718&recrs=ab&draw=2&rank=1 [accessed 2021-04-12]
24. Seva. Sustainability. URL: https://www.seva.org/site/SPageServer/?pagename=programs/sustainability [accessed 2021-04-11]
25. Census 2011. Population Census 2011. URL: https://www.census2011.co.in/ [accessed 2021-04-06]
26. Thomas R, Paul P, Muliyil J. Glaucoma in India. J Glaucoma 2003 Feb;12(1):81-87. [doi: 10.1097/00061198-200302000-00016] [Medline: 12567118]

Abbreviations

CI: confidence interval
IEC: information, education, and communication
OPD: outpatient department
VC: vision center
VCMS: vision center management software

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Protocol

mHealth for Anemia Reduction: Protocol for an Entertainment Education–Based Dual Intervention

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Abstract

Background: More than half of the women of reproductive age (aged 15-49 years) are anemic in India. The uptake of and adherence to iron folic acid (IFA) supplements remain low despite sustained efforts to increase their use. With India's burgeoning digital environment, mobile phones offer a potential medium for increasing their uptake, especially when combined with interactive voice messages that deliver entertaining stories infused with norms-based educational messages.

Objective: This study aims to investigate whether a norms-based entertainment education mobile health intervention can increase self-efficacy for IFA adherence among women of reproductive age in Odisha, India.

Methods: Mobile reduction in anemia through normative innovations (mRANI) is a randomized 2-arm study that includes assessments before and after the intervention. All study participants will be recruited from the intervention arm of the parent reduction in anemia through normative innovations trial only. Although the usual practice is to randomize participants either to a treatment arm or a usual care control arm, we will assign the mRANI control group to another entertainment education–based treatment group that is designed to improve bystander intervention to reduce violence against women. Data collection for the mRANI study is embedded in the parent trial and will include baseline and end line assessments. The primary outcomes are self-efficacy for IFA adherence and violence against women–related bystander intervention. The inclusion criteria for the mRANI study are participation in the parent trial and phone ownership. Women (approximately n=400) who meet the mRANI inclusion criteria will be randomly assigned to the IFA arm or the bystander arm. Ordinary least squares regression with robust SEs will be conducted to assess between-group comparisons at the end line. A mediation analysis will be conducted to examine whether social norms and interactivity mediate the relationship between intervention exposure and primary outcomes in both arms. Real-time monitoring data will offer insights into intervention receptivity and audience engagement.

Results: Data collection for the mRANI study is integrated within the parent trial. Household surveys were conducted between February and March of 2021. Responses on the mRANI study's primary and secondary outcomes were collected from 381 participants. The data analysis is expected to be completed by October 2021.

Conclusions: This study will provide evidence on whether a mobile health norms–based entertainment education intervention can increase self-efficacy for IFA adherence and violence against women–related bystander intervention.

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KEYWORDS

mHealth; interactive; voice response; entertainment; education; rural; anemia; bystander; violence against women

Introduction

Endemic Anemia Among Women of Reproductive Age

More than half of the women of reproductive age (aged 15-49 years) in Odisha, India, are anemic [1]. Low dietary iron intake, reduced iron absorption, and iron loss contribute to iron deficiency among women of reproductive age [2]. Anemia diminishes work productivity [3,4], increases the risk of adverse birth outcomes [5], and hinders the healthy development of children of pregnant mothers with anemia [6]. It is often not explicitly identified by women, but they do report high levels of fatigue [3]. The reduction in anemia through normative innovations (RANI) project [2] investigates the potential of an adaptive, multilevel social norms–based behavior change intervention to reduce anemia among women of reproductive age in Odisha.

The RANI project targets nonpregnant women who are currently underserved by the government's anemia reduction programs. Various government initiatives in India (eg, National Nutritional Anemia Control Program, National Iron Plus Initiative, and Anemia Mukt Bharat) provide iron syrup to infants and iron tablets to both adolescent girls in schools and pregnant women linked with the health system. Non–school-going women of reproductive age and those not pregnant are neglected in most national and state programs, although they are listed as government priority populations. Research on this group is also scant: for example, the Indian National Family Health Survey collects data only for pregnant women [1,7]. Adherence to the recommended iron folic acid (IFA) regimen is low even among pregnant women specifically targeted by various government programs. The 2015-2016 National Family Health Survey found that 91% of mothers reported receiving IFA supplements; however, only 30.3% reported consuming them for ≥100 days during pregnancy [1].

Considering these insights, the RANI project has adopted a social norms–based approach for improving IFA uptake and adherence. The strategy includes the following: (1) participatory learning delivered through in-person activities and games; (2) a series of tablet- and computer-based health communication videos that target various audiences (pregnant women, nonpregnant women, husbands, and mothers-in-law), followed by discussion sessions; and (3) monthly community-based testing of hemoglobin levels of 15 women in each village, followed by a discussion about trends in anemia and village-level comparisons (based on the hemoglobin readings) with neighboring communities. A full protocol of the intervention and evaluation design is published elsewhere [2], as is the process used to develop the intervention from formative evaluation findings (Table 1) [7].

Table 1. Intervention components, exposure, and sample size.

Group	Exposure	Components	Sample size, n
RANI[a] control	Usual care	None (usual care)	2000
RANI treatment, not in mRANI[b]	All RANI treatment components	Interactive learning sessions, RANI communication videos, and hemoglobin testing	1700
RANI treatment+mRANI treatment (mIFA[c])	All RANI treatment components+entertainment education and mRANI IFA[d] adherence arm	All components in RANI treatment that are not in mRANI+entertainment education story and mHealth[e] anemia intervention	206
RANI treatment+mRANI control (mBI[f])	All RANI treatment components+entertainment education and mRANI bystander intervention arm	All components in RANI treatment, not in mRANI+entertainment education story and mHealth bystander intervention	205

[a]RANI: reduction in anemia through normative innovations.

[b]mRANI: mobile reduction in anemia through normative innovations.

[c]mIFA: mobile iron folic acid.

[d]IFA: iron folic acid.

[e]mHealth: mobile health.

[f]mBI: mobile bystander intervention.

Emergence of a Dual Burden of Anemia and Violence Against Women

In the formative evaluation phase, the RANI project sought to identify key issues faced by women in Odisha that would shed light on their anemia-specific behaviors. A primary theme that emerged was the role of gender norms, which illustrated the multiple ways through which women experienced social, structural, and individual-level disadvantages and barriers [7]. Unprompted by the research team, a key issue that respondents brought up was the high level of violence against women in their communities.

Violence against women is a global problem, with more than 1 in 3 women worldwide reporting physical or sexual violence by an intimate partner or nonpartner [8-11]. This estimate precludes violence against women that manifests in other forms, such as gender-based household or familial violence and maltreatment and emotional or economic domestic violence [11-14]. Lived experiences of multiple forms of violence toward women are especially egregious in India, where approximately 1 out of 2 women report having survived physical violence, experienced psychological abuse, or experienced multiple forms of violence [11-15]. Similarly, in rural Odisha, 2 out of 5 women have reported various forms of violence directed toward them [16]. Self-disclosure of violence to a friend or relative is far

more commonplace (40%) than formal sources of support (7%) [13,17]. Most occurrences of violence against women continue to be undisclosed because of stigma and fear of reprisals [13,17]. Because of lax enforcement of extant laws, social and gender norms appear to condone widespread violence toward women [13,17-21]. As such, interventions that focus on societal and collective transformation (eg, bystander interventions) by influencing inequitable social and gender norms to reduce violence against women are necessary [13,17-21]. Although the RANI project was not explicitly funded to address this issue, as we note in the section below, we have found a creative way to incorporate it into our intervention design.

Mobile RANI: Bridging the Gap With Mobile Health Infused With Entertainment Education

Recent years have seen tremendous growth in both the scope and number of mobile health (mHealth) interventions worldwide, especially in low-resource settings [22]. Many mHealth programs have demonstrated potential for improving a variety of health outcomes related to sexual and reproductive health, maternal and child health, and medication adherence in urban and rural settings in several countries in Asia [23-25] and Africa [26]. However, a dearth of high-quality trials in low-resource settings limits evidence of their efficacy, which is a key barrier for institutional adoption and uptake of digital health solutions [22,27].

India is one of the largest and fastest growing markets for information and communication technologies, with 1.2 billion phone and internet subscriptions, respectively [28]. To the best of our knowledge, only 2 prior mHealth interventions have been conducted to promote IFA adherence in India. They also focused only on pregnant women with anemia, and thus, the vast majority of women of reproductive age remained neglected [29]. One of these efforts used personalized automated voice calls from health care providers [29], whereas the other relied on live calls [30]. Both studies not only demonstrated the potential of using voice calls as a medium for promoting IFA adherence but also highlighted a number of inherent challenges. The most critical challenge faced by Pai et al [29] was the inability to retain program participants, which led to nonsignificant changes in IFA adherence despite a positive trend. To maximize retention, they recommended increasing participant involvement in addition to appealing to the listener's self-efficacy or perceived ability to adhere to IFA. Studies in the field of behavior change have also shown the important role that self-efficacy can play in predicting behaviors; people are most likely to engage in a behavior when they feel confident that they can do so in the face of barriers [31].

Following these recommendations, the mobile RANI (mRANI) study will center its efforts on improving self-efficacy for IFA adherence as one of its primary goals. We have powered our mRANI study for this outcome as well. As described below, the control arm for the mRANI study is another intervention that focuses on reducing violence against women by promoting bystander intervention, which also uses self-efficacy as its outcome.

Conceptual Background

Our overall approach is anchored in the entertainment education (EE) literature [32,33]. The idea behind an EE approach is that when people are being entertained by media, their defenses against persuasive attempts are significantly lower (than they would be while viewing an appeal explicitly trying to change their attitude or behavior). This provides interventions with an entrée for embedding health-related information in the main storyline. EE is rooted in an oral and performing arts tradition, and its research and application have evolved in parallel with the ongoing movement for digital innovation and social equity and change [32,33]. It leverages the power of narratives and storytelling to exact a transformative effect on its audiences [34]. Interventions are most commonly delivered via soap operas on television or radio, commercial music, and music videos. Comic books, films, news media, radio talk shows, mobile vans, and telephone hotlines also serve as supplementary channels [33].

As the research and practice of EE has evolved, so has the theoretical scholarship focused on understanding how it works [34]. Scholars are expanding beyond individual factors, such as the direct effects of role modeling or observational learning, and turning their attention to the influence of social norms and social consequences on EE effects [32,34-38]. On the basis of empirical evidence, many such programs have successfully transformed social norms related to tissue and organ donation in Korea [34,35], gender norms related to sexual and reproductive health in 6 states within India [36], and stigma related to HIV/AIDS [35-38]. Building on the efficacy of these prior studies, the mRANI study will run an EE mHealth program delivered exclusively via mobile phones to shift social norms related to IFA consumption and promote self-efficacy for IFA adherence.

Another component of the intervention we explore in this study is the role of interactivity in EE. We propose two competing mechanisms of change that we will test in this project. On the one hand, when the program promotes interactivity, user engagement with the content is expected to increase [39], with greater educational impact. On the other hand, interactivity can serve as a distraction from full immersion in story content, particularly when users are being entertained; this effect is more pronounced among those whose cognitive capacity has been compromised [40], as might be the case for people with anemia [41].

Objective and Hypotheses

The objective of this study is to investigate the ability of a norms-based EE mHealth intervention in increasing self-efficacy for IFA adherence among women of reproductive age in Odisha, India. Our hypothesis is that women in the intervention arm will display greater positive improvements in self-efficacy, pre- to postintervention, than women in the control arm.

In addition to testing this hypothesis, we will also ask questions about the underlying process of change. In particular, our secondary aims are two-fold: to determine (1) the extent to which social norms and (2) interactivity mediate the relationship between intervention exposure and study outcomes.

Methods

Reciprocal Control Double Intervention Study Design

The mRANI study is a randomized 2-arm study that includes assessments before and after the intervention. All study participants are recruited only from the intervention arm of the parent RANI trial (the trial itself has a usual care control group and a social norms–based treatment group, see the study by Yilma et al [2] for the study protocol). Hence, we will randomize a subset of women in the parent intervention arm to either the treatment or control arm of the mRANI study. This design results in the following four groups: (1) the usual care control group (from the parent study arm) in which no RANI activities will occur, (2) the RANI intervention group not involved in the mRANI trial, (3) the RANI intervention group in the mRANI control arm, and (4) the RANI intervention group in the mRANI treatment arm. This allocation and each group's exposure to the intervention components are shown in Table 1.

In this study, we introduce an innovative approach. Although the usual practice is to randomize participants either to a treatment arm or to a usual care control arm (this is also the design of the parent RANI trial), we will assign the mRANI control group to another EE-based treatment group designed to improve bystander intervention to reduce violence against women. We will call this the reciprocal control double treatment (RCDT) design. In this RCDT design, the treatment group for one intervention (mobile iron and folic adherence [mIFA] to improve IFA consumption self-efficacy) will serve as the control group for the other intervention (mobile bystander intervention [mBI] to improve bystander intervention self-efficacy), and vice versa.

The decision to center the second arm on bystander intervention (as opposed to another health issue) was based on two considerations. First, anemia and violence against women are empirically unrelated [42], which provides independence between the 2 arms. Second, violence against women is a significant public health issue in Odisha [16]—an issue that came up spontaneously in our formative assessment. Hence, incorporating this issue as an alternative intervention arm in our study seemed appropriate.

Taking this RCDT design into account, the hypothesis we proposed earlier will be tested by comparing changes from baseline to end line in self-efficacy to take IFA tablets in the treatment arm with the corresponding change in bystander self-efficacy to intervene in the control arm (and vice versa).

Study Setting

The RANI project is currently underway in 2 blocks (administrative units below the district) in the Angul district of Odisha, India [2]. Most of our residents (83%) live in rural areas and are Hindu (94%) [43]. Anemia prevalence is higher among women with less education and those who belong to scheduled tribes [1]. Approximately two-thirds of women in Odisha are literate [43]. Anemia prevalence (50%) for Angul is similar to the state of Odisha and the overall countrywide anemia prevalence [1]. Likewise, according to recent estimates from a systematic review on violence against women in India, 30% of women reported having experienced multiple forms of abuse within the past year [11-15].

Development and Implementation of mRANI

Overview

The mRANI intervention was developed based on the literature as well as quantitative analyses conducted using the RANI study's formative and baseline surveys. Using these data, we developed a mobile ownership and user profile and identified an optimal intervention delivery channel. We first conducted a feasibility analysis to determine whether a phone-based intervention would be viable in our study sites. Our data from baseline assessments (n=1874) of the parent RANI trial revealed that 43.97% (824/1874) of women owned mobile phones, and 42.63% (799/1874) of those who did not outright own a mobile phone could borrow one from a close family member with permission. Only 13.39% (250/1874) of our study participants were classified as those without access to a mobile phone. Accounting for these structural limitations, to be eligible for the mRANI study, participants have to be mobile phone owners with an active phone line.

We also conducted formative research in the form of qualitative story testing to select an overall storyline for both arms. Once the overall storyline was finalized, we developed subplots for each arm, integrated them into the broader storyline, and translated them into scripts. Finally, we conceptualized and developed interactive components. Audio recording and production of both EE) programs took place as a final step. Multimedia Appendices 1 and 2 detail the methods for story testing and the overall mRANI EE narrative.

EE Program Delivery

EE programs will be delivered with 13 episodes over 5 weeks, each lasting approximately 3-5 minutes. A total of 3 new episodes will be released every week. The exact day and time of delivery will be personalized according to participant preferences. Episodes will be delivered using an interactive voice response (IVR) system that can provide individualized messages to participants and interact with them through voice recognition or a touch-tone keypad. Prior studies have demonstrated the effectiveness of the IVR system in mHealth interventions, especially in rural settings with populations with limited educational and digital literacy [29,44,45]. Calls received by participants will be free of cost.

Story Manipulations

The overall story was kept similar across both mRANI arms—that is, the mIFA arm and the mBI arm. However, we inserted messages about either taking IFA tablets (in the mIFA arm) or intervening to prevent violence as a bystander (mBI arm) at strategically chosen points in the storyline. Multimedia Appendix 3 includes episode summaries for both arms that convey how the broader storyline remained the same for the 2 arms whereas the subplots purposefully deviated to integrate educational and theoretical concepts.

Interactive Components

Interactive components for the mRANI study have been conceptualized at 3 levels: program-driven, audience-driven,

and responsive interactions (Textbox 1). Program-driven interactions are initiated by the mRANI team and take place both before and during the intervention delivery. Examples of program-driven orientations include program jingles, episode teasers, and recaps. Audience-driven interactions are functionally built into the IVR system, allowing mRANI listeners to like and replay individual episodes. Finally, responsive interactions played at the end of each episode are also functionally built into the IVR system, allowing mRANI listeners to respond to prerecorded quizzes and questions on related prosocial themes, character identification, engagement and satisfaction with the narrative, and agreement with major plot points.

Textbox 1. Mobile reduction in anemia through normative innovations interactive components.

Program-driven interactions

- Entertainment education (EE) program release announcements
- EE program jingles
- EE program episode teasers
- EE program episode recaps

Audience-driven interactions

- Like or replay EE episodes on an interactive voice response system
- Call a mobile reduction in anemia through normative innovations hotline

Responsive interactions

- Quizzes and questions on the following:
- Topics related to prosocial themes
- Character identification
- Engagement with the narrative
- Agreement with major plot points
- Satisfaction with the narrative
- Perception of the most important problems in the village

Sample Size

We calculated the required sample size based on the findings of Constantino et al [46] in which they observed an improvement in self-efficacy in the treatment group (mean 3.30, SD 0.68) that was higher than that in the control group (mean 2.89, SD 0.6; $P<.001$). On the basis of similar assumptions, with a power of 0.8 and α of .05, our required sample size was 39 participants in each arm, which was rounded up to 40. To account for the subanalyses that we will conduct based on participants' caste (tribal, scheduled caste, and other), we increased the sample size to 40×3=120 participants in each arm, for a total of 240 participants.

Inclusion Criteria

All women of reproductive age who meet the inclusion criteria for the larger RANI trial will be eligible to participate in the mRANI trial. For the parent RANI trial, inclusion criteria included being a woman aged between 15 and 49 years, speaking Odiya, and residing in our study sites. In addition, for the mRANI trial subsample, we require participants to be mobile phone owners with an active phone line. Before the start of the study, data collectors tested the phone numbers provided by participants to investigate which phone lines were still active.

Randomization

Upon confirmation of the operating phone numbers (n=411), we listed eligible women in random order using a random number generator. We selected every other woman, starting with the first woman, for the IFA arm (206/411, 50.1%); similarly, we selected every other woman, starting with the second woman, for the violence against women arm (205/411, 49.9%).

Outcomes

The primary evaluation outcome for the mIFA arm is self-efficacy for IFA adherence. IFA use and anemia among women of reproductive age will also be measured as secondary outcomes. The primary evaluation outcome for the mBI arm is bystander self-efficacy in preventing violence against women.

Data Collection

The mRANI study data collection will be embedded within the overall RANI trial, similar to its intervention delivery strategy. Women between the ages of 15 and 49 years residing in treatment (n=2061) and control (n=2049) clusters have been recruited and randomly selected to participate in the impact evaluation of the RANI project. Baseline survey of the RANI participants took place in September 2019, and an end line survey was scheduled to take place in February 2021. Baseline data collection for the larger RANI project served as formative

data toward developing the mRANI EE programs and segmenting potential participants. The study team will conduct the impact evaluation for the mRANI study using data from end line assessments, controlling for baseline estimates.

The average time to complete a survey during the baseline and midline data collection was 55 minutes for all RANI measures and outcomes. The mRANI-specific modules take an average of 15 minutes to complete. Translation and back translation of the entire survey instrument, including mRANI-specific modules, will be conducted to check the accuracy of the questionnaire's translation. Pretesting of mRANI-specific modules will be conducted in nonsampled villages to ascertain reliability and appropriateness in this intervention context. A description of the data collection methods for the parent trial can be found in the parent trial's protocol [2].

Overall Measures

Demographics

We will collect demographic information from the RANI sample, including age, education, number of children, and caste or tribe membership.

mIFA Measures

Self-efficacy for IFA Adherence

Self-efficacy in adhering to an IFA regimen was conceptualized as the extent to which women feel confident that they can continuously take IFA when facing a number of relevant barriers. At baseline, we asked the participants the extent to which they agreed they (1) could take IFA every week when not pregnant, (2) believed they could easily take IFA, (3) could take IFA even if their husband or father does not want them to, and (4) could take IFA even if their mother-in-law or mother does not want them to. Responses were coded on a 5-point Likert scale and averaged into a scale for self-efficacy for adherence at baseline.

We will measure self-efficacy for adherence at the end line using a modified scale that includes additional barriers for adherence. Participants will be asked the extent to which they are confident they (1) will continue to take IFA every day (for pregnant women) and every week (for nonpregnant women), (2) are anemic, (3) are not anemic, and (4) receive advice from others to discontinue taking IFA. Barriers were identified during the formative research phase of the RANI project [7]. Women will also be asked the extent to which they are confident they can take IFA every day if they are pregnant (or every week if they are not pregnant), as these are the recommended doses for this population. The four items will be answered on a 5-point Likert scale, ranging from *strongly disagree* to *strongly agree*. Scores will be averaged into a scale for self-efficacy to adhere to IFA at the end line.

IFA-Related Social Norms

The RANI project operationalizes three forms of social norms: descriptive, injunctive, and collective. This study conceptualizes IFA-related descriptive norms as the extent to which women believe others regularly consume IFA. At baseline, women were asked, "what proportion of a) non-pregnant, b) pregnant and c) adolescent girls take IFA regularly?" Responses were recorded as *none*, *some*, *about half*, *most*, or *all* and averaged into a three-item scale for descriptive norms related to IFA. Similar questions will be asked at the end line. Women will also be asked new descriptive norms questions at the end line related to adherence: "How many a) non-pregnant, b) pregnant c) adolescent girls do not miss a dose or two of IFA?" and "How many a) non-pregnant, b) pregnant and c) adolescent girls continue to take IFA even after missing a dose or two?"

IFA-related injunctive norms were conceptualized as the extent to which women believe others expect them to consume IFA regularly. At baseline, women were asked, "how many women in your community think you should take IFA tablets regularly if you are pregnant?" as well as if they are not pregnant. Responses were recorded on the same scale as descriptive norms, ranging from *none* to *all*. In addition, women were asked the extent to which they agreed that their (1) mothers-in-law (or mothers) and (2) husbands (or fathers) think they should take IFA regularly if they are pregnant, as well as not pregnant. Responses were recorded on a 5-point Likert scale ranging from *strongly disagree* to *strongly agree*. All responses were averaged into a 6-item scale for injunctive norms related to IFA use. Similar measures will be collected at end line. Similar to descriptive norms, women will also be asked new injunctive norms questions at the end line relating to adherence. We will ask women, "Do you agree that your a) mother-in-law (or mother) and b) husband (or father) will think badly of you if you miss a dose?"

Previous studies have conceptualized collective norms as the prevalence of a focal behavior within a community [47], and it has been operationalized as the mean of the behaviors of everyone in one's community except that of the referent person, also called the *nonself mean* [48,49]. For the mIFA arm, we will operationalize collective norms as the prevalence of nonself mean of self-reported adherence to IFA supplements within a cluster, weighted by the number of women in the cluster who are also in the mRANI arm.

mBI Measures

Bystander Self-efficacy to Prevent Violence Against Women

This study conceptualizes bystander self-efficacy as the extent to which women feel confident in their ability to intervene when they witness another woman experiencing violence. At the end line, we will ask women the degree to which they agree with 8 statements stating, "If I witness violence against a woman, I am confident I could intervene by distracting (e.g. beating pots and pans); delaying (e.g. checking in after witnessing violence with the victim); delegating (e.g. seeking help from SHG group members or influential community leaders); documenting the violence (e.g. calling a hotline or recording on a cell phone) as a bystander." Responses will be scored on a 5-point Likert scale, ranging from *strongly disagree* to *strongly agree*, and averaged into an eight-item measure for bystander self-efficacy to prevent violence against women.

Violence Against Women–Related Social Norms

Violence against women–related descriptive norms were conceptualized as the extent to which women believe that others

intervene when witnessing violence in their community. We will measure descriptive norms by asking participants to report how many women in their community and friends would intervene if they saw a woman experiencing violence. Responses will be recorded as *none*, *some*, *about half*, *most*, or *all* and averaged across the two items.

Violence against women–related injunctive norms were conceptualized as the extent to which women believe that others expect them to intervene if they witness a woman experiencing violence. This study will operationalize these injunctive norms by asking participants the extent to which they agree with the following statement: "If you saw a woman experiencing violence, [referent] will expect you to intervene," in which the referent will be (1) most women in the community, (2) most friends, and (3) most women in self-help groups. We will record responses on a 5-point Likert scale ranging from *strongly disagree* to *strongly agree* and average them across the two items.

The operationalization of violence against women–related collective norms will mirror the mIFA arm, except that we will use intentions to engage in bystander intervention strategies in lieu of behaviors [48,49]. As such, for the mBI arm, we will operationalize collective norms as the prevalence of nonself mean intentions to engage in bystander intervention strategies within a cluster, weighted by the number of participants in the cluster who are also in the mBI arm.

Process Evaluation

Prior EE interventions leveraging IVR systems have reported success in their ability to facilitate and track audience engagement in real time and at scale [50]. Following their lead, monitoring of the mRANI intervention delivery and receptivity will occur in real time. Textbox 2 summarizes process evaluation measures and indicators for mRANI. Data on intervention dose, audience attention and involvement or engagement, character identification, narrative satisfaction and engagement, and perception of the most important problem in their village at the end of the EE program will be autogenerated by the IVR system immediately upon episode release and delivery. Process evaluation measures and indicators gauging recall and interpersonal communication related to mRANI will also be measured during the end line assessment.

Textbox 2. Mobile reduction in anemia through normative innovations process evaluation indicators.

Dose

- Number of calls sent
- Number of calls received
- Number of entertainment education (EE) episodes heard in full by the mobile reduction in anemia through normative innovations (mRANI) participants

Audience involvement or engagement

- Number of interactions with interactive components
- Number of likes on episodes
- Number of replays of episodes
- Number of calls and queries on the mRANI hotline
- Number of referrals to community and clinical linkages

Attention

- Number of seconds spent listening to episodes
- Number of seconds spent relistening to episodes
- Number of seconds spent listening to jingles
- Number of seconds spent listening to episode teasers
- Number of seconds spent listening to episode recaps

Recall

- Percentage of participants who accurately recall prosocial themes addressed in the episodes
- Percentage of participants who accurately recall mRANI characters
- Percentage of participants who accurately recall major mRANI plot points

Narrative satisfaction and engagement

- Percentage of participants engaged with the narrative
- Percentage of participants satisfied with the narrative

Character identification

- Percentage of participants who identify with Malati (protagonist) or Dolly (protagonist's daughter)

Most important problem in the village

- Percentage of participants who identify anemia or violence against women (depending on their assignment) as the most important problem at the end of the mRANI EE program

Ethical Considerations

Research Ethics Approval

The full RANI trial, including the mHealth intervention, has been reviewed and approved by appropriate institutions in the United States and India. These institutions include the George Washington University institutional review board in the United States; the Sigma Science and Research in New Delhi, India; and the Indian Council for Medical Research's Health Ministry's Screening Committee. The trial has also been registered with the Clinical Trial Registry of India.

Participant Orientation, Consent, and Confidentiality

Participants will be contacted with preintervention delivery for validation of phone numbers, followed by orientation and enrollment. The orientation and enrollment activities will take place a week before the mRANI intervention delivery commences. A structured script will be prepared to orient potential participants to mRANI and inform them of the objectives and intervention delivery channel and duration. For participants who express interest in enrolling in the mRANI study, we will obtain verbal informed consent. Next, we will note their preferences for the day and time to receive the mRANI EE programs. Participants will also receive contact information for additional questions and feedback.

Risk Mitigation Plan

Given the short duration and digital delivery format of this intervention, we anticipate low levels of exposure to adverse events for mRANI participants. In addition, considering that

the mRANI educational messages are strategically masked within an entertaining narrative tested in the field, we expect minimal sensitivity and negative reactions from our audience or their family members. However, the study team acknowledges that violence against women is a sensitive subject matter in Angul, Odisha. The mRANI study will adhere to the risk mitigation plan in place for the larger RANI trial [2]. Enrolled mRANI participant names and their data will be documented in an encrypted file. To maintain confidentiality, only 1 team member will have access to these data. To prevent unintended consequences for potential mRANI participants, the study team limited intervention delivery to women who are phone owners; thus, they have more agency and privacy related to their phone use. In addition, special consideration will be given to the delivery of EE programs during the day and time selected by the participant to ensure their privacy and security. The name of the mRANI study will appear on the caller ID when delivering new episodes so that participants and their family members will not face ambiguity tied to the source of the EE programs. Community and clinical referrals will be provided to participants who call the mRANI hotline. Local experts and consultants will triage requests beyond the scope and sphere of influence of the mRANI study. Finally, participants will have the option to opt out of mRANI EE programs at any time by contacting the mRANI hotline or by pressing 0 on their phone.

Statistical Analysis

The primary analyses planned for the mRANI impact evaluation will test the hypotheses that participants assigned to the treatment arm will have higher levels of self-efficacy in IFA adherence (primary end point) and self-reported IFA use (secondary end point) at follow-up and that participants assigned to the control arm will have higher levels of bystander self-efficacy for prevention of violence against women. We will test these three hypotheses in three ways. First, because participants are randomized to treatment and control groups, a simple comparison of those groups should produce an unbiased estimate of the treatment effect. Therefore, we will estimate, for each end point, the linear regression model $Yij = b1 + b2 \times TREATij + eij$, where i indexes the individual participant, j indexes the study cluster, and $b2$ is the treatment effect. We will estimate this model by using ordinary least squares regression but use robust standard errors to test the null hypothesis (H_0: b1=0) because of the nesting of participants in study clusters.

Although these analyses should produce unbiased estimates of treatment effects, they may miss key opportunities to increase statistical power and precision through two analytic elaborations. The first is to introduce cluster fixed effects to the model, which effectively results in a within-cluster comparison of the treatment and control group participants. As treatment assignment is within clusters, cluster and treatment assignments are orthogonal, so the addition of cluster fixed effects should increase statistical power and precision by reducing the residual error variance. In this case, the analytic model for each end point will be $Yij = aj + g1 \times TREATij + eij$, where aj is a vector of cluster fixed effects, and $g1$ is the treatment effect. As with the first modeling approach, we will estimate this model using ordinary least squares; however, in this case, the inclusion of cluster fixed effects obviates the need to use robust SEs.

Another opportunity to improve statistical power while retaining unbiased estimation is to control for pretreatment variables that are likely to be highly correlated with the primary and secondary end points. These include measures of the same variables taken before randomization: baseline and midline self-efficacy for serum hemoglobin levels, IFA adherence, and IFA use. Note that bystander self-efficacy for violence against women was not measured at baseline or midline and thus cannot be included as a covariate. In addition, sociodemographic variables assessed at baseline and midline, such as age, education, and parity, can also be considered for inclusion. We will choose covariates for inclusion based on their marginal associations with each end point. The resulting model for each end point will be $Yij = aj + d1 \times TREATij + Xij \times h + eij$, where aj is once again a vector of cluster fixed effects, Xij is a vector of select control variables assessed at baseline and midline, and $d1$ is the treatment effect. As with the second modeling approach, we will estimate this model using ordinary least squares with no need for robust SEs.

This approach will produce three estimates of the treatment effect for each end point: b1, g1, and d1. All are unbiased, and we expect them to be similar across the three specifications. The main difference we expect would be in the SEs, which we expect will be highest in the first and lowest in the third specification. For transparency, we will report the estimates from all three specifications for each end point.

To assess the extent to which social norms and interactivity mediate the relationship between intervention exposure and primary outcomes in both mIFA and mBI arms, we will use a structural equation model to estimate the effects of the intervention on the mediator variables, the effects of the mediators on the 2 self-efficacy variables (IFA use and bystander intervention), and the direct effect of the treatment arm on both self-efficacy variables. From this model, we will estimate the percentage of the intervention effect on each aspect of self-efficacy mediated by each of the mediators [51]. All analyses will be performed using Stata (StataCorp) for Windows, version 14.2 [52].

Results

Data collection for the mRANI intervention is integrated within the parent RANI trial. Household surveys collected responses for the primary and secondary outcomes of the mRANI study between February and March 2021. End line data were collected from all 381 (192/381, 50.4% women in the IFA treatment arm and 189/381, 49.6% women in the violence against women's control arm) study participants. Data analysis is expected to be completed by October 2021.

Discussion

Principal Findings

The primary aims of the mRANI intervention are three-fold. First, we wish to determine whether an intervention delivered through a rather thin medium, an IVR channel, can propel behavior change. By relying on a social norms–based theory

[21,47,53] as the underlying conceptual guide and an EE theme to capture listeners' attention, we believe we can improve participants' self-efficacy. In resource-constrained settings, where internet access is low, voice calls may be one of the most effective ways to reach women [54-56]. As shown by our mHealth user data, most women in these communities own basic phones, and voice messages may be an efficient way to reach them. This may be particularly true in these communities and other rural areas in India, as our formative research showed that women do all the household work and also often work outside the home to earn money. Therefore, their time is limited, and brief voice calls may be more convenient than in-person meetings for social behavior change interventions.

The second aim of the study is to determine whether embedding an mHealth trial within the intervention arm of a larger field trial can further add to the effects of the parent trial. We will use these data to inform the next iteration of the RANI intervention. Finally, we also wish to determine whether the reciprocal control double intervention design can yield meaningful results.

This study does have a few noteworthy limitations. First, the generalizability of our study is confined to women who are cell phone owners. Although ownership is increasing rapidly in India [28], only 43.97% of women in our sample are cell phone owners. It may be that the factors limiting ownership (including low socioeconomic status, being a member of a marginalized group, and lack of power in interpersonal relationships) also drive poor health. Study generalizability is also compromised as those participating in the parent RANI trial (who form the basis of our recruitment) may not be representative of the larger population. Despite these limitations, we envision robust internal validity, given the randomized nature and longitudinal components of the study design.

Dissemination

In spring 2021, at the end of the RANI evaluation, we will hold a virtual convening in Bhubaneswar, India (the capital of Odisha), to present the mRANI findings along with the main trial findings. We will invite key stakeholders from Angul, such as district officials, program planners, researchers, and policy makers working on anemia reduction efforts in Odisha. We will also disseminate findings locally back to the communities where the intervention will take place through smaller presentations and dissemination materials.

Conclusions

To our knowledge, an mHealth intervention has not been used to reduce anemia among nonpregnant women, the subpopulation that makes up the largest number of women with anemia [1,29]. As anemia continues to affect women's work productivity, overall health, and the health of future generations, it is critical to explore innovative ways to increase IFA use and reduce anemia levels. If mRANI proves to be effective, other districts and states within India and Southeast Asia may follow suit, thus reducing the overall global burden of anemia among women.

Finally, although the inception of this mRANI intervention predated the COVID-19 pandemic, the need to reach women via mobile phones rather than in-person settings is critical now more than ever. Given the uncertainty of when and how in-person interventions will unfold, contactless interventions are critical to be able to continue providing information to communities staying home. Furthermore, violence against women was rampant before the COVID-19 pandemic; however, research shows that the incidence is rising worldwide and specifically in India [57,58]. mRANI may provide an efficient, cost-effective medium to reduce this incidence and change social norms around bystander intervention against violence against women.

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Authors' Contributions

IP and RNR were responsible for the conception of the study, its objectives, the design, the rationale, the development of research questions, and the drafting and revising of the protocol. IP also provided digital health and monitoring and evaluation expertise. SB contributed to intervention delivery and development, data collection, recruitment, implementation, and risk mitigation procedures. HY contributed to the sampling plan, measures, and outcomes procedures. JBB contributed to statistical analysis procedures. ES contributed to the *Discussion* and *Dissemination* sections. All authors contributed to the drafting of the components of the protocol and its revision.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Extended details on story testing.
[DOCX File , 31 KB - resprot_v10i11e26252_app1.docx]

Multimedia Appendix 2
Overall mobile reduction in anemia through normative innovations entertainment education narrative.
[DOCX File , 30 KB - resprot_v10i11e26252_app2.docx]

Multimedia Appendix 3
Episode summaries for both mobile reduction in anemia through normative innovations arms.
[DOCX File , 35 KB - resprot_v10i11e26252_app3.docx]

References

1. National Family Health Survey (NFHS-4), India, 2015-16. In: International Institute for Population Sciences (IIPS) and ICF. Mumbai: IIPS; 2015.
2. Yilma H, Sedlander E, Rimal R, Pant I, Munjral A. The reduction in anemia through normative innovations (RANI) project: study protocol for a cluster randomized controlled trial in Odisha, India. BMC Public Health 2020 Feb 07;20(1):203 [FREE Full text] [doi: 10.1186/s12889-020-8271-2] [Medline: 32033546]
3. Horton S, Ross J. The economics of iron deficiency. Food Policy 2003 Feb;28(1):51-75. [doi: 10.1016/s0306-9192(02)00070-2]
4. Yilma H, Sedlander E, Rimal RN, Pattnaik S. Is fatigue a cue to obtain iron supplements in Odisha, India? A mixed methods investigation. BMJ Open 2020 Oct 20;10(10):e037471 [FREE Full text] [doi: 10.1136/bmjopen-2020-037471] [Medline: 33082184]
5. Scholl T, Hediger M, Fischer R, Shearer J. Anemia vs iron deficiency: increased risk of preterm delivery in a prospective study. Am J Clin Nutr 1992 May;55(5):985-988. [doi: 10.1093/ajcn/55.5.985] [Medline: 1570808]
6. Casey GJ, Phuc TQ, Macgregor L, Montresor A, Mihrshahi S, Thach TD, et al. A free weekly iron-folic acid supplementation and regular deworming program is associated with improved hemoglobin and iron status indicators in Vietnamese women. BMC Public Health 2009 Jul 24;9(1):261 [FREE Full text] [doi: 10.1186/1471-2458-9-261] [Medline: 19630954]
7. Sedlander E, Long MW, Mohanty S, Munjral A, Bingenheimer JB, Yilma H, et al. Moving beyond individual barriers and identifying multi-level strategies to reduce anemia in Odisha, India. BMC Public Health 2020 Apr 06;20(1):457 [FREE Full text] [doi: 10.1186/s12889-020-08574-z] [Medline: 32252698]
8. World Health Organization. Global and Regional Estimates of Violence Against Women: Prevalence and Health Effects of Intimate Partner Violence and Non-partner Sexual Violence. Geneva: World Health Organization; 2013.
9. Devries KM, Mak JY, García-Moreno C, Petzold M, Child JC, Falder G, et al. Global health. The global prevalence of intimate partner violence against women. Science 2013 Jun 28;340(6140):1527-1528. [doi: 10.1126/science.1240937] [Medline: 23788730]
10. Mikton C. Preventing intimate partner and sexual violence against women: taking action and generating evidence. Inj Prev 2010 Oct;16(5):359-360. [doi: 10.1136/ip.2010.029629] [Medline: 20921563]
11. Silverman JG, Balaiah D, Decker MR, Boyce SC, Ritter J, Naik DD, et al. Family violence and maltreatment of women during the perinatal period: associations with infant morbidity in Indian slum communities. Matern Child Health J 2016 Jan 6;20(1):149-157 [FREE Full text] [doi: 10.1007/s10995-015-1814-y] [Medline: 26440937]
12. Kalokhe AS, Potdar RR, Stephenson R, Dunkle KL, Paranjape A, Del Rio C, et al. How well does the World Health Organization definition of domestic violence work for India? PLoS One 2015 Mar 26;10(3):e0120909 [FREE Full text] [doi: 10.1371/journal.pone.0120909] [Medline: 25811374]
13. Daruwalla N, Machchhar U, Pantvaidya S, D'Souza V, Gram L, Copas A, et al. Community interventions to prevent violence against women and girls in informal settlements in Mumbai: the SNEHA-TARA pragmatic cluster randomised controlled trial. Trials 2019 Dec 17;20(1):743 [FREE Full text] [doi: 10.1186/s13063-019-3817-2] [Medline: 31847913]
14. Kalokhe A, Del Rio C, Dunkle K, Stephenson R, Metheny N, Paranjape A, et al. Domestic violence against women in India: a systematic review of a decade of quantitative studies. Glob Public Health 2017 Apr 17;12(4):498-513 [FREE Full text] [doi: 10.1080/17441692.2015.1119293] [Medline: 26886155]
15. Raj A, McDougal L. Sexual violence and rape in India. Lancet 2014 Mar;383(9920):865. [doi: 10.1016/s0140-6736(14)60435-9]
16. Kar S, Samataray P, Thakur B, Das B, Burma A. Domestic violence in women of reproductive age group in rural Odisha-a cross sectional study data results. Womens Health Complicat 2018;1(1):1-5 [FREE Full text]
17. Palermo T, Bleck J, Peterman A. Tip of the iceberg: reporting and gender-based violence in developing countries. Am J Epidemiol 2014 Mar 01;179(5):602-612 [FREE Full text] [doi: 10.1093/aje/kwt295] [Medline: 24335278]
18. Michau L, Horn J, Bank A, Dutt M, Zimmerman C. Prevention of violence against women and girls: lessons from practice. Lancet 2015 Apr;385(9978):1672-1684. [doi: 10.1016/s0140-6736(14)61797-9]
19. Jewkes R, Flood M, Lang J. From work with men and boys to changes of social norms and reduction of inequities in gender relations: a conceptual shift in prevention of violence against women and girls. Lancet 2015 Apr;385(9977):1580-1589. [doi: 10.1016/s0140-6736(14)61683-4]

20. Alexander-Scott M, Bell E, Holden J. DFID Guidance Note: shifting social norms to tackle violence against women and girls (VAWG). UK Department for International Development - VAWG Helpdesk, London. 2016. URL: https://www.oecd.org/dac/gender-development/VAWG%20HELPDESK_DFID%20GUIDANCE%20NOTE_SOCIAL%20NORMS_JAN%202016.pdf [accessed 2021-10-20]
21. World Health Organization. Changing Cultural and Social Norms That Support Violence. Series of Briefings on Violence Prevention: The Evidence. Geneva: World Health Organization; 2009.
22. Chib A, van Velthoven MH, Car J. mHealth adoption in low-resource environments: a review of the use of mobile healthcare in developing countries. J Health Commun 2015 Mar;20(1):4-34. [doi: 10.1080/10810730.2013.864735] [Medline: 24673171]
23. Ahmed T, Lucas H, Khan AS, Islam R, Bhuiya A, Iqbal M. eHealth and mHealth initiatives in Bangladesh: a scoping study. BMC Health Serv Res 2014 Jun 16;14:260 [FREE Full text] [doi: 10.1186/1472-6963-14-260] [Medline: 24934164]
24. Gul X, Hameed W, Hussain S, Sheikh I, Siddiqui J. A study protocol for an mHealth, multi-centre randomized control trial to promote use of postpartum contraception amongst rural women in Punjab, Pakistan. BMC Pregnancy Childbirth 2019 Aug 08;19(1):283 [FREE Full text] [doi: 10.1186/s12884-019-2427-z] [Medline: 31395034]
25. Pant I, Poudyal A. #Ringingthealarm: chronic "pilotitis" stunts digital health in Nepal. In: Proceedings of the ITU Kaleidoscope: ICT for Health: Networks, Standards and Innovation (ITU K). 2019 Presented at: ITU Kaleidoscope: ICT for Health: Networks, Standards and Innovation (ITU K); Dec. 4-6, 2019; Atlanta, GA, USA p. 1-9. [doi: 10.23919/ituk48006.2019.8996139]
26. Gross R, Ritz J, Hughes MD, Salata R, Mugyenyi P, Hogg E, et al. Two-way mobile phone intervention compared with standard-of-care adherence support after second-line antiretroviral therapy failure: a multinational, randomised controlled trial. Lancet Digital Health 2019 May;1(1):26-34 [FREE Full text] [doi: 10.1016/S2589-7500(19)30006-8]
27. Kahn JG, Yang JS, Kahn JS. 'Mobile' health needs and opportunities in developing countries. Health Aff (Millwood) 2010 Feb;29(2):252-258. [doi: 10.1377/hlthaff.2009.0965] [Medline: 20348069]
28. Kaka N, Madgavkar A, Ksihirsagar A, Gupta R, Manyika J, Bahi K, et al. Digital India: technology to transform a connected nation. McKinsey Global Institute. 2019. URL: https://www.mckinsey.com/~/media/McKinsey/Business%20Functions/McKinsey%20Digital/Our%20Insights/Digital%20India%20Technology%20to%20transform%20a%20connected%20nation/MGI-Digital-India-Report-April-2019.ashx [accessed 2021-10-20]
29. Pai N, Supe P, Kore S, Nandanwar Y, Hegde A, Cutrell E, et al. Using automated voice calls to improve adherence to iron supplements during pregnancy: a pilot study. In: Proceedings of the Sixth International Conference on Information and Communication Technologies and Development. 2013 Presented at: ICTD 2013: International conference on information and communication technologies and development; December 7 - 10, 2013; Cape Town, South Africa p. 153-163. [doi: 10.1145/2516604.2516608]
30. Vasudeva N, Aggarwal AK, Aggarwal N. Tele-follow-up empowers anemic pregnant lady to create demand for therapeutic treatment of anemia and improve compliance: a case study. Int J Health Syst Implement Res 2019;1(1):49-56 [FREE Full text]
31. Náfrádi L, Nakamoto K, Schulz PJ. Is patient empowerment the key to promote adherence? A systematic review of the relationship between self-efficacy, health locus of control and medication adherence. PLoS One 2017;12(10):e0186458 [FREE Full text] [doi: 10.1371/journal.pone.0186458] [Medline: 29040335]
32. Singhal A, Rogers EM. The status of entertainment-education worldwide. In: Singhal A, Cody MJ, Rogers EM, Sabido M, editors. Entertainment-Education and Social Change. New Jersey: Erlbaum Associates; 2003:3-20.
33. Storey D, Sood S. Increasing equity, affirming the power of narrative and expanding dialogue: the evolution of entertainment education over two decades. Critical Arts 2013 Feb;27(1):9-35. [doi: 10.1080/02560046.2013.767015]
34. Riley AH, Sood S, Mazumdar PD, Choudary NN, Malhotra A, Sahba N. Encoded exposure and social norms in entertainment-education. J Health Commun 2017 Jan 06;22(1):66-74. [doi: 10.1080/10810730.2016.1250843] [Medline: 28060582]
35. Bae H. Entertainment-education and recruitment of cornea donors: the role of emotion and issue involvement. J Health Commun 2008 Feb 08;13(1):20-36. [doi: 10.1080/10810730701806953] [Medline: 18307134]
36. Ramasubban R. Shifting deeply rooted gender norms using an entertainment-education transmedia initiative. Population Foundation of India Case Study Series. 2016. URL: http://mkbksh.com/wp-content/uploads/2015/01/MKBKSH-Case-Study.pdf [accessed 2020-12-15]
37. Creel AH, Rimal RN, Mkandawire G, Böse K, Brown JW. Effects of a mass media intervention on HIV-related stigma: 'Radio Diaries' program in Malawi. Health Educ Res 2011 Jun 10;26(3):456-465. [doi: 10.1093/her/cyr012] [Medline: 21393376]
38. Rimal RN, Creel AH. Applying social marketing principles to understand the effects of the radio diaries program in reducing HIV/AIDS stigma in Malawi. Health Mark Q 2008 Jul 02;25(1-2):119-146. [doi: 10.1080/07359680802126186] [Medline: 18935882]
39. Sundar S, Xu Q, Bellur S. Designing interactivity in media interfaces: a communications perspective. In: Proceedings of the SIGCHI Conference on Human Factors in Computing Systems. 2010 Presented at: CHI '10: CHI Conference on Human Factors in Computing Systems; April 10 - 15, 2010; Atlanta Georgia USA p. 2247-2256. [doi: 10.1145/1753326.1753666]

40. Vorderer P, Knobloch S, Schramm H. Does entertainment suffer from interactivity? The impact of watching an interactive TV movie on viewers' experience of entertainment. Media Psychol 2001 Nov;3(4):343-363. [doi: 10.1207/s1532785xmep0304_03]
41. Sen A, Kanani SJ. Deleterious functional impact of anemia on young adolescent school girls. Indian Pediatr 2006 Mar;43(3):219-226 [FREE Full text] [Medline: 16585816]
42. Gautam S, Min H, Kim H, Jeong H. Determining factors for the prevalence of anemia in women of reproductive age in Nepal: evidence from recent national survey data. PLoS One 2019 Jun 12;14(6):e0218288 [FREE Full text] [doi: 10.1371/journal.pone.0218288] [Medline: 31188883]
43. Census of India: 2011. Office of the Registrar General & Census Commissioner, Government of India, New Delhi. 2012. URL: https://censusindia.gov.in/ [accessed 2021-10-20]
44. Crawford AG, Sikirica V, Goldfarb N, Popiel RG, Patel M, Wang C, et al. Interactive voice response reminder effects on preventive service utilization. Am J Med Qual 2005 Sep 03;20(6):329-336. [doi: 10.1177/1062860605281176] [Medline: 16280396]
45. Kassavou A, Sutton S. Automated telecommunication interventions to promote adherence to cardio-metabolic medications: meta-analysis of effectiveness and meta-regression of behaviour change techniques. Health Psychol Rev 2017 Sep 12:1-18. [doi: 10.1080/17437199.2017.1365617] [Medline: 28805162]
46. Constantino R, Wu L, de la Cruz D, Burroughs J, Hwang JG, Henderson A, et al. Exploring the feasibility of text messaging intervention in intimate partner violence. Open J Nurs 2014;04(07):528-537. [doi: 10.4236/ojn.2014.47056]
47. Lapinski MK, Rimal RN. An explication of social norms. Commun Theory 2005 May;15(2):127-147. [doi: 10.1111/j.1468-2885.2005.tb00329.x]
48. Stark L, Asghar K, Seff I, Cislaghi B, Yu G, Gessesse T, et al. How gender- and violence-related norms affect self-esteem among adolescent refugee girls living in Ethiopia. Glob Ment Health (Camb) 2018 Jan 17;5:e2 [FREE Full text] [doi: 10.1017/gmh.2017.28] [Medline: 29435352]
49. Sedlander E, Rimal RN. Beyond individual-level theorizing in social norms research: how collective norms and media access affect adolescents' use of contraception. J Adolesc Health 2019 Apr;64(4S):31-36 [FREE Full text] [doi: 10.1016/j.jadohealth.2018.12.020] [Medline: 30914165]
50. Wang H, Singhal A. Unfurling the voicebook of Main Kuch Bhi Kar Sakti Hoon: real-time audience engagement, rising fandom, and spurring of prosocial actions. A Research Report for Population Foundation of India. 2017. URL: http://utminers.utep.edu/asinghal/Reports/WangSinghal-MKBKSH_IVRSreport_2017May_Final_Final.pdf [accessed 2021-10-20]
51. MacKinnon DP. Introduction to Statistical Mediation Analysis. New York: Routledge; 2008:1-488.
52. STATA Corporation, College Station, Texas. 2015. URL: https://www.stata.com/ [accessed 2021-10-20]
53. Rimal RN, Lapinski MK. A re-explication of social norms, ten years later. Commun Theor 2015 Oct 21;25(4):393-409. [doi: 10.1111/comt.12080]
54. Johri M, Chandra D, Kone KG, Sylvestre M, Mathur AK, Harper S, et al. Social and behavior change communication interventions delivered face-to-face and by a mobile phone to strengthen vaccination uptake and improve child health in rural India: randomized pilot study. JMIR Mhealth Uhealth 2020 Sep 21;8(9):e20356 [FREE Full text] [doi: 10.2196/20356] [Medline: 32955455]
55. Barboni G, Field E, Pande R, Rigol N, Schaner S, Moore C. A Tough Call: understanding barriers to and impacts of women's mobile phone adoption in India. Evidence for Policy Design - Harvard Kennedy School, Cambridge, MA. 2018. URL: https://wappp.hks.harvard.edu/files/wappp/files/a_tough_call_epod.pdf [accessed 2020-12-15]
56. Alozie N, Akpan-Obong P. The digital gender divide: confronting obstacles to women's development in Africa. Dev Policy Rev 2016 Dec 21;35(2):137-160 [FREE Full text] [doi: 10.1111/dpr.12204]
57. Ghoshal R. Twin public health emergencies: Covid-19 and domestic violence. Indian J Med Ethics :1-5 [FREE Full text] Preprint published online May 7, 2020. [doi: 10.20529/IJME.2020.056] [Medline: 32546463]
58. Kumar S, Jeyaseelan L, Suresh S, Ahuja RC. Domestic violence and its mental health correlates in Indian women. Br J Psychiatry 2005 Jul 02;187(1):62-67. [doi: 10.1192/bjp.187.1.62] [Medline: 15994573]

Abbreviations

EE: entertainment education
IFA: iron folic acid
IVR: interactive voice response
mBI: mobile bystander intervention
mHealth: mobile health
mIFA: mobile iron and folic adherence
mRANI: mobile reduction in anemia through normative innovations
RANI: reduction in anemia through normative innovations
RCDT: reciprocal control double treatment

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Protocol

Comparison of (Cost-)Effectiveness of Magnetic Resonance Image–Guided High-Intensity–Focused Ultrasound With Standard (Minimally) Invasive Fibroid Treatments: Protocol for a Multicenter Randomized Controlled Trial (MYCHOICE)

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Abstract

Background: Magnetic resonance image–guided high-intensity–focused ultrasound (MR-HIFU) is a rather new, noninvasive option for the treatment of uterine fibroids. It is safe, effective, and has a very short recovery time. However, a lack of prospectively collected data on long-term (cost-)effectiveness of the MR-HIFU treatment compared with standard uterine fibroid care prevents the MR-HIFU treatment from being reimbursed for this indication. Therefore, at this point, when conservative treatment for uterine fibroid symptoms has failed or is not accepted by patients, standard care includes the more invasive treatments hysterectomy, myomectomy, and uterine artery embolization (UAE). Primary outcomes of currently available data on MR-HIFU treatment often consist of technical outcomes, instead of patient-centered outcomes such as quality of life (QoL), and do not include the use of the latest equipment or most up-to-date treatment strategies. Moreover, data on cost-effectiveness are rare and seldom include data on a societal level such as productivity loss or use of painkillers. Because of the lack of reimbursement, broad clinical implementation has not taken place, nor is the proper role of MR-HIFU in uterine fibroid care sufficiently clear.

Objective: The objective of our study is to determine the long-term (cost-)effectiveness of MR-HIFU compared with standard (minimally) invasive fibroid treatments.

Methods: The MYCHOICE study is a national, multicenter, open randomized controlled trial with randomization in a 2:1 ratio to MR-HIFU or standard care including hysterectomy, myomectomy, and UAE. The sample size is 240 patients in total. Women are included when they are 18 years or older, in premenopausal stage, diagnosed with symptomatic uterine fibroids, conservative treatment has failed or is not accepted, and eligible for MR-HIFU. Primary outcomes of the study are QoL 24 months after treatment and costs of treatment including direct health care costs, loss of productivity, and patient costs.

Results: Inclusion for the MYCHOICE study started in November 2020 and enrollment will continue until 2024. Data collection is expected to be completed in 2026.

Conclusions: By collecting data on the long-term (cost-)effectiveness of the MR-HIFU treatment in comparison to current standard fibroid care, we provide currently unavailable evidence about the proper place of MR-HIFU in the fibroid treatment spectrum. This will also facilitate reimbursement and inclusion of MR-HIFU in (inter)national uterine fibroid care guidelines.

Trial Registration: Netherlands Trial Register NL8863; https://www.trialregister.nl/trial/8863

International Registered Report Identifier (IRRID): DERR1-10.2196/29467

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KEYWORDS

high-intensity–focused ultrasound ablation; magnetic resonance imaging, interventional; leiomyoma; randomized controlled trial; cost-effectiveness analysis; clinical trial protocol

Introduction

Fibroids are the most common benign gynecological tumors in women of reproductive age, occurring in up to 70% of the population. Approximately 25% of the uterine fibroids are symptomatic [1]. Symptoms include abdominal pain, menstrual disorders, lower urinary tract or bowel symptoms, and fertility disorders [2]. On a global level, fibroids represent an enormous economic burden to the health care system and costs can reach as much as US $5.9-34.4 billion each year in the United States [3]. Conservative treatment of fibroids fails in 50% of patients, many of whom subsequently opt for surgical procedures [4]. Hysterectomy is currently the most common treatment for symptomatic uterine fibroids, with millions of procedures performed annually around the world [5]. However, hysterectomies and myomectomies have a high risk of complications, long recovery, and might compromise future pregnancies [6], with the latter mainly due to peritoneal and intrauterine adhesions, a high rate of abnormal placentation, and fragility of myometrium as a result of myomectomy [7]. Furthermore, even a hysterectomy does not guarantee an intervention-free life, mostly because of complications caused by the operation itself [8]. This has led to a strong desire for less invasive treatments [4].

Currently, uterine artery embolization (UAE) is the only reimbursed minimally invasive treatment available in the Netherlands. The general treatment results after UAE are 60% fibroid volume reduction and on average 80%-90% patient satisfaction [9]. Complications after UAE include nontarget embolization, infection/septicemia and ovarian failure due to impairment of ovarian blood flow, and infection leading to fallopian tube damage with subsequent infertility [9,10].

Magnetic resonance image–guided high-intensity–focused ultrasound (MR-HIFU) is a thermal ablation technique, which enables noninvasive treatment of symptomatic uterine fibroids by selective tissue heating [11]. The ultrasound transducer produces convergent high-intensity ultrasound waves. The targeted tissue absorbs the acoustic energy leading to a temperature rise, which causes coagulative necrosis [12]. Magnetic resonance imaging (MRI) facilitates treatment planning and real-time monitoring by temperature mapping [13]. Directly after MR-HIFU, a contrast-enhanced MRI scan can visualize the ablated tissue, referred to as the nonperfused volume (NPV). NPV% (NPV divided by the initial fibroid volume) is one of the commonly used parameters to indicate technical treatment success [11].

When the MR-HIFU therapy of uterine fibroids was first introduced in clinical practice, it was allowed to ablate only 33%, and later on 50%, of the uterine fibroid. However, it soon became clear that clinical outcomes are closely related to high NPV percentages. Therefore, nowadays full ablation protocols are used [12,14]. In addition, better results and less adverse events were seen when using the latest generation of treatment devices [11]. Not all patients with symptomatic uterine fibroid are eligible for MR-HIFU treatment due to either patient or fibroid tissue characteristics, such as the number of fibroids or the extent of vascularization of a fibroid and the possibility to heat the tissue [15]. A wish to conceive is not a contraindication, although data on pregnancy outcomes remain sparse [16,17]. Careful screening is in all cases recommended [18]. Hitherto, only 5 studies were published on the cost-effectiveness of the MR-HIFU uterine fibroid treatment [19-23]. All used outdated, less effective MR-HIFU treatment protocols and costs of sanitary products, over-the-counter remedies, and alternative and complementary therapies were typically not taken into account. Nevertheless, these cost-effectiveness studies still concluded that MR-HIFU can be cost-effective at commonly accepted willingness-to-pay thresholds [11].

At this point, phase 1, 2a, and 2b studies according to the Idea, Development, Exploration, Assessment and Long-term study (IDEAL) framework have been completed in numerous sites all over the world [24], confirming safety and short- to middle-term technical and clinical outcomes. Conversely, no (non)randomized controlled trials are available in which MR-HIFU is directly compared with the current standard of care, and in which the full ablation protocol or the latest version of the MR-HIFU equipment was used. For example, in a comprehensive cohort trial comparing MR-HIFU with UAE, lower reintervention rates and greater improvement in symptoms were observed after UAE [25]. However, these results could be explained by impairment of ovarian reserve at follow-up in the UAE group and the use of outdated MR-HIFU equipment, which resulted in a rather low average NPV of 42.9% after treatment. With regard to follow-up, only 2 single-arm studies [26,27] with a follow-up of more than 12 months and using a full ablation protocol have been performed until now [11].

Because of the lack of randomized controlled trials (RCTs) that established long-term treatment outcomes and cost-effectiveness of MR-HIFU using an unrestricted, full ablation protocol and the latest equipment, we are now embarking on phase 3 of the IDEAL framework and will perform a randomized controlled (cost-)effectiveness study with a long-term follow-up.

The primary aim of this MYCHOICE study is to compare quality of life (QoL) at 24 months after MR-HIFU with QoL 24 months after standard fibroid care, which consists of hysterectomy, myomectomy, and UAE. Furthermore, we aim to determine the long-term cost-effectiveness of MR-HIFU compared with standard (minimally) invasive fibroid care. We expect that QoL after MR-HIFU is noninferior to QoL after standard care and that MR-HIFU is cost-effective compared with standard care.

Methods

This protocol was developed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement [28].

Study Design and Setting

The MYCHOICE study (MYoma treatment Comparison study: High-intensity image–guided fOcused ultrasound versus standard [minimally] Invasive fibroid care—a (Cost-)Effectiveness analysis; Netherlands Trial Register NL8863) is designed as an open, national, multicenter, RCT. By including both academic and nonacademic centers as participating hospitals in the MYCHOICE study, high volume and expertise are warranted. Participating hospitals provide a representative geographic spread across the country. All participating hospitals are specialized uterine fibroid centers and perform standard (minimally) invasive fibroid care. The MR-HIFU treatment will, however, be performed in the only 2 hospitals in the Netherlands that offer MR-HIFU treatment (Isala Zwolle and University Medical Center Utrecht) in addition to standard uterine fibroid care.

Study Population and Eligibility

Overview

Our study population consists of women in the premenopausal phase visiting the gynecological outpatient clinic with symptoms caused by uterine fibroids. Symptoms of fibroids may comprise heavy menstrual bleeding and bulk symptoms such as pelvic pressure, micturition/defecation problems, or pain symptoms. A combination of several symptoms or a single symptom will be equally qualified as “symptomatic.” To optimize external validity of our study results, the inclusion and exclusion criteria defined in this study (Textbox 1) are similar to the inclusion and exclusion criteria applied for MR-HIFU in clinical practice. However, 2 exceptions are made. Women need to be motivated to undergo 1 of the 3 treatments in the control group, in case of being randomized to the control group, before participating in the MYCHOICE study. Furthermore, a wish to conceive within 1 year after inclusion is a reason to be not eligible for participating, because there is not yet a consensus about the standard of care for these women. Women without an active child wish but for whom a pregnancy in the future is not ruled out can be included in the study.

The MYCHOICE study procedure consists of several steps (Figure 1).

The eligibility procedure for this study consists of 2 screening phases. Only women that are considered eligible for participating in the study based on these 2 screening phases will be randomized.

Textbox 1. Inclusion criteria for participation in the MYCHOICE (MYoma treatment Comparison study: High-intensity image–guided fOcused ultrasound versus standard [minimally] Invasive fibroid care—a [Cost] Effectiveness analysis) study.

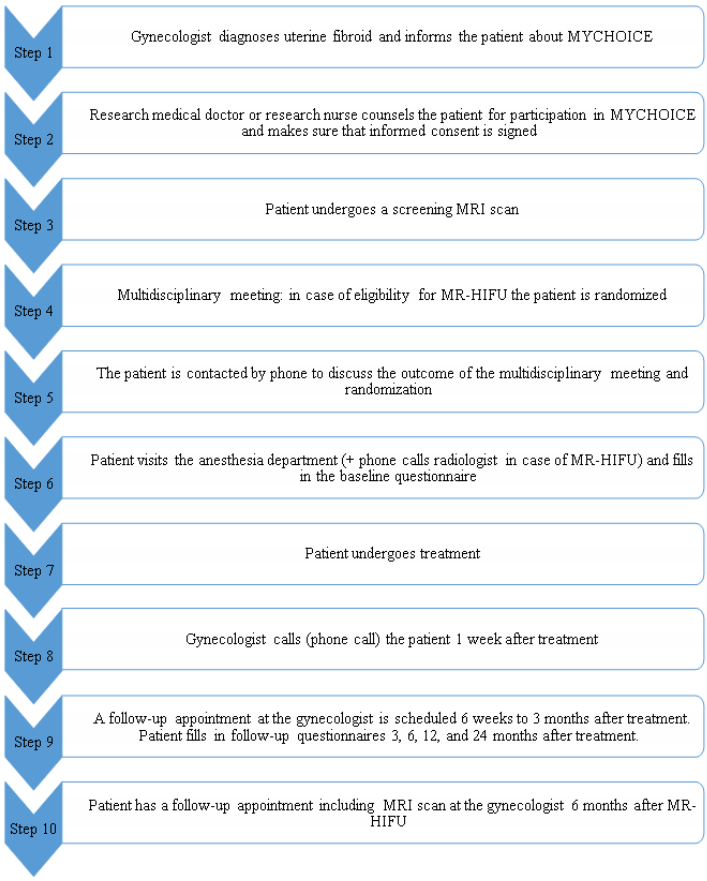
Inclusion criteria

- Symptomatic fibroids warranting (minimally) invasive treatment, that is, either hysterectomy, myomectomy, or uterine artery embolization
- Conservative treatment failed or not accepted
- Premenopausal
- Age ≥18 years
- Eligible for magnetic resonance image–guided high-intensity focused ultrasound (MR-HIFU) treatment.

Exclusion criteria

- Asymptomatic fibroids
- Postmenopausal
- BMI of ≥35 kg/m^2 or abdominal subcutis ≥4 cm or both
- More than 5 uterine fibroids unless 1 or 2 fibroids causing the symptoms can be clearly identified
- Magnetic resonance imaging contraindications or contrast allergy
- Current pregnancy
- A wish to conceive within 1 year after inclusion
- Suspicion of malignancy
- Dominant adenomyosis, defined as more volume of adenomyosis rather than fibroids
- Not willing to accept pretreatment with leuprorelin before MR-HIFU in case of a uterine fibroid with a diameter >10 cm or classified as Funaki 3
- Not willing to remove an interfering intrauterine contraception device prior to MR-HIFU
- Not eligible for MR-HIFU as determined by the multidisciplinary MR-HIFU team in Isala based on a screening magnetic resonance imaging:
  - Uterine fibroid(s) either submucosal or subserosal stalked or with a diameter <2 cm
  - Fibroids suitable for hysteroscopical removal
  - Distance of abdominal wall to the dorsal side of uterine fibroids expected to be >12 cm even after the use of manipulation techniques
  - Calcified uterine fibroids or fibroids without contrast enhancement

Figure 1. Flow diagram of the MYCHOICE procedure. MR-HIFU: magnetic resonance image–guided high-intensity focused ultrasound; MRI: magnetic resonance imaging; MYCHOICE: MYoma treatment Comparison study: High-intensity image–guided fOcused ultrasound versus standard (minimally) Invasive fibroid care—a (Cost-)Effectiveness analysis.



Phase 1 of the Screening Procedure

Patients presenting with uterine fibroid–related symptoms at the Department of Gynecology of the participating centers will undergo standard consultation, physical examination, and vaginal ultrasonography. The patient is briefly informed about the study when she appears to be eligible for participation in the study based on the physical examination and the vaginal ultrasonography (step 1 in Figure 1). In case the patient is interested in participating in the study, an appointment with a member of the research team or local research nurse will be made and the patient will receive more detailed study information to read at home (step 2 in Figure 1). In case a patient does not want to participate, the gynecologist asks the patient if she is willing to disclose the reason for not participating. During the appointment with a member of the research team or local research nurse, additional counseling will take place.

Phase 2 of the Screening Procedure

Once the patient has signed the informed consent form, a screening MRI scan according to a predefined protocol will be planned in the local hospital (step 3 in Figure 1).

Final eligibility of the patients of all participating centers will be determined by the multidisciplinary MR-HIFU team in the coordinating center based on the screening MRI scan and the inclusion and exclusion criteria (step 4 in Figure 1). These meetings will be accessible to members of the other participating hospitals. By performing central screening, a bias caused by differences per site is minimized and eligibility for MR-HIFU is secured.

Intervention

Pretreatment

The participant's gynecologist and general practitioner are informed about the outcome of the eligibility assessment and, if the patient is considered eligible, the randomization outcome (step 5 in Figure 1). Subsequently, the gynecologist will inform the patient about the outcome and baseline data will be collected by a member of the research team or the local research nurse and entered into the electronic case report form (Research Manager). In case a patient is randomized to the MR-HIFU treatment arm, she will be referred to an MR-HIFU performing hospital if her hospital is not 1 of the 2 hospitals in which the MR-HIFU treatment is performed. In case she is randomized to the standard care treatment arm, she can be treated in her own hospital.

MR-HIFU

MR-HIFU will be performed by well-trained and experienced radiologists using the latest version of the CE-marked Sonalleve MR-HIFU platform (Profound Medical Inc.) integrated into a 1.5-T MR-scanner (Achieva; Philips Healthcare) using a full ablation protocol. A uniform treatment protocol will be used in accordance with the manufacturer's guidelines on the use of the device and the latest insights in the field of MR-HIFU treatment of uterine fibroids. Six months after treatment, a follow-up MRI

scan will be performed before the follow-up appointment at the gynecologist (step 10 in Figure 1).

Control Group

The care as usual group will be offered surgery or UAE. Surgery will be either hysterectomy or myomectomy. Both hysterectomies and myomectomies can be performed by laparoscopy or laparotomy depending on the size and location of the fibroids. Participants allocated to the control group can decide together with their gynecologist which of the (minimally) invasive treatments they wish to undergo. All of the usual care treatments are performed extensively at the participating centers and will be performed according to national guidelines and local protocols. Surgery is preceded by a preoperative screening for anesthetic risk assessment. Depending on the modus of the hysterectomy or myomectomy, patients will be hospitalized for a minimum of 1-3 nights. UAE will be performed by well-trained and experienced radiologists. UAE can be either unilateral or bilateral. The patient usually has to stay in the hospital for 1-3 nights for careful pain monitoring after the procedure. Six weeks after all usual care treatments, a follow-up appointment at the gynecology department will be scheduled.

Use of Co-interventions

All included treatments aim for complete symptom reduction; however, clinical practice shows that additional treatment can be necessary during, for example, menstruation. Women can choose to use additional over-the-counter pain medication or prescribed medication such as oral contraception pills or antifibrinolytic drugs. These pills can influence symptom severity (both bleeding and pain). Therefore, data on the use of this medication are collected at both baseline and follow-up as part of the patient characteristics and medical consumption questionnaires.

Data Collection

Data collection will take place before treatment, and at 3, 6, 12, and 24 months after treatment by questionnaires. Furthermore, baseline data of patient and treatment costs will be collected before treatment and after data lock-in (Table 1).

Table 1. Timeline of data collection.

Data	Baseline	Treatment	3 months	6 months	12 months	24 months	Data lock-in
Informed consent	X						
Patient characteristics[a]	X						
Pregnancy outcomes[b]	X					X	
UFS-QoL[b,c]	X		X	X	X	X	
EQ-5D-5L[b,d]	X		X	X	X	X	
Onset of menopause[b]						X	
(Time to) reintervention[a]			X	X	X	X	X
Adverse events/complications[a]		X	X	X	X	X	
PREM[b,e]	X		X	X	X	X	
Recovery time[a]		X	X	X			
Medical Consumption Questionnaire[b,f]	X		X	X	X	X	
Productivity Costs Questionnaire[b,f]	X		X	X	X	X	
Costs of treatment[a]							X
Reason for not participating[a,g]	X						

[a]Retrieved from questionnaires and medical record.

[b]Retrieved from questionnaires solely.

[c]UFS-QoL: Uterine Fibroid Symptom and Quality of Life questionnaire.

[d]EQ-5D-5L: 5-level version of the EuroQoL Questionnaire.

[e]PREM: patient-reported experience measurement

[f]Used for the cost-effectiveness analysis.

[g]Data collected by the gynecologist in case of not willing to participate.

Outcomes

Primary Outcomes

In the MYCHOICE study, primary outcomes include (1) QoL at the follow-up time point of 24 months after treatment and (2) cost-effectiveness of MR-HIFU.

QoL is commonly measured with the validated Uterine Fibroid Symptom and Quality of Life questionnaire (UFS-QoL) [29]. This questionnaire consists of 2 parts: 8 symptom questions and 29 questions concerning health-related QoL with 6 subscales. The 8 symptom severity questions concern duration, frequency and severity of menstruation, urination pattern, tightness or pressure in the pelvic area, and fatigue. The 6 subscales of the HR QoL part of the questionnaire are concern, activities, energy/mood, control, self-consciousness, and sexual function. All items are scored on a 5-point Likert scale. Both internal consistency reliability (subscale Cronbach α=.83-.95, overall health-related QoL score α=.97) and test–retest reliability (intraclass correlation coefficients 0.76–0.93) of this questionnaire were shown to be adequate. Moreover, the UFS-QoL has an excellent construct and discriminative validity [29]. From the symptom-specific part of the questionnaire, a symptom severity score (SSS; range 0-100, with higher scores indicating more [severe] symptoms) can be calculated. Because symptom reduction is the main aim of all uterine fibroid treatments, we define QoL at the follow-up time point of 24 months as a change in reported symptom severity compared with baseline.

The cost-effectiveness analysis will be performed from a societal perspective. Cost-effectiveness will be reported as incremental cost-effectiveness ratio, that is, the ratio between the expected difference in cost and the expected difference in effect (clinical effect or utility [quality-adjusted life year] and net [monetary] benefit). Cost-effectiveness acceptability curves will be presented to summarize the impact of uncertainty on the result of the economic evaluation.

The Dutch value set will be applied to the 5-level version of the EuroQoL questionnaire (EQ-5D-5L) to produce quality-adjusted life year values [30].

We consider 4 cost categories: (1) direct medical in-hospital costs (eg, preprocedural costs, in-hospital costs related to the intervention, any additional in-hospital medical costs during follow-up); (2) direct medical out-of-hospital costs (eg, unscheduled general practitioner visits and use of medication out of hospital); (3) direct nonmedical costs (patient expenses such as travel costs and sanitary measures); and (4) indirect costs (productivity-related costs due to absence from work) [31].

The unit costs of direct medical in-hospital cost volumes will be based on Dutch guidelines for economic evaluations. The cost volumes of MR-HIFU, UAE, myomectomy, and hysterectomy are based on detailed microcosting by using data recorded in the case record forms and patient records in all participating hospitals. The cost volumes related to complications will be recorded prospectively in the case record form (eg, type of complication, unscheduled outpatient visit, subsequent diagnostic and therapeutic measures). All interventions include 1 follow-up by phone (at 1 week after primary intervention; Figure 1). In case of an UAE, myomectomy, and hysterectomy, 1 follow-up visit at the outpatient gynecology department will be planned at 6 weeks after the primary intervention; in case of MR-HIFU at 3 and 6 months, a follow-up appointment at the gynecology department will take place, at 6 months combined with an MRI scan. This will be considered standard care, and will therefore be included in our cost analysis. Any further follow-up visits conducted for study purposes will be excluded from our analysis unless these are unscheduled follow-up visits for medical problems related to the primary intervention.

The unit costs of direct medical out-of-hospital costs, direct nonmedical costs, and indirect costs will also be based on Dutch guidelines for cost calculations in health care. The following altered patient questionnaires will be used: iMTA Productivity Cost Questionnaire (iPCQ) and iMTA Medical Consumption Questionnaire (iMCQ). The iPCQ questionnaire is a short generic measurement instrument on the impact of disease on the ability of a person to perform work. It also contains questions about absence from unpaid labor. This questionnaire is a generic instrument for measuring medical costs, including questions related to frequently occurring contacts with health care providers. All questionnaires will be sent by email or post according to the preference of the participant at baseline and at 3, 6, 12, and 24 months after treatment (Table 1). Patients will receive an automatic reminder by email. Indirect costs due to absence from work will be estimated as the actual working time lost (hours) multiplied by the average net income according to the friction cost method.

A decision analytic model with lifetime horizon will be developed by combining costs and effects. Complete uncertainty analyses (deterministic and probabilistic sensitivity analyses) will be performed.

In addition, a budget impact model will be constructed, taking the (gradual) implementation of MR-HIFU over time, the initial investments, and the savings into account that were shown to be realistic in the trial. The model will use different perspectives: (1) The net Dutch Budgetary Framework for Healthcare (Budgettair Kader Zorg) perspective; and (2) health insurance/third-party payer perspective.

The budget impact model is performed through modeling and analyzed in a probabilistic way.

Because MR-HIFU is an outpatient treatment with a fast(er) recovery, it is expected to be cheaper than the current standard (minimally) invasive treatments, especially from a societal perspective.

Secondary Outcomes

Data on several secondary outcomes will be collected (Table 2). These include adverse events and complications during treatment and recovery, cost-effectiveness–relevant outcomes such as hospital stay duration and use of (co)medication, patient-reported experiences, reintervention rate in case a uterine-sparing treatment was performed, reproductive outcomes when applicable, and technical outcomes after MR-HIFU, such as NPV reached.

Table 2. Secondary outcomes of the MYCHOICE[a] study, including measurement tool and statistical analyses.

Outcome	Description	Measurement	Statistical analyses
QoL[b] parameters	QoL is expected to be negatively correlated with symptom severity. When symptoms decrease, the QoL is expected to improve.	UFS-QoL[c] questionnaire and EQ-5D-5L[d] questionnaire.	The time course of the change in health-related quality of life after treatment will be analyzed using longitudinal covariance analysis similar to the analysis of the change in SSS[e].
Adverse events and complications	The nature of adverse events and complications of the 2 treatment arms are expected to differ.	Adverse events will be classified according to the classification of surgical complications [32].	Adverse events are analyzed using descriptive statistics. Adverse events per treatment group and treatment will be presented with their occurrence rate.
Length of hospital stay	Reduced hospital stay is beneficial in terms of health care costs and is also considered as a great advantage by patients.	Length of hospital stay will be collected from the patient hospital file.	The average length of the hospital stay will be reported as mean (SD) or median (interquartile range).
Periprocedural and postprocedural pain	Pain perception may influence treatment experience and therefore satisfaction with the treatment.	Periprocedural and postprocedural pain will be measured on a numerical rating scale from 0 to 10 in the 3 months' follow-up questionnaire. Pain complaints at 3, 6, 12, and 24 months after treatment will be registered by the amount and duration of pain killers used.	The numerical rating score is considered to be a semicontinuous measure (range 0-10: higher score represents more pain). Pain experienced will be reported as mean (SD) or median interquartile range.
Patient-reported satisfaction with treatment and treatment preference (PREM[f])	Because a randomized controlled trial will be performed, satisfaction with treatment might be affected by not being allocated to preferred treatment. Furthermore, we expect women declining participation because of the randomization aspect of the trial.	The PREM consists of a concise set of statements about the experience of the patients with the treatment and whether they would recommend the treatment to a friend. In addition, the preference will be registered for a particular treatment of potential participants before randomization. Women who decline participation in the study will also be asked if they are willing to disclose their reasons for declining.	The PREM score is scored on a 5-point Likert scale: higher score represents better experience. Whether there is a difference in PREM outcome between the 2 treatment arms is determined by linear regression analysis.
(Co)medication	Women (still) experiencing symptoms after treatment may take or may start to take medication to relieve these symptoms. Medication might also be used as contraceptive and to mask possible fibroid-related symptoms at the same time.	Data on any prescribed or over-the-counter medication taken to reduce fibroid symptoms as reported by the patient will be collected via the questionnaires at baseline, 3, 6, 12, and 24 months after treatment.	The number of women taking medication to suppress fibroid-related symptoms is measured at baseline and 3, 6, 12, and 24 months after treatment. The absolute numbers and percentage of women taking comedication per group per time point will be presented.
Reintervention rate and time to reintervention	A reintervention is defined as an additional intervention due to persisting or recurring symptoms of the treated fibroid or due to complications of the initial fibroid treatment.	Occurrence and type of reintervention are collected via both electronic patient file and questionnaires at 3-, 6-, 12-, and 24-month follow-up.	The reintervention rate at the follow-up time point of 24 months after MR-HIFU[g] is presented as percentage reinterventions with its 95% CI. Reintervention rate will be presented per treatment arm but also per treatment. To investigate whether the time to reintervention differs between the 2 treatment arms, Cox proportional hazards analysis will be used.
Onset of menopause after uterus-saving treatments	Uterine fibroid symptoms diminish after menopause along with fibroid-related symptoms. Because this may affect symptom reduction, QoL, and the possible need for a reintervention, the menopausal state of the participants will be determined.	Onset of menopause is defined as 1 year without menstrual bleeding and measured by a questionnaire at the 24-month follow-up.	The absolute numbers and percentage of postmenopausal women per group and treatment will be presented.
Reproductive outcomes after uterus-saving treatments	Only women with an active wish to conceive within 1 year after treatment will be excluded from this study. Thus, some women may get pregnant after the uterus-saving treatment.	Reproductive outcomes will be collected of all women that underwent a uterus-saving treatment by a questionnaire at 24-month follow-up.	Reproductive outcomes will be presented per uterus-saving group using absolute numbers and percentage.

Outcome	Description	Measurement	Statistical analyses
NPV[h] and fibroid shrinkage after MR-HIFU treatment	Technical success of MR-HIFU is commonly presented as NPV percentage directly after treatment or fibroid shrinkage 6 months after treatment, as determined on an MRI[i] scan.	NPV% will be measured on an MRI scan performed directly after treatment. Fibroid shrinkage will be measured by comparing volume measured on 6 months' follow-up MRI scan with pretreatment volume.	We will investigate whether technical success (NPV% [NPV/initial volume of the fibroid] or fibroid shrinkage) is associated with (long-term) effectiveness using regression analysis.
Other study parameters	Several patient characteristics are collected from the medical record of the patients and from the baseline questionnaire such as age, amount and size of fibroids, location of fibroid, position of uterus, duration of treatment, ethnicity, parity, height, weight, relevant medical, and medical history.	Data analysis will be stratified by center to check for differences in results between centers.	In case necessary, multilevel analysis will be used to correct for differences between centers. Multivariate analysis will be performed for symptom reduction, QoL improvement, and reintervention correcting for comedication or menopause as possible confounder. In addition, we will investigate whether certain baseline characteristics such as age, BMI, number of uterine fibroids, and target fibroid size are associated with symptom reduction and reintervention using linear, logistic, and Cox regression analysis.

[a]MYCHOICE: MYoma treatment Comparison study: High-intensity image–guided fOcused ultrasound versus standard (minimally) Invasive fibroid care—a (Cost-)Effectiveness analysis.

[b]QoL: quality of life.

[c]UFS-QoL: Uterine Fibroid Symptom and Quality of Life questionnaire.

[d]EQ-5D-5L: 5-level version of the EuroQoL questionnaire.

[e]SSS: symptom severity score.

[f]PREM: patient-reported experience measurement.

[g]MR-HIFU: magnetic resonance image–guided high-intensity focused ultrasound.

[h]NPV: nonperfused volume.

[i]MRI: magnetic resonance imaging.

Sample Size

The MYCHOICE study is a noninferiority trial for which we hypothesize that MR-HIFU is noninferior to the group of standard (minimally) invasive treatments, accepted by a ≤15 points difference in symptom reduction at 24 months' follow-up as determined with the SSS (range 0-100 points) part of the UFS-QoL questionnaire. We expect that women participating in this trial have a slight preference for the noninvasive MR-HIFU treatment. We therefore choose to use an unbalanced design in which participants are allocated to the intervention or usual care group at a 2:1 ratio, resulting in a larger sample size in the MR-HIFU treatment group. With a larger sample size of the MR-HIFU treatment group, we will be able to gather more data on this new treatment while the effectiveness of standard care is already much better documented. Randomization, stratified by center, will be performed using a computer-generated randomization system, which randomly selects block sizes of 3, 6, or 9. Previous studies concerning (minimally) invasive treatments were performed with women with an average baseline UFS-QoL SSS of 55-65 points [33]. Treatment initiated a decrease of 30-47 points on SSS 12 months after these combined treatments. Hitherto, there are 2 MR-HIFU studies published that used a full ablation protocol, had the same 12-month follow-up period as the studies on (minimally) invasive treatments, and in which women participated with a baseline UFS-QoL SSS of 55-65 points. These women showed an SSS reduction of 30-40 points at follow-up [34,35]. In our study population we expect comparable baseline SSS in the MR-HIFU and standard care group. However, because hysterectomy results in a somewhat higher SSS reduction than the uterus-saving treatments, we assume in our power calculation an a priori 5-point delta between both the MR-HIFU and standard care group in favor of the standard care group. Using a noninferiority margin of 15 points with α (1-sided)=0.025, β=.1, and an SD of 20 points, we estimate that 192 participants (128 patients in the MR-HIFU treatment group and 64 patients in the [minimally] invasive treatment group) will be required to test noninferiority of MR-HIFU. Anticipating a 20% loss to follow-up, we need to include 160 patients in the MR-HIFU group and 80 patients in the (minimally) invasive treatment group. The noninferiority margin and the SD of 20 points were determined in consultation with the Dutch Society for Obstetrics and Gynecology and were similar to the noninferiority margin used in the MYOMEX-2 study [36].

Recruitment

In all participating hospitals, patients will be recruited during a visit at the gynecologist. Furthermore, a study website is created to inform patients from all over the country, providing information and contact details to directly contact the study team. By promoting this website among general practitioners, gynecologists, and potential participants, we expect women with an interest in MR-HIFU to become acquainted with our study. Because MR-HIFU treatment for uterine fibroids is not reimbursed in the Netherlands, participating in the MYCHOICE study is the only possibility for women to undergo MR-HIFU treatment.

Statistical Methods

In this study, data will initially be analyzed on an intention-to-treat-basis (including treatment failures) but a per-protocol analysis will also be performed. QoL at the follow-up time point of 24 months after treatment is determined as a change in SSS between baseline and 24 months' follow-up. The difference between the symptom reduction after MR-HIFU and standard (minimally) invasive fibroid care including 97.5% CI is determined using linear regression analysis with a correction for baseline SSS. Although symptom reduction 24 months after MR-HIFU will be expected to be noninferior to standard (minimally) invasive fibroid care, the time course of symptom reduction may differ between the 2 treatment arms. This will be investigated with longitudinal covariance analysis. A faster symptom reduction in the usual care arm may be caused by a faster symptom reduction after hysterectomy. Therefore, a subgroup analysis in which the individual treatments are compared will be performed.

Patients can leave the study at any time for any reason if they wish to do so, without any consequences. In case they decide to withdraw before treatment or within the first 3-month follow-up, they will be included in the database, but an additional patient will be included to achieve the required sample size and reach primary outcome. In case patients withdraw after the 3-month follow-up, they are considered nonresponders. As much precautions as possible will be taken to prevent missing data. However, missing values are expected to occur in our trial due to technical failures and loss to follow-up. In case missing data reach 5%, additional analyzes will be performed to identify a plausible assumption, that is, missing not at random, missing at random, or missing completely at random. Subsequently, an analysis method that is valid under that assumption will be used.

Data Monitoring

No data monitoring committee will be installed because the risks of participation in this study is categorized as insignificantly low. A data management plan is developed, detailing data management procedures, data standards, minimal data set requirements, and protocols (Isala Institutional Research Board). Data are collected in an online data management platform (Research Manager). Data will be securely stored for at least 15 years, according to hospital Institutional Research Board storage protocols. The study sponsor will be in charge of overseeing data management and access procedures. The Research Manager software will assign a "study ID." The reference between the study ID and the hospital patient number is listed in the patient identification log. The patient identification log will only be accessible by authorized personnel. Each electronic case report form will be completed on-site by the investigator or an authorized staff member. All imaging data will be stored on location but transferred in preparation of the multidisciplinary meeting. After the multidisciplinary meeting these data will be destroyed for privacy reasons. All individual patient data records will be collected on a confidential basis and according to the applicable national data protection, privacy, and secrecy laws.

Safety Reporting

Adverse events are defined as undesirable experiences of a participant within 30 days after treatment and related to participation in this study. All adverse events reported by the participant or observed by the investigator or study staff will be recorded. A serious adverse event is any untoward medical occurrence, within 30 days after treatment and related to participation in this study and results in death, is life threatening (at the time of the event), requires hospitalization or prolongation of existing inpatients' hospitalization, results in persistent or significant disability or incapacity, or any other important medical event that did not result in any of the outcomes listed above. The investigator will report all serious adverse events to the sponsor without undue delay after obtaining knowledge of the events.

Auditing

The clinical monitor will be responsible for verifying adherence to the protocol, reviewing participant records and source data, maintaining records of all actions taken to correct protocol deficiencies during the investigation, and assuring that the data needed to complete the study are complete and accurate.

Patient and Public Involvement

The Foundation Bekkenbodem4All (Pelvicfloor4All) was consulted on the design of the study from a patient perspective and their opinion and feedback were taken into consideration. In addition, an evaluation meeting with previous MR-HIFU patients took place. Outcomes of this meeting were used to improve MR-HIFU treatment routine and to point out important patient outcomes. During inclusion, Bekkenbodem4All will promote the study via their network and participate in the yearly meetings in which the progression of the study is discussed. When the results of the study warrant uptake of the treatment in standard reimbursed care, they will aid in the final implementation of the treatment.

Ethics Approval

This protocol, informed consents, and patient information have been approved by the local medical ethical committee of Isala Hospital (NL74716.075.20) on September 24, 2020, with respect to scientific content and compliance with applicable research and human patient regulations. The research activities of the MYCHOICE study comply with the international conventions and codes of conduct, and the latest Helsinki Declaration of the World Medical Association adopted by the World Medical Assembly.

Dissemination Policy

We aim to make all data Findable, Accessible, Interoperable and Reusable (FAIR) according to the FAIR principles [37]. Therefore, we will assign all (meta)data with a unique and persistent (global) identifier and register or index them in a searchable digital data repository at the end of the study for long-time archiving and data reuse purposes. Results will be presented in (inter)national congresses and meetings, and will be published in peer-reviewed journals, publications of the patient associations, in health-related journals, and on various websites such as the MYCHOICE study website.

Results

Inclusion for the MYCHOICE study started in November 2020. Patient enrollment is expected to last approximately 36 months. Because of the 24-month follow-up, we expect to complete data collection in 2026 and plan the dissemination of the results subsequently.

Discussion

Added Value of MYCHOICE

The MYCHOICE study distinguishes itself from previous MR-HIFU trials in that it is an RCT in which full ablation protocols and the latest MR-HIFU equipment are used for uterine fibroid treatment. Moreover, patient follow-up is 24 months. Furthermore, it answers important research questions on both effectiveness and cost-effectiveness with outcomes that are relevant for policy makers, physicians, and patients.

Strengths

As a primary outcome, we will use QoL in terms of symptom reduction 24 months after treatment. We did not choose the commonly used outcome in uterine fibroids studies, reintervention rate, as our primary outcome because re-interventions are not expected to occur after hysterectomy. Symptom reduction will most likely also differ between hysterectomy and uterus-saving treatment options. However, the influence of symptom reduction after hysterectomies in the control group is probably limited, because we expect that most women who will participate in the MYCHOICE study prefer a uterus-preserving treatment option, just like the intervention under study. This is further enhanced by the 2:1 randomization ratio. This ratio will lead to a higher chance to undergo MR-HIFU treatment, and we believe is therefore an important strength of the design. Another strength is the fact that this unbalanced design will enable us to gather more data on our intervention, while the effectiveness of standard care is already much better documented.

Our follow-up duration of 24 months is based on the long-term outcomes of a retrospective study on MR-HIFU treatment results performed by our group [14]. In this study, we found that all reinterventions were performed within 24 months after the initial treatment, indicating that the treatment effect reaches a steady state within 24 months after treatment. Thus, it is not useful to prolong follow-up of these patients.

Limitations

A possible limitation of the MYCHOICE study is the uncommon use of a mixed control group. However, in current daily practice, usual care for women with symptomatic uterine fibroids in whom conservative treatment failed or is undesired consist of several (minimally) invasive treatments. The minimally invasive UAE is reimbursed in the Netherlands, and would therefore be an appropriate reference treatment for the noninvasive MR-HIFU treatment. However, hysterectomies are by far the most frequently performed and should thus not be omitted from the standard care group. The standard care group is complemented with myomectomies. We expect that women willing to participate in this study are mostly searching for a uterus-saving treatment option, sometimes because of a future pregnancy wish. For this category of women, myomectomy is the only alternative and therefore a mixed control group qualifies the most. By using this mixed group, we believe we best represent the real-world situation. Furthermore, the information on treatment preference in the control group can be used to gain more insights into patient preferences.

Although an RCT design is commonly considered to provide the best evidence on the effectiveness of a new intervention compared with usual care, our RCT design also poses several challenges [38]. Women may not be willing to be randomized, which may delay enrollment, and our 2:1 randomization ratio with a mixed control group may lead to low sample sizes for the individual treatment options in the mixed control group, which will limit valid comparisons between outcomes of individual treatments. However, sufficient data on primary outcomes are already available for all treatments in this control group. Other possible limitations of the MYCHOICE study are that not all (secondary) outcomes are equally relevant for all included treatments and that the MR-HIFU treatment cannot be performed in all participating centers. However, because of the restricted number of patients eligible for treatment and the complexity of the treatment, it might not be cost efficient to have more than 2-4 uterine fibroid MR-HIFU facilities in the Netherlands.

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Authors' Contributions

KJA and IMN contributed equally to the conceptual design of the study and writing of the manuscript. KJA obtained ethical approval. IMN provided statistical expertise. JRD, GWJF, EI, IMV, SV, JAFH, WJKH, and JMS contributed to the study design and the design of the manuscript. SV and JAFH contributed to the design of the manuscript. MFB is the principal investigator of this study and responsible for the conceptual design of the study. All authors critically revised the manuscript for important intellectual content and approved the final manuscript.

Conflicts of Interest

None declared

References

1. Stewart EA. Uterine fibroids. Lancet 2001 Jan 27;357(9252):293-298. [doi: 10.1016/S0140-6736(00)03622-9] [Medline: 11214143]
2. Pérez-López FR, Ornat L, Ceausu I, Depypere H, Erel CT, Lambrinoudaki I, et al. EMAS position statement: management of uterine fibroids. Maturitas 2014 Sep;79(1):106-116. [doi: 10.1016/j.maturitas.2014.06.002] [Medline: 24975954]
3. Fortin C, Flyckt R, Falcone T. Alternatives to hysterectomy: The burden of fibroids and the quality of life. Best Pract Res Clin Obstet Gynaecol 2018 Jan;46:31-42. [doi: 10.1016/j.bpobgyn.2017.10.001] [Medline: 29157931]
4. Pron G. Magnetic Resonance-Guided High-Intensity Focused Ultrasound (MRgHIFU) Treatment of Symptomatic Uterine Fibroids: An Evidence-Based Analysis. Ont Health Technol Assess Ser 2015;15(4):1-86 [FREE Full text] [Medline: 26357530]
5. Aarts JWM, Nieboer TE, Johnson N, Tavender E, Garry R, Mol BWJ, et al. Surgical approach to hysterectomy for benign gynaecological disease. Cochrane Database Syst Rev 2015 Aug 12(8):CD003677 [FREE Full text] [doi: 10.1002/14651858.CD003677.pub5] [Medline: 26264829]
6. Silberzweig JE, Powell DK, Matsumoto AH, Spies JB. Management of Uterine Fibroids: A Focus on Uterine-sparing Interventional Techniques. Radiology 2016 Sep;280(3):675-692. [doi: 10.1148/radiol.2016141693] [Medline: 27533290]
7. Metwally M, Raybould G, Cheong YC, Horne AW. Surgical treatment of fibroids for subfertility. Cochrane Database Syst Rev 2020 Jan 29;1:CD003857 [FREE Full text] [doi: 10.1002/14651858.CD003857.pub4] [Medline: 31995657]
8. van der Kooij SM, Hehenkamp WJK, Volkers NA, Birnie E, Ankum WM, Reekers JA. Uterine artery embolization vs hysterectomy in the treatment of symptomatic uterine fibroids: 5-year outcome from the randomized EMMY trial. Am J Obstet Gynecol 2010 Aug;203(2):105.e1-105.13. [doi: 10.1016/j.ajog.2010.01.049] [Medline: 20579960]
9. Lohle PNM, Higué D, Herbreteau D. Uterine artery embolisation in women with symptomatic uterine fibroids. Presse Med 2019 Apr;48(4):440-446. [doi: 10.1016/j.lpm.2019.03.012] [Medline: 31036388]
10. Arthur R, Kachura J, Liu G, Chan C, Shapiro H. Laparoscopic myomectomy versus uterine artery embolization: long-term impact on markers of ovarian reserve. J Obstet Gynaecol Can 2014 Mar;36(3):240-247. [doi: 10.1016/S1701-2163(15)30632-0] [Medline: 24612893]
11. Verpalen IM, Anneveldt KJ, Nijholt IM, Schutte JM, Dijkstra JR, Franx A, et al. Magnetic resonance-high intensity focused ultrasound (MR-HIFU) therapy of symptomatic uterine fibroids with unrestrictive treatment protocols: A systematic review and meta-analysis. Eur J Radiol 2019 Nov;120:108700. [doi: 10.1016/j.ejrad.2019.108700] [Medline: 31634683]
12. Fennessy FM, Tempany CM, McDannold NJ, So MJ, Hesley G, Gostout B, et al. Uterine leiomyomas: MR imaging-guided focused ultrasound surgery--results of different treatment protocols. Radiology 2007 Jun;243(3):885-893. [doi: 10.1148/radiol.2433060267] [Medline: 17446521]
13. Hesley GK, Gorny KR, Henrichsen TL, Woodrum DA, Brown DL. A clinical review of focused ultrasound ablation with magnetic resonance guidance: an option for treating uterine fibroids. Ultrasound Q 2008 Jun;24(2):131-139. [doi: 10.1097/RUQ.0b013e31817c5e0c] [Medline: 18528271]
14. Verpalen IM, de Boer JP, Linstra M, Pol RLI, Nijholt IM, Moonen CTW, et al. The Focused Ultrasound Myoma Outcome Study (FUMOS); a retrospective cohort study on long-term outcomes of MR-HIFU therapy. Eur Radiol 2020 May;30(5):2473-2482. [doi: 10.1007/s00330-019-06641-7] [Medline: 32040725]
15. Mindjuk I, Trumm CG, Herzog P, Stahl R, Matzko M. MRI predictors of clinical success in MR-guided focused ultrasound (MRgFUS) treatments of uterine fibroids: results from a single centre. Eur Radiol 2015 May;25(5):1317-1328. [doi: 10.1007/s00330-014-3538-6] [Medline: 25510445]
16. Wang Y, Geng J, Bao H, Dong J, Shi J, Xi Q. Comparative Effectiveness and Safety of High-Intensity Focused Ultrasound for Uterine Fibroids: A Systematic Review and Meta-Analysis. Front Oncol 2021;11:600800 [FREE Full text] [doi: 10.3389/fonc.2021.600800] [Medline: 33767979]
17. Anneveldt KJ, van 't Oever HJ, Nijholt IM, Dijkstra JR, Hehenkamp WJ, Veersema S, et al. Systematic review of reproductive outcomes after High Intensity Focused Ultrasound treatment of uterine fibroids. Eur J Radiol 2021 Aug;141:109801. [doi: 10.1016/j.ejrad.2021.109801] [Medline: 34116454]
18. Duc NM, Keserci B. Review of influential clinical factors in reducing the risk of unsuccessful MRI-guided HIFU treatment outcome of uterine fibroids. Diagn Interv Radiol 2018 Sep;24(5):283-291 [FREE Full text] [doi: 10.5152/dir.2018.18111] [Medline: 30211682]
19. Zowall H, Cairns JA, Brewer C, Lamping DL, Gedroyc WMW, Regan L. Cost-effectiveness of magnetic resonance-guided focused ultrasound surgery for treatment of uterine fibroids. BJOG 2008 Apr;115(5):653-662 [FREE Full text] [doi: 10.1111/j.1471-0528.2007.01657.x] [Medline: 18333948]
20. O'Sullivan AK, Thompson D, Chu P, Lee DW, Stewart EA, Weinstein MC. Cost-effectiveness of magnetic resonance guided focused ultrasound for the treatment of uterine fibroids. Int J Technol Assess Health Care 2009 Jan;25(1):14-25 [FREE Full text] [doi: 10.1017/S0266462309090035] [Medline: 19126247]

21. Kong CY, Meng L, Omer ZB, Swan JS, Srouji S, Gazelle GS, et al. MRI-guided focused ultrasound surgery for uterine fibroid treatment: a cost-effectiveness analysis. AJR Am J Roentgenol 2014 Aug;203(2):361-371 [FREE Full text] [doi: 10.2214/AJR.13.11446] [Medline: 25055272]
22. Cain-Nielsen AH, Moriarty JP, Stewart EA, Borah BJ. Cost-effectiveness of uterine-preserving procedures for the treatment of uterine fibroid symptoms in the USA. J Comp Eff Res 2014 Sep;3(5):503-514 [FREE Full text] [doi: 10.2217/cer.14.32] [Medline: 24878319]
23. Babashov V, Palimaka S, Blackhouse G, O'Reilly D. Magnetic Resonance-Guided High-Intensity Focused Ultrasound (MRgHIFU) for Treatment of Symptomatic Uterine Fibroids: An Economic Analysis. Ont Health Technol Assess Ser 2015;15(5):1-61 [FREE Full text] [Medline: 26357531]
24. McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, et al. No surgical innovation without evaluation: the IDEAL recommendations. Lancet 2009 Sep 26;374(9695):1105-1112. [doi: 10.1016/S0140-6736(09)61116-8] [Medline: 19782876]
25. Laughlin-Tommaso S, Barnard EP, AbdElmagied AM, Vaughan LE, Weaver AL, Hesley GK, et al. FIRSTT study: randomized controlled trial of uterine artery embolization vs focused ultrasound surgery. Am J Obstet Gynecol 2019 Feb;220(2):174.e1-174.e13. [doi: 10.1016/j.ajog.2018.10.032] [Medline: 30696556]
26. Funaki K, Fukunishi H, Sawada K. Clinical outcomes of magnetic resonance-guided focused ultrasound surgery for uterine myomas: 24-month follow-up. Ultrasound Obstet Gynecol 2009 Nov;34(5):584-589 [FREE Full text] [doi: 10.1002/uog.7455] [Medline: 19852041]
27. Gorny KR, Borah BJ, Brown DL, Woodrum DA, Stewart EA, Hesley GK. Incidence of additional treatments in women treated with MR-guided focused US for symptomatic uterine fibroids: review of 138 patients with an average follow-up of 2.8 years. J Vasc Interv Radiol 2014 Oct;25(10):1506-1512. [doi: 10.1016/j.jvir.2014.05.012] [Medline: 24998103]
28. Chan A, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 2013;346:e7586 [FREE Full text] [Medline: 23303884]
29. Spies JB, Coyne K, Guaou Guaou N, Boyle D, Skyrnarz-Murphy K, Gonzalves SM. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. Obstet Gynecol 2002 Feb;99(2):290-300. [doi: 10.1016/s0029-7844(01)01702-1] [Medline: 11814511]
30. Versteegh MM, Vermeulen KM, Evers SMAA, de Wit GA, Prenger R, Stolk EA. Dutch Tariff for the Five-Level Version of EQ-5D. Value Health 2016 Jun;19(4):343-352 [FREE Full text] [doi: 10.1016/j.jval.2016.01.003] [Medline: 27325326]
31. Hehenkamp WJK, Volkers NA, Birnie E, Reekers JA, Ankum WM. Pain and return to daily activities after uterine artery embolization and hysterectomy in the treatment of symptomatic uterine fibroids: results from the randomized EMMY trial. Cardiovasc Intervent Radiol 2006;29(2):179-187. [doi: 10.1007/s00270-005-0195-9] [Medline: 16447002]
32. Dindo D, Demartines N, Clavien P. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004 Aug;240(2):205-213. [Medline: 15273542]
33. Manyonda IT, Bratby M, Horst JS, Banu N, Gorti M, Belli A. Uterine artery embolization versus myomectomy: impact on quality of life--results of the FUME (Fibroids of the Uterus: Myomectomy versus Embolization) Trial. Cardiovasc Intervent Radiol 2012 Jun;35(3):530-536. [doi: 10.1007/s00270-011-0228-5] [Medline: 21773858]
34. Dobrotwir A, Pun E. Clinical 24 month experience of the first MRgFUS unit for treatment of uterine fibroids in Australia. J Med Imaging Radiat Oncol 2012 Aug;56(4):409-416. [doi: 10.1111/j.1754-9485.2012.02376.x] [Medline: 22883648]
35. Tan N, Lu D, Raman S, Bahrami S. MR guided focused US for treatment of uterine fibroids: symptom reduction in a multicenter trial using a novel treatment algorithm. J Ther Ultrasound 2015 Jun 30;3:O91. [doi: 10.1186/2050-5736-3-s1-o91]
36. Middelkoop M, Huirne JAF, van der Weide MCJ, Bosmans JE, Hehenkamp WJK. A multi-centre, randomized, non-inferiority trial to compare ulipristal with standard surgical treatment in women with symptomatic uterine fibroids: Protocol of the MYOMEX-2 trial. Eur J Obstet Gynecol Reprod Biol 2021 Jan;256:63-69 [FREE Full text] [doi: 10.1016/j.ejogrb.2020.10.058] [Medline: 33171419]
37. Wilkinson MD, Dumontier M, Aalbersberg IJJ, Appleton G, Axton M, Baak A, et al. The FAIR Guiding Principles for scientific data management and stewardship. Sci Data 2016 Mar 15;3:160018 [FREE Full text] [doi: 10.1038/sdata.2016.18] [Medline: 26978244]
38. Bhide A, Shah PS, Acharya G. A simplified guide to randomized controlled trials. Acta Obstet Gynecol Scand 2018 Apr;97(4):380-387 [FREE Full text] [doi: 10.1111/aogs.13309] [Medline: 29377058]

Abbreviations

EQ-5D-5L: 5-level version of the EuroQoL questionnaire
FAIR: Findable, Accessible, Interoperable and Reusable
IDEAL: Idea, Development, Exploration, Assessment and Long-term study
iMCQ: iMTA Medical Consumption Questionnaire
iPCQ: iMTA Productivity Cost Questionnaire
MR-HIFU: magnetic resonance image–guided high-intensity focused ultrasound
MRI: magnetic resonance imaging

MYCHOICE: MYoma treatment Comparison study: High-intensity image–guided fOcused ultrasound versus standard (minimally) Invasive fibroid care—a (Cost-)Effectiveness analysis
NPV: nonperfused volume
PREM: patient-reported experience measurement
QoL: quality of life
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SSS: symptom severity score
UAE: uterine artery embolization
UFS-QoL: Uterine Fibroid Symptom and Quality of Life questionnaire

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Protocol

A Parent Coach–Led Model of Well-Child Care for Young Children in Low-Income Communities: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: The Parent-focused Redesign for Encounters, Newborns to Toddlers (PARENT) intervention was created as a team-based approach to well-child care (WCC) that relies on a health educator (*Parent Coach*) to provide the bulk of WCC services, address specific needs faced by families in low-income communities, and decrease reliance on the clinician as the primary provider of WCC services.

Objective: This study aims to evaluate the impact of PARENT using a cluster randomized controlled trial.

Methods: This study tested the effectiveness of PARENT at 10 clinical sites in 2 federally qualified health centers in Tacoma, Washington, and Los Angeles, California. We conducted a cluster randomized controlled trial that included 916 families with children aged ≤12 months at the time of the baseline survey. Parents will be followed up at 6 and 12 months after enrollment. The Parent Coach, the main element of PARENT, provides anticipatory guidance, psychosocial screening and referral, developmental and behavioral surveillance, screening, and guidance at each WCC visit. The coach is supported by parent-focused previsit screening and visit prioritization, a brief, problem-focused clinician encounter for a physical examination and any concerns that require a clinician's attention, and an automated text message parent reminder and education service for periodic, age-specific messages to reinforce key health-related information recommended by Bright Futures national guidelines. We will examine parent-reported quality of care (receipt of nationally recommended WCC services, family-centeredness of care, and parental experiences of care), and health care use (WCC, urgent care, emergency department, and hospitalizations), conduct a cost analysis, and conduct a separate time-motion study of clinician time allocation to assess efficiency. We will also collect data on exploratory measures of parent-and parenting-focused outcomes. Our primary outcomes were receipt of anticipatory guidance and emergency department use.

Results: Participant recruitment began in March 2019. After recruitment, 6- and 12-month follow-up surveys will be completed. As of August 30, 2021, we enrolled a total of 916 participants.

Conclusions: This large pragmatic trial of PARENT in partnership with federally qualified health centers will assess its utility as an evidence-based and financially sustainable model for the delivery of preventive care services to children in low-income communities.

Trial Registration: ClinicalTrials.gov: NCT03797898; https://clinicaltrials.gov/ct2/show/NCT03797898

International Registered Report Identifier (IRRID): DERR1-10.2196/27054

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KEYWORDS

preventive care; well-child care; community health centers

Introduction

Background

Well-child care (WCC) visits for child preventive care during the first 3 years of life are important opportunities to address social, developmental, behavioral, and health concerns of young children and their families [1]. Despite the great potential of WCC to positively impact child health and well-being, multiple studies have demonstrated that many children do not receive all recommended preventive and developmental services during these visits, and that most parents do not have all of their psychosocial, developmental, and behavioral concerns addressed at these WCC visits [2-8]. Unfortunately, this unmet need is often the greatest for low-income families [9] as they often have substantial needs.

In the United States, WCC is not optimally structured to meet the vast array of preventive care needs that families in low-income communities often have [8]. Major structural problems with WCC include (1) reliance solely on busy clinicians (pediatricians, family physicians, or nurse practitioners) for most basic, routine WCC services [10-13], (2) limited to brief (often 15- to 20-minute) face-to-face clinician-directed WCC visits to address the wide array of education and guidance services in WCC [1,7,14]; (3) the need for high-level clinicians to focus clinical time on patients with complex medical needs, and (4) lack of a systematic, patient-driven method for visit customization to best meet families' needs [15,16]. These problems in the structure of WCC are a key contributor to the wide variations in both, the processes of WCC and the receipt of preventive care services. This can lead to suboptimal quality of WCC services, resulting in missed opportunities to intervene and support the health and well-being of children in low-income communities.

To address the gaps in current WCC, we partnered with federally qualified health centers (FQHCs) to develop a new model of WCC to meet the needs of children in low-income communities. The Parent-focused Redesign for Encounters, Newborns to Toddlers (PARENT) intervention is a team-based approach to WCC relying on a health educator (*Parent Coach*) to provide the bulk of WCC services, address specific needs faced by families in low-income communities, and decrease reliance on the clinician as the primary provider of WCC services [17-19].

Although several strategies to redesign the structure of WCC have been proposed and studied, there are few evidence-based comprehensive models that are financially sustainable alternatives to the current WCC [11,20]. In a systematic review of tools and strategies for WCC clinical practice redesign for young children in the United States, we highlighted 17 published articles that focused on interventions to improve WCC delivery [11]. In this review, and a more recent update of the review, we identified 2 WCC practice-based interventions (PARENT and Healthy Steps for Young Children) in which a nonclinician was added as part of the WCC team to enhance preventive care services for young children [8,11]. These 2 WCC practice interventions demonstrate the effectiveness of using a team-based approach to preventive care services. However, only PARENT has randomized controlled trial (RCT) evidence of improvements in both the receipt of preventive care services and decreased emergency department (ED) use.

The central element of PARENT is the Parent Coach, a health educator who meets one-on-one with the family for approximately 15-20 minutes, depending on the needs of the parent, at the time of the WCC visit. The Parent Coach receives 4-6 weeks of WCC Parent Coach training and provides (1) anticipatory guidance (counseling and education on a broad variety of parenting-related topics), (2) psychosocial screening and community resource referral, and (3) developmental and behavioral surveillance, screening, and guidance. Parents complete a previsit screening questionnaire to help the Parent Coach prioritize their time with the family. After the family meets with the Parent Coach, the pediatrician enters the examination room to conduct the physical examination, address any clinical concerns, and provide additional guidance to parents regarding any concerns identified by the Parent Coach. Parents also receive weekly automated text messages that reinforce key health-related, age-specific guidance and education; these text messages are also designed to promote parental engagement in WCC guidance between visits.

In an initial pilot RCT of PARENT among 251 low-income families in 2 urban areas, we found strong and consistent intervention effects on the quality of preventive care provided to families and on reducing ED use (Table 1) [18,19].

Table 1. Parent-focused Redesign for Encounters, Newborns to Toddlers intervention pilot trial findings (n=226).

RCT[a] results	Control	Intervention	Effect size (Cohen *d*)	*P* value
Use, n (%)				
Well-visits up-to-date	84 (75.7)	86 (74.8)	N/A[b]	.88
Two or more sick visits	44 (39.6)	43 (37.7)	N/A	.77
Two or more emergency department visits	24 (21.6)	12 (10.4)	0.47	.02
Receipt of WCC[c] services, mean (SD)				
Anticipatory guidance	77.4 (24.5)	89.3 (12.9)	0.49	<.001
Health information	89.6 (22.2)	96.3 (13.8)	0.30	.008
Social needs assessment	77.9 (29.0)	94.9 (13.5)	0.59	<.001
Receipt of WCC services, n (%)				
Developmental screening	90 (81.1)	106 (92.2)	0.12	.01
Parent concerns addressed	59 (73.8)	83 (90.2)	0.28	.005
Experiences of care, mean (SD)				
Family-centered care	92.4 (13)	96.3 (8.2)	0.30	.008
Helpfulness of care	82.1 (19.4)	91.3 (12.3)	0.47	<.001
Overall rating of care	91.7 (11.6)	94.5 (9.8)	0.24	.049

[a]RCT: randomized controlled trial.

[b]N/A: not applicable.

[c]WCC: well-child care.

Objectives

To examine the effectiveness of PARENT as a potential evidence-based, financially sustainable model for WCC delivery, we are conducting a large, cluster RCT, in partnership with 10 clinics that are part of 2 large, multisite FQHCs. This study has 2 major phases. In phase 1, we used a community engagement and intervention implementation process [17,21-23] to guide the intervention adaptation process, Parent Coach training, practice workflow, and intervention implementation in the practices. In phase 2 (described in this protocol), we are conducting a cluster RCT of PARENT (practice-level randomization) to determine the effects on WCC quality, use, and clinician efficiency, and its costs and cost-offsets.

The cluster RCT has the following study aims and hypotheses:

- Aim 1: measure the effect of PARENT on the receipt of nationally recommended WCC services and parent experiences of care.
- Hypothesis 1: PARENT will improve the receipt of WCC services and parent experiences of care.
- Aim 2: determine the effects of PARENT on WCC, urgent care, ED use, and net costs.
- Hypothesis 2a: PARENT will result in improved up-to-date rates for WCC visits and reduced ED use.
- Hypothesis 2b: in a cost analysis, we demonstrate that the direct intervention costs of PARENT are offset by net reductions in ED use.
- Aim 3: examine the effect of PARENT on clinician time allocation for WCC and urgent care visits.
- Hypothesis 3: clinicians will shift the time from providing routine WCC services in well-visits to chronic disease management and urgent care.

Methods

Study Design

Our community clinical partners are 2 FQHCs located in and around Tacoma, Washington and Los Angeles, California, with 4 and 6 participating clinics, respectively. Using computer-generated random allocation, the study biostatistician block-randomized the clinics to intervention (n=5) and control (n=5), stratified by state to ensure equal numbers per state across the study arm. The 5 intervention clinics are implementing PARENT for all WCC visits through the age of 2 years at their clinical site, and the control clinics are continuing usual care (clinician-directed WCC visits). A total of 940 families (94 per clinic) with infants aged ≤12 months are being enrolled and will remain in the study for a period of 12 months. Parents will complete a survey at baseline and at 6 and 12 months after enrollment. We will examine parent-reported quality of care (receipt of nationally recommended WCC services, family-centeredness of care, and parental experiences of care) and health care use (WCC, urgent care, ED, and hospitalizations), conduct a cost analysis, and conduct a time-motion study to assess clinician time allocation for efficiency. Data on exploratory measures of parent-and parenting-focused outcomes will also be collected.

Intervention Components

The intervention components are as follows:

- Parent Coach
  - The Parent Coach is a Spanish and English bilingual, bachelor's degree level health educator hired by the FQHC, who has participated in a 6-week training led by our academic research team. The coaches hired by the clinics are bicultural, bilingual Latinx individuals who have previously worked as care coordinators or medical interpreters; they all have experience in child health fields and in working with low-income families. The training consisted of self-directed learning based on Bright Futures Guidelines, Fourth Edition [1], relationship-building with community organizations (for resource referral) near each clinical site, simulated WCC visits with trainer feedback, coach-observed WCC visits, and pediatric provider-observed WCC visits with feedback at the clinics. The Parent Coach is available at the intervention clinics to serve as the primary provider of anticipatory guidance, psychosocial screening and referral, and developmental and behavioral guidance and screening during each WCC visit.
  - The Parent Coach is available at other times to answer parents' preventive care–related questions and conduct parent follow-up calls and visit reminders during clinic business hours.
- WCC visit process
  - Upon arrival, the child is registered, weighed, and measured by the medical assistant and then taken to an examination room per the usual care process. The coach then enters the patient room and uses the completed, adapted version of the Bright Futures Previsit Questionnaire (completed in the waiting room or examination room) to guide the WCC visit [24]. The coach discusses the parents' priorities for the visit, addressing parental concerns on topics such as feeding, sleeping, parenting, safety, and other issues. Next, the coach reviews any red flags from the questionnaire, conducts social needs and psychosocial screening, and provides any needed community resource referrals. Finally, the coach reviews developmental milestones or the structured developmental screen, if used at that visit, and addresses any behavioral concerns that the parent has.
  - The Parent Coach documents the visit by the family in the electronic health record, highlighting the results of developmental and behavioral screening and any issues that the clinician needs to review at the top of the encounter page. The Parent Coach spends 15-20 minutes with the parent based on parent needs.
  - After the Parent Coach completes their time with the family, the clinician enters the patient room, conducts a physical examination, and reviews the Parent Coach's notes within the electronic health record. The clinician addresses any Parent Coach's findings that need further clinical investigation (eg, concern for speech delay on developmental surveillance), any additional parent concerns, and any chronic or urgent care issues. In cases where the Parent Coach identifies concerns that need immediate attention from the clinician, the Parent Coach will directly communicate with the clinician about the parents' needs and follow-up plan (warm hand-off).
- Healthy text messages
  - Parents enrolled in the intervention clinics are offered a child health-focused text messaging service at study enrollment. Research staff help parents enroll into the text messaging service by texting their cell phone number, language preference (English or Spanish), clinic location, and child's date of birth to a number provided by Healthy-TXT, a text messaging service (Healthy-TXT LLC). The library of text messages was adapted from Healthy-TXT to meet the needs of the FQHCs. If the parent chooses to sign up for the text message service (parents can be enrolled into the study and decline text messages), they receive weekly messages focused on age-appropriate anticipatory guidance, health education, and reminders for WCC visits. These messages are tailored to the child's age and parent's language preference (Spanish or English). Most messages include a link to an educational website (eg, healthychildren.org) with a video or written information on that specific topic. Some messages include the clinic's telephone number for visit scheduling, the Parent Coach's number, or other information (eg, poison control hotline). At any time, parents can text "STOP" to end the service.

Procedures

Patient Recruitment and Enrollment at Intervention and Control Clinics

Parents or legal guardians checking in for a WCC visit or follow-up visit for an infant aged ≤12 months are approached by research staff in the waiting room. The research staff obtain a schedule of WCC visits via an encrypted email sent by the clinic staff. The schedule includes the date and time of all WCC visits for infants aged ≤12 months—no protected health information is included in the schedule. The research staff determine which clinics to visit for recruitment based on this schedule, using a systematic approach. On the day of clinic recruitment, research staff, clinic staff, and front desk staff closely coordinate recruitment. The front desk staff verifies the WCC visits each day with the research staff and obtains verbal permission from the parent (or legal guardians) to be approached by research staff at the clinic that day to talk about the study. Those who agree are approached while waiting for their WCC visit.

Participants and Enrollment Procedures

For families who are approached in clinics, the study staff explain the study and screen for the following eligibility criteria: (1) be an adult (aged ≥18 years) parent or legal guardian of a child aged ≤12 months arriving for a visit, (2) have no plans to change clinic providers for the next 12 months, and (3) have English or Spanish language proficiency. Eligible families provide informed consent and parental permission. For multiple gestations, one of the infants is selected at random as the index child enrolled in the study. Children with special health care

needs are not excluded from the study; these children generally receive the same recommended preventive care services.

Contact information is collected from the enrolled parent or legal guardian and spouse or partner (home and cell phone and email) to contact them to complete the baseline survey, if needed. The information is verified at each subsequent research contact for the follow-up surveys at 6 and 12 months from the date of enrollment. We also ask parents to provide the contact information of 3 relatives or friends who will always know their whereabouts.

Although this study involves direct interaction with economically and educationally disadvantaged persons, we are careful to minimize the risk of coercion or undue influence. The recruitment process for the study is completely voluntary, and families are informed that they can withdraw from the study at any point. Those who agree to participate receive a cash or gift card incentive for each survey. Consent forms have been so written as to be understood by those with limited reading or writing proficiency in both English and Spanish. However, if a participant is unable to read the consent form, the research assistant reads the form aloud, and a witness initials the form, acknowledging that the terms of agreement have been read to the participant.

Data Collection

We shall conduct 3 waves of parent survey data collection (baseline, 6-month and 12-month), and will review the child's electronic chart at 12 months follow-up. Interviewers are not blinded to the group assignment.

- Baseline survey (at enrollment, in person or via phone): Upon enrollment, parents participate in a 35-minute survey for the collection of baseline demographic data on the infant, parent, household, child's medical history, and health care use during the 3 months before the survey.
- Six-month survey: Research staff conduct a 15-minute phone survey that updates the child's medical history, household changes, and health care use since enrollment (eg, ED use). The 6-month survey is designed to increase participant retention over the 12-month study period, by providing an opportunity for engagement at 6 months, and is designed to improve data accuracy by using a 6-month recall period, rather than a 12-month recall, for use-related questions.
- Twelve-month survey: All participants will be asked to complete a 40-minute survey by phone. This survey administration includes questions from the Promoting Healthy Development Survey, a parent survey that assesses the receipt of nationally recommended WCC services [25]. It is endorsed by the National Quality Forum and has been used by 10 State Medicaid agencies, 4 health plans, 38 pediatric practices, and nationally through the National Survey of Early Childhood Health to collect data for over 45,000 children [26]. It is available in English and Spanish and is written at an 8th grade reading level. It has strong construct validity (mean factor loading: 0.69) and internal consistency (mean Cronbach α=.80) [27]. A previous study using this survey revealed that quality measure scores for children in 3 health plans ranged from 17 to 75 (on a 100-point scale) and varied significantly across health plans [27].

We will use the Promoting Healthy Development Survey to measure the parent-perceived receipt of recommended WCC services. Questions are also included on social determinant screening and referral drawn from the Promoting Healthy Development Survey and health care use since the 6-month survey. We will also use items on overall satisfaction with care from the Consumer Assessment of Health care Providers and Systems Health Plan Survey [28,29] and family-centeredness of care from the National Survey of Children's Health [30]. We shall collect data on exploratory measures of parental mental health [31] and parenting behaviors [25,30].

For the 6- and 12-month follow-up surveys, we will contact the study participants 2 weeks before the due date. If we are unable to reach them by the due date, we will continue calling them up to 3 months after the due date to complete the survey. After completing the 3 waves of survey data collection, we will conduct chart reviews to extract the number of clinic visits (total, WCC, and acute care) and immunization records. The parent or legal guardian will receive a gift card or cash incentive after completing the baseline survey (US $30) and follow-up surveys at 6 months (US $20) and 12 months (US $40) after enrollment.

Finally, to assess changes in clinician time and WCC content covered during visits, we will conduct a time-motion study, consisting of direct observations of clinic teams (clinician and Parent Coach) at 20 randomly selected WCC visits at each clinical site (intervention and control) before and during intervention implementation. This data collection is not part of the RCT but is a supplemental observational study that will allow us to understand how the visit differs with and without the Parent Coach. A total of 200 time-motion study visits will be observed during the first year for the control and intervention clinics. During the fourth and fifth project years, we will observe an additional 200 time-motion study visits for intervention and control clinics.

Safeguarding

To ensure quality control of data, the study team member who collects the data enters the data into the protected database, and another team member validates the data entry. In addition, to ensure confidentiality, parent or child participant data are entered directly into a REDCap (Research Electronic Data Capture; Vanderbilt University) database on password-protected laptops and electronic tablets. Any data initially collected from a hard copy is transferred to the secure database. Hard copy documents are kept in locked cabinets in a locked office. Identifiable information, such as consent forms, is kept separately from data collection forms to ensure deidentification of the data. Hard copy documents collected from clinics and transported to study offices are kept in secure document holders to protect against breaches of confidentiality.

Main Outcomes

Overview

Our dual primary outcome measures are *the receipt of preventive care services* for anticipatory guidance received and ED use.

Secondary outcomes include other measures for the receipt of preventive care services, use, experiences of care, costs, and allocation of provider time. Multimedia Appendix 1 [1-41] presents a table of all study measures.

Primary Outcomes Selection

Our primary outcomes are receipt of anticipatory guidance and ED use. We will select a WCC quality measure and a health care use measure to represent the outcomes most important to the stakeholders within WCC (parents, providers, and payers). We considered that costs may be most important for the sustainability of PARENT, but the receipt of WCC services may be most important to its acceptability with parents and pediatric providers. We do not consider downstream child or parent health outcomes as primary measures, but we will conduct an analysis of exploratory measures such as effective parenting and parent mental health that have been related to child outcomes [32-36].

Analysis

Overview

Once all data are collected, we will compile descriptive statistics on all outcome variables, composite scores, and covariates. We will report means and SDs (or medians and IQRs as appropriate) for continuous variables, create graphical displays to visualize distributions, and transform variables with nonnormal distributions, such as cost offsets. Next, we will use multivariable analyses to examine the differences between the control and intervention groups at 12 months on the measures described above. From these analyses, we will estimate the intervention effects. An intent-to-treat approach rather than a per-protocol approach will be used; that is, parents will be analyzed according to the assigned group regardless of deviations from the study protocol. Missing outcome data will be handled using a strategy described by White et al [37]. Observations with missing values will be excluded from the initial analysis (complete case analysis) [37]. We will examine and report the patterns and plausible causes of any missing data. This will then inform additional analyses using multiple imputation, comparing the effects of different plausible assumptions about the nature of the missing data. Results with and without multiple imputations will be presented. Additional sensitivity analyses will be conducted by performing the analyses with and without outliers and influential data points. All tests will be 2-sided, and P values <.05, will be considered statistically significant.

Primary Outcome 1: Anticipatory Guidance

We will analyze anticipatory guidance based on data collected at 12 months after enrollment. We will assess the intervention effect on anticipatory guidance via linear mixed-effects models that include random effects to account for clustering by clinic. The outcome may be transformed before fitting the model if nonnormality is observed. The analysis will include intervention status as the main independent variable and may be adjusted for potential confounding factors that differ between the 2 groups at baseline. We will also test for possible interaction effects between the intervention and these covariates. All other outcome variables to measure experiences of care and receipt of other nationally recommended WCC services are regarded as secondary. Each outcome will be analyzed using linear or generalized linear mixed effects models.

Primary Outcome 2: Health Care Use

Intervention effects on health care use (ED visits, hospitalizations, and urgent care visits) will be assessed using generalized linear mixed-effects models for binary or count data. The model will include random effects to capture data clustering within the clinic; the primary independent variable will be intervention status. The analysis will be adjusted for any baseline child, parent, or household characteristics that differ between the control and intervention groups. We will also test for interaction between child age and the intervention, as well as between the intervention and any covariates that differ across study arms at baseline.

Cost Analysis

We will conduct our analysis from the perspective of the health sector and consider intervention costs (direct and indirect) and cost offsets [38].

Intervention Costs

We will distinguish between start-up costs (eg, Parent Coach training), fixed annual maintenance costs (eg, text message service), and the marginal cost of adding patients to the existing intervention (eg, additional time spent by Parent Coaches if WCC caseloads increase). The primary source of direct intervention costs is staff time, particularly the Parent Coach time. Staff time will be tracked during randomly selected weeks throughout the study using intervention service logs valued at total compensation (salary+benefits). Other intervention costs, such as the opportunity costs of using clinic space (included at the value of its opportunity cost) and parents' time (valued using national average wage rates from the Bureau of Labor Statistics) will be tracked by study accounting procedures. We will exclude evaluation-related costs from our estimates.

Cost Offsets

To explore health care use, we will collect parent survey data on the use of services that we hypothesize may be affected by PARENT. This includes additional services (eg, more referrals for behavioral problems because of better identification) and cost offsets (eg, reduced ED visits). We will construct parent-specific measures as the weighted sum of the number of units used in each service category, weighted by the unit cost of that type of service. We will use national estimates of unit costs by condition and age group, such as the Disease Expenditure Study estimates of unit cost per outpatient visit, ED visit, and hospital stay [39]. To test whether the intervention leads to budget neutrality or even net cost savings, we will estimate the mean difference in nonintervention costs between intervention and control using multivariate regression methods. The analysis may be conducted with the log of cost or other transformation, as the distribution of costs often has a long right tail representing a few patients with high expenditures. We will then compare the average intervention cost per child with the estimated savings in nonintervention costs. Although the average intervention cost could increase if the clinic is not large enough to use Parent Coaches at their optimal capacity, we will test the

sensitivity of our conclusions to varying assumptions about the size of the patient panel versus the minimum full-time equivalent level at which the Parent Coach can be hired.

Time-Motion

We will collect time-motion data on at least 20 randomly selected well-visits per clinic, before and after PARENT implementation. In-person visit observations will provide the number of minutes (total and per visit) of clinician time and Parent Coach time in rooms with family for each WCC visit from 2-24 months, and data on visit content (discussion of preventive, chronic, or urgent care issues) of clinician WCC time with families (enrolled participants for WCC visits). We will examine clinician and Parent Coach time allocation for WCC visits from ages 0 to 2 years, comparing the mean time for each activity before and after the intervention implementation using linear mixed-effects models. This model will include random effects for the clinic to account for clustering, a binary variable as a primary predictor to indicate whether measurement occurred before or after intervention implementation, and an indicator for the group (intervention vs control). The analysis will also be adjusted for other factors as deemed appropriate. We will qualitatively describe the intervention versus control differences in the content discussed during visits.

Power Assessment

The power calculation is based on WCC quality (anticipatory guidance) and ED visits (2 or more), with a 1:1 randomization of 10 sites to the intervention and control groups. We will use the mean and SD of anticipatory guidance and the rates of 2 or more ED visits, as observed in our pilot RCT intervention and control groups. For anticipatory guidance, we will use the larger SD from the 2 groups to obtain a conservative power estimation for this variable. The calculation assumes an intraclass correlation of 0.01 based on previous cluster RCTs of similar delivery systems among similar populations, and the fact that the data analysis may be adjusted for important baseline covariates when comparing the intervention with control groups [40,41]. A conservative 20% dropout rate is assumed at the patient level; in other words, the retention of at least 75 of the 94 participants enrolled per site. Two-sided tests will be used with a type I error rate of 0.05. With a total of 94 participants enrolled per site, we will have at least 80% power to detect the anticipated intervention effect for both anticipatory guidance and ED visits, assuming a 20% dropout rate at the patient level.

For the time-motion study analysis, time measurements for 20 randomly selected participant visits (at each clinic, before and after implementation) will provide 80% power to detect an effect size of 0.30, using a 2-sided test at a significance level of .05, assuming an intraclass correlation of 0.01, and interperiod correlation of 0.01. This is based on an average provider time of 15 minutes (SD 5 minutes) in the control group, and a detectable intervention-related change of approximately 2 minutes 2 seconds.

Results

Participant recruitment began in March 2019. After recruitment, 6- and 12-month follow-up surveys will be completed. As of August 30, 2021, we have enrolled a total of 916 participants.

Discussion

Principal Findings

PARENT is an innovative WCC delivery model designed to meet the needs of low-income families. Promising preliminary findings suggest that PARENT may be a more effective system for the delivery of WCC, providing family-centered, comprehensive preventive care for infants and toddlers in low-income communities. This study contributes to the assessment of the effectiveness of PARENT across multiple practices, with a larger population of families and multiple Parent Coaches.

Conclusions

Through this research, we will examine PARENT across a larger number of practices, assess its effects on receipt of nationally recommended WCC services, parent experiences of care, health care use, costs, and impact on clinicians' allocation of time, and explore its effect on parent outcomes known to be associated with subsequent child outcomes.

If PARENT is shown to improve quality, improve experiences of care, and prove financially viable, it can be scaled to FQHCs and other practices nationally.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Study measures.
[DOCX File , 20 KB - resprot_v10i11e27054_app1.docx]

References

1. Hagan J, Shaw J, Duncan P. Bright Futures: Guidelines for Health Supervision of Infants, Children and Adolescents. 4th ed. Elk Grove, IL: American Academy of Pediatrics; 2017.
2. Bethell C, Reuland C, Schor E, Abrahms M, Halfon N. Rates of parent-centered developmental screening: disparities and links to services access. Pediatrics 2011 Jul 06;128(1):146-155. [doi: 10.1542/peds.2010-0424] [Medline: 21646266]
3. Chung PJ, Lee TC, Morrison JL, Schuster MA. Preventive care for children in the United States: quality and barriers. Annu Rev Public Health 2006 Apr;27(1):491-515. [doi: 10.1146/annurev.publhealth.27.021405.102155] [Medline: 16533127]
4. Schuster MA, Duan N, Regalado M, Klein DJ. Anticipatory guidance: what information do parents receive? What information do they want? Arch Pediatr Adolesc Med 2000 Dec 01;154(12):1191-1198. [doi: 10.1001/archpedi.154.12.1191] [Medline: 11115301]
5. Bethell C, Reuland CH, Halfon N, Schor EL. Measuring the quality of preventive and developmental services for young children: national estimates and patterns of clinicians' performance. Pediatrics 2004 Jun;113(6 Suppl):1973-1983. [Medline: 15173469]
6. Halfon N, Regalado M, Sareen H, Inkelas M, Reuland CHP, Glascoe FP, et al. Assessing development in the pediatric office. Pediatrics 2004 Jun;113(6 Suppl):1926-1933. [Medline: 15173463]
7. Norlin C, Crawford M, Bell C, Sheng X, Stein M. Delivery of well-child care: a look inside the door. Acad Pediatr 2011;11(1):18-26 [FREE Full text] [doi: 10.1016/j.acap.2010.12.008] [Medline: 21272820]
8. Freeman BK, Coker TR. Six questions for well-child care redesign. Acad Pediatr 2018 Aug;18(6):609-619. [doi: 10.1016/j.acap.2018.05.003] [Medline: 29857062]
9. Olson LM, Inkelas M, Halfon N, Schuster MA, O'Connor KG, Mistry R. Overview of the content of health supervision for young children: reports from parents and pediatricians. Pediatrics 2004 Jun;113(6 Suppl):1907-1916. [Medline: 15173461]
10. Coker TR, Thomas T, Chung PJ. Does well-child care have a future in pediatrics? Pediatrics 2013 Apr 01;131 Suppl 2(Supplement):149-159 [FREE Full text] [doi: 10.1542/peds.2013-0252f] [Medline: 23547059]
11. Coker TR, Windon A, Moreno C, Schuster MA, Chung PJ. Well-child care clinical practice redesign for young children: a systematic review of strategies and tools. Pediatrics 2013 Mar 01;131 Suppl 1(Supplement 1):5-25 [FREE Full text] [doi: 10.1542/peds.2012-1427c] [Medline: 23457149]
12. Coker T, Casalino LP, Alexander GC, Lantos J. Should our well-child care system be redesigned? A national survey of pediatricians. Pediatrics 2006 Nov 01;118(5):1852-1857. [doi: 10.1542/peds.2006-1425] [Medline: 17079554]
13. Mooney K, Moreno C, Chung PJ, Elijah J, Coker TR. Well-child care clinical practice redesign at a community health center: provider and staff perspectives. J Prim Care Community Health 2014 Jan 01;5(1):19-23 [FREE Full text] [doi: 10.1177/2150131913511641] [Medline: 24327599]
14. Committee on Practice and Ambulatory Medicine, Bright Futures Periodicity Schedule Workgroup. 2017 recommendations for preventive pediatric health care. Pediatrics 2017 Apr 17;139(4):e20170254 [FREE Full text] [doi: 10.1542/peds.2017-0254] [Medline: 28213605]
15. Coker TR, Chung PJ, Cowgill BO, Chen L, Rodriguez MA. Low-income parents' views on the redesign of well-child care. Pediatrics 2009 Jul 29;124(1):194-204 [FREE Full text] [doi: 10.1542/peds.2008-2608] [Medline: 19564300]
16. Radecki L, Olson LM, Frintner MP, Tanner JL, Stein MT. What do families want from well-child care? Including parents in the rethinking discussion. Pediatrics 2009 Sep 24;124(3):858-865. [doi: 10.1542/peds.2008-2352] [Medline: 19706562]
17. Coker TR, Moreno C, Shekelle PG, Schuster MA, Chung PJ. Well-child care clinical practice redesign for serving low-income children. Pediatrics 2014 Jul 16;134(1):229-239 [FREE Full text] [doi: 10.1542/peds.2013-3775] [Medline: 24936004]
18. Coker TR, Chacon S, Elliott MN, Bruno Y, Chavis T, Biely C, et al. A parent coach model for well-child care among low-income children: a randomized controlled trial. Pediatrics 2016 Mar 10;137(3):e20153013 [FREE Full text] [doi: 10.1542/peds.2015-3013] [Medline: 26908675]
19. Mimila NA, Chung PJ, Elliott MN, Bethell CD, Chacon S, Biely C, et al. Well-child care redesign: a mixed methods analysis of parent experiences in the parent trial. Acad Pediatr 2017 Sep;17(7):747-754 [FREE Full text] [doi: 10.1016/j.acap.2017.02.004] [Medline: 28232142]
20. Minkovitz CS, Strobino D, Mistry KB, Scharfstein DO, Grason H, Hou W, et al. Healthy steps for young children: sustained results at 5.5 years. Pediatrics 2007 Sep 31;120(3):658-668. [doi: 10.1542/peds.2006-1205] [Medline: 17766506]
21. Contreras S, Porras-Javier L, Zima BT, Soares N, Park C, Patel A, et al. Development of a telehealth-coordinated intervention to improve access to community-based mental health. Ethn Dis 2018 Sep 06;28(Supp):457-466. [doi: 10.18865/ed.28.s2.457]
22. Jones KA, Do S, Porras-Javier L, Contreras S, Chung PJ, Coker TR. Feasibility and acceptability in a community-partnered implementation of centeringparenting for group well-child care. Acad Pediatr 2018 Aug;18(6):642-649. [doi: 10.1016/j.acap.2018.06.001] [Medline: 29890229]
23. Patel M, Andrea N, Jay B, Coker TR. A community-partnered, evidence-based approach to improving cancer care delivery for low-income and minority patients with cancer. J Community Health 2019 Oct 1;44(5):912-920 [FREE Full text] [doi: 10.1007/s10900-019-00632-x] [Medline: 30825097]
24. Bright futures tool and resource kit, second edition. American Academy of Pediatrics. URL: https://brightfutures.aap.org/materials-and-tools/tool-and-resource-kit/Pages/default.aspx [accessed 2021-10-21]

25. Bethell C, Reuland C, Latzke B. The Promoting Healthy Development Survey (PHDS)-PLUS: implementation guidelines for medicaid and other settings. The Commowealth Fund. 2005. URL: https://www.commonwealthfund.org/publications/other-publication/2005/nov/promoting-healthy-development-survey-phds-plus [accessed 2021-10-21]
26. Preventive services for young children: promoting healthy development survey. Child and Adolescent Health Measurement Initiative. 2006. URL: https://www.ahrq.gov/patient-safety/quality-resources/tools/chtoolbx/measures/measure-6.html#:~:text=The%20Promoting%20Healthy%20Development%20Survey,%2C%20and%20Adolescents%E2%80%94Third%20Edition [accessed 2021-10-21]
27. Bethell C, Peck C, Schor E. Assessing health system provision of well-child care: the Promoting Healthy Development Survey. Pediatrics 2001 May 01;107(5):1084-1094. [doi: 10.1542/peds.107.5.1084] [Medline: 11331691]
28. Topics and related items in the CAHPS Health Plan Survey 4.0 Core Questionnaires. Agency for Healthcare Research and Quality. 2006. URL: https://www.ahrq.gov/cahps/surveys-guidance/hp/index.html [accessed 2021-11-01]
29. Reporting measures for the CAHPS Clinician and Group Survey. CAHPS Clinician & Group Survey. 2010. URL: https://www.ahrq.gov/sites/default/files/wysiwyg/cahps/surveys-guidance/cg/cgkit/HowtoReportResultsofCGCAHPS080610FINAL.pdf [accessed 2021-10-21]
30. Bramlett MD, Blumberg SJ, Zablotsky B, George JM, Ormson AE, Frasier AM, et al. Design and operation of the National Survey of Children's Health, 2011-2012. Vital Health Stat 1 2017 Jul(59):1-256 [FREE Full text] [Medline: 28796596]
31. Hays RD, Schalet BD, Spritzer KL, Cella D. Two-item PROMIS® global physical and mental health scales. J Patient Rep Outcomes 2017 Sep 12;1(1):2 [FREE Full text] [doi: 10.1186/s41687-017-0003-8] [Medline: 29757325]
32. Reyno SM, McGrath PJ. Predictors of parent training efficacy for child externalizing behavior problems--a meta-analytic review. J Child Psychol Psychiatry 2006 Jan;47(1):99-111. [doi: 10.1111/j.1469-7610.2005.01544.x] [Medline: 16405646]
33. Jones TL, Prinz RJ. Potential roles of parental self-efficacy in parent and child adjustment: a review. Clin Psychol Rev 2005 May;25(3):341-363. [doi: 10.1016/j.cpr.2004.12.004] [Medline: 15792853]
34. Petterson SM, Albers AB. Effects of poverty and maternal depression on early child development. Child Dev 2001 Nov;72(6):1794-1813. [doi: 10.1111/1467-8624.00379] [Medline: 11768146]
35. Goodman SH, Rouse MH, Connell AM, Broth MR, Hall CM, Heyward D. Maternal depression and child psychopathology: a meta-analytic review. Clin Child Fam Psychol Rev 2011 Mar 4;14(1):1-27. [doi: 10.1007/s10567-010-0080-1] [Medline: 21052833]
36. Brennan PA, Hammen C, Andersen MJ, Bor W, Najman JM, Williams GM. Chronicity, severity, and timing of maternal depressive symptoms: relationships with child outcomes at age 5. Develop Psychol 2000;36(6):759-766. [doi: 10.1037/0012-1649.36.6.759]
37. White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analysis in randomised trials with missing outcome data. Br Med J 2011 Feb 07;342(feb07 1):d40 [FREE Full text] [doi: 10.1136/bmj.d40] [Medline: 21300711]
38. Neumann P, Ganiats T, Russell L, Sanders G, Siegel J. Cost-Effectiveness in Health and Medicine. 2nd Edition. Oxford, New York: Oxford University Press; 2016.
39. Dieleman JL, Cao J, Chapin A, Chen C, Li Z, Liu A, et al. US health care spending by payer and health condition, 1996-2016. J Am Med Assoc 2020 Mar 03;323(9):863-884 [FREE Full text] [doi: 10.1001/jama.2020.0734] [Medline: 32125402]
40. Garg A, Toy S, Tripodis Y, Silverstein M, Freeman E. Addressing social determinants of health at well child care visits: a cluster RCT. Pediatrics 2015 Feb 05;135(2):296-304 [FREE Full text] [doi: 10.1542/peds.2014-2888] [Medline: 25560448]
41. Garbutt JM, Highstein G, Yan Y, Strunk RC. Partner randomized controlled trial: study protocol and coaching intervention. BMC Pediatr 2012 Apr 02;12(1):42 [FREE Full text] [doi: 10.1186/1471-2431-12-42] [Medline: 22469168]

Abbreviations

ED: emergency department
FQHC: federally qualified health center
PARENT: Parent-focused Redesign for Encounters, Newborns to Toddlers
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
WCC: well-child care

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Protocol

Optimizing Coaching During Web-Based Relationship Education for Low-Income Couples: Protocol for Precision Medicine Research

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Abstract

Background: In-person relationship education classes funded by the federal government tend to experience relatively high attrition rates and have only a limited effect on relationships. In contrast, low-income couples tend to report meaningful gains from web-based relationship education when provided with individualized coach contact. However, little is known about the method and intensity of practitioner contact that a couple requires to complete the web-based program and receive the intended benefit.

Objective: The aim of this study is to use within-group models to create an algorithm to assign future couples to different programs and levels of coach contact, identify the most powerful predictors of treatment adherence and gains in relationship satisfaction *within* 3 different levels of coaching, and examine the most powerful predictors of treatment adherence and gains in relationship satisfaction *among* the 3 levels of coach contact.

Methods: To accomplish these goals, this project intends to use data from a web-based Sequential Multiple Assignment Randomized Trial of the OurRelationship and web-based Prevention and Relationship Enhancement programs, in which the method and type of coach contact were randomly varied across 1248 couples (2496 individuals), with the hope of advancing theory in this area and generating accurate predictions. This study was funded by the US Department of Health and Human Services, Administration for Children and Families (grant number 90PD0309).

Results: Data collection from the Sequential Multiple Assignment Randomized Trial of the OurRelationship and web-based Prevention and Relationship Enhancement Program was completed in October of 2020.

Conclusions: Some of the direct benefits of this study include benefits to social services program administrators, tailoring of more effective relationship education, and effective delivery of evidence- and web-based relationship health interventions.

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KEYWORDS

online relationship education; precision medicine; low-income couples; coaching; OurRelationship; ePREP

Introduction

Background

It is estimated that one-third of marriages in the United States are classified as relationally distressed [1]. Individuals with low-income experience, especially high rates of relationship distress and divorce, report significantly lower marital quality, and experience greater fluctuations in marital quality than high-income earners [2-4]. Low-income couples also have higher levels of alcohol use and infidelity and recent analyses indicate that a meaningful percentage break up during federally funded trials [4-6]. Even when low-income couples have access to free relationship education, they are only able to complete between 10% and 60% of the offered classes in nationwide studies [3,7]. Furthermore, a recent meta-analysis of relationship education for low-income couples revealed that even among

the statistically significant findings, the effect sizes were trivial (eg, Cohen *d*=0.06-0.09) [8] and not meeting the widely accepted *small* cutoffs for a meaningful-sized change (ie, Cohen *d*≥0.20) [9]. In the light of these limitations, the authors of this meta-analysis called for innovations in curriculum design, improvements in programmatic elements, and exploration of new ways to sustain participant engagement among low-income couples [8].

The Law of Attrition and Precision Medicine

Attrition problems are not unique to the field of relationship education and appear to be an inevitable outcome of web-based randomized controlled trials (RCTs) [10]. This has led some to propose the law of attrition [11], which argues that participant dropout is a fundamental methodological challenge inherent in RCTs, which makes investigating the effects of web-based interventions particularly challenging. The law of attrition argues that couples are initially drawn to web-based programs because of their innovative properties (eg, they are brief, can be completed from home, and are inexpensive). However, after registering for the program, reasons that individuals may not continue their participation could include (1) being exposed to conflicting messages about the program, (2) rejecting the program for something better, or (3) leaving the program as the individual was dissatisfied with the services they received [11].

Others have argued that the law of attrition could be enhanced by the inclusion of user characteristics [10]. User characteristics (ie, couple- or individual-level differences) may moderate adherence to the intervention. Some of these differences may include relationship problems, levels of motivation to complete the program, baseline levels of symptomology, the need for anonymity, lack of available resources, or living in a remote location. Simply because of couple-level differences, some percentage of the population is likely to complete and benefit from web-based interventions, and some percentage of the population will not, with most of the population likely falling somewhere in between [12].

Thus, determining who is likely to drop out of the program and who is likely to complete the program at the program outset would be a major benefit to administering effective web-based relationship education. Focusing on completion of the program (and its specific activities) rather than aiming to increase the desired outcome (eg, relationship satisfaction) not only decreases attrition but may also increase the desired behavioral changes [12]. The addition of couple-level differences to the law of attrition suggests that sensitivity to couple-level differences would likely decrease attrition and increase the efficacy of web-based interventions.

Recently, strides have been made in machine learning to mirror these ideas, allowing researchers to predict and compare the predicted treatment effects for couples [13,14]. This approach is often referred to as precision medicine. At the heart of this area of research is the idea that average treatment effects from an RCT may not generalize well to treatment targets (ie, individuals or couples). Although treatment decisions made by humans are typically based on a small number of characteristics (eg, race, ethnicity, or gender), humans are unable to make decisions at the multivariate level without computational resources. The ability to estimate couple-level treatment effects would allow for treatment options that are directly tailored to estimate the unique needs of each unique couple that a practitioner would encounter [13,14].

A Review of Evidence-Based Relationship Education Programs

This precision medicine and machine learning approach is relatively new to the field of relationship education and web-based health interventions. Thus, starting a precision medicine approach with programs that have already been shown to be evidence-based and beneficial would be worthwhile. Arguably, OurRelationship and web-based Prevention and Relationship Enhancement Program (ePREP) are the 2 web-based relationship education programs with the largest evidence base. OurRelationship and ePREP contain only 6 to 10 hours of content—substantially less content than comprehensive programs previously delivered by the federal government. The OurRelationship program is a web-based, self-help adaptation of integrative behavioral couple therapy that emphasizes acceptance and change [15]. The program includes tailored feedback, filmed examples of couples experiencing relationship distress, and i and activities encouraging couples to be more mindful of their relationship dynamics. Currently, the standard of care includes delivering the program in conjunction with four 15-minute calls with a coach to reinforce the material that is learned throughout the program [15-17]. In a nationwide RCT of 300 couples, this short program led to small- to medium-sized gains (Cohen *d*=0.15-0.69) in key areas of individual and relationship well-being compared with a waitlist control group [16]. Furthermore, couples maintained these effects for at least a year following the intervention [18]. The OurRelationship program appears to benefit couples regardless of income, demographic characteristics, and sexual orientation across a number of outcomes of interest (eg, depression, anxiety, relationship satisfaction, relationship positives, and relationship negatives) [19].

The ePREP program is a web-based adaptation of the Prevention and Relationship Enhancement Program, which emphasizes skill building [20,21]. Accordingly, ePREP introduces a set of healthy communication strategies to reduce conflict in relationships. Some of these strategies include the time-out strategy and the speaker-listener technique, as well as how to maintain fun and friendship in the relationship after the program has ended. In several randomized clinical trials, those that have participated in ePREP have reported small- to medium-sized gains in relationship functioning [21-24]. Follow-up studies have found that the improvements in functioning attributable to ePREP were maintained over a 10- to 12-month follow-up period [22,24]. In addition, those who master the strategies taught in ePREP experience superior improvements in constructive communication and relationship satisfaction [23].

Recently, both OurRelationship and ePREP were compared with one another and to a waitlist control condition in a large Administration for Children and Families (ACF)–funded RCT with low-income couples (N=742) [17]. When delivered in conjunction with four 15-minute coach videoconferences or

telephone calls, adherence rates in the OurRelationship and ePREP programs were equal, with 69% of couples completing the assigned material. When compared with the waitlist control condition, those in the OurRelationship and ePREP conditions reported increases in relationship satisfaction (Cohen $d_{\text{OurRelationship}}$=0.53; Cohen d_{ePREP}=0.42) and emotional support (Cohen $d_{\text{OurRelationship}}$=0.46; Cohen d_{ePREP}=0.36), along with decreases in breakup potential (Cohen $d_{\text{OurRelationship}}$=−0.53; Cohen d_{ePREP}=−0.43), communication conflict (Cohen $d_{\text{OurRelationship}}$=−0.78; Cohen d_{ePREP}=−0.54), and intimate partner violence (IPV; Cohen $d_{\text{OurRelationship}}$=−0.10; Cohen d_{ePREP}=−0.08) [17]. Furthermore, these effects were maintained over a 6-month follow-up period [17]. When the 2 programs were compared, only one significant effect emerged; those in the OurRelationship program experienced greater decreases in communication conflict when compared with those in the ePREP program (Cohen d=−0.24) [17]. These findings were later reproduced in an independently collected sample [25].

Predictors of Treatment Adherence and Gains in Web-Based Interventions: An Inconclusive Science

The literature examining general predictors of adherence and treatment gains in web-based interventions is filled with a mix of inconclusive findings. Regularly, demographic variables have been examined as predictors of adherence to and treatment gains in web-based protocols. Gender and education, for instance, were significant predictors of treatment adherence in some studies but nonsignificant predictors in others [26-32]. Findings on the effects of age, in particular, are difficult to disentangle. Younger age has been associated with better treatment adherence in some studies [28], worse treatment adherence in some others [33,34], and still other studies concluded that age might not be associated with treatment adherence at all [29,31,35]. In a study investigating the OurRelationship program, for instance, identifying as Hispanic predicted better adherence to the program [32]; however, other studies have found no ethnic or racial differences between those who do and do not adhere to the program and their subsequent treatment gains [36,37]. An individual's level of technical competency has been argued to be a barrier in some scenarios but not in others [31]. Some have found that users who are more familiar with technology are more likely to drop out [38], whereas others argue that technological competency positively predicts program adherence [28].

Equally, the literature examining the role that baseline levels of psychopathology or symptomology play in adherence to web-based protocols usually yields inconsistent findings, even among reviews and meta-analyses. For instance, in a recent meta-analysis of self-guided web-based programs (ie, programs without a coach) for depression, levels of depression did not significantly predict treatment adherence [33]. However, other reviews of adherence to web-based programs for depression anxiety have concluded that lower baseline levels of depressive symptoms are reliable predictors of treatment adherence [28]. Several studies have also found that baseline symptoms of anxiety are significant predictors of treatment adherence [28,33], whereas other studies have concluded the opposite [31]. In addition, although some studies concluded that *lower* levels of depression and anxiety predict better adherence to web-based programs for mood disorders [28], *higher* baseline levels of alcohol use predicted better adherence to web-based alcohol intervention programs [34]. A possible reason for these differing effects is that the direction (or lack) of an effect could be moderated by the treatment being provided. For example, studies that concluded that lower baseline levels of depression and anxiety predict better adherence are investigating web-based treatment protocols for anxiety, depression, and relationship distress [28,32], whereas those that do not are investigating adherence to web-based programs to treat specific phobias and posttraumatic stress disorder [31]. In all, the literature examining the role that baseline levels of symptomology play in adherence to web-based interventions is convoluted and often inconclusive.

Despite the inconsistencies in this area, 2 predictors yield relatively consistent findings. First, much like in-person relationship education, high levels of external stress seem to be an important barrier. Specifically, participants who reported that the treatment was too demanding, who reported greater perceived external barriers, more time constraints, more pressure to complete the program, the presence of a physical illness, a family history of mental illness, and those who reported that school or work got in the way were all less likely to adhere to web-based protocols and reported less improvement [28,30,39,40]. The second consistent predictor was motivation. Higher baseline levels of intrinsic motivation have been shown to predict greater treatment adherence in several studies [28,34,39,40].

Coaching and Supportive Accountability

Although research suggests that brief web-based relationship education yields promising completion rates and relationship outcomes, one area of interest is not well understood: the type and amount of coaching needed for couples to complete the web-based material. Coaches in the OurRelationship and ePREP programs are usually master's-level clinicians with a degree in psychology that help reinforce the content taught in web-based curricula using telephone or video chat. The supportive accountability model argues that adherence to web-based interventions is primarily predicted by a couple's accountability to complete the program, that is, the implicit or explicit expectation that the couple is required to complete the material [12]. Accountability, first and foremost, requires the presence of another human being (ie, a coach). This coach can foster a working alliance with the couple, set expectations for program completion, regularly monitor the couple's progress, and set goals for them in the future. The supportive accountability model further argues that the effect of accountability on program completion can primarily be moderated via 2 processes: motivation to complete the program and how the communication is being delivered [12].

The lack of motivation to complete the program may prevent a couple from completing the agreed upon material [12]. Ideally, coaches can attempt to increase motivation by increasing the importance of tasks through verbal rewards. For example, having more coach calls or sending more frequent reminders are ways of increasing verbal rewards. However, this can often be a

balancing act—too much communication could be perceived as being overbearing but too little as a lack of support.

The method of communication can also serve as a moderator for the effect of accountability on material completion. For example, some couples may enjoy the additional connection video conference meetings that their coach provides, whereas others might find regular email contact to be less intrusive. This variability highlights the need to tailor coaching to meet the needs of specific couples. Thus, identifying the best way to determine the amount of coaching a couple needs as well as the right method of communication is critical to the success of relationship education [12].

The Effect of Having a Coach on Program Outcomes

The effect of a coach has garnered significant attention in the field of web-based interventions. Several studies of individual interventions have investigated the effect of not having a coach (ie, a stand-alone program), conditional coach support (eg, as-needed calls), some coach support (eg, one phone call for all couples), and full-coach support (eg, several phone calls for all couples). The definitions of coach contact vary widely across studies and have, unfortunately, yielded a series of mixed results. Studies of web-based interventions for both couples and individuals have found that more intensive coach support yields (1) better adherence rates, program completion, and treatment outcomes [32,41]; (2) improvements in program completion and some (but not all) outcomes [37,42]; or (3) some effect on program completion but little effect on treatment outcomes [35,39,43].

Some studies have compared web-based content coupled with coach support with only web-based content. For instance, when completion rates from a no-coach version of the OurRelationship program were compared with those of a trial with full coaching (ie, 4 coach calls), 6.1% of individuals in the no-coach trial completed the program compared with 66.1% in the full-coach version of the program [32]. Furthermore, in a web-based problem-solving intervention for depression and anxiety, those who received scheduled support were likely to complete more of the intervention than those who received no support [42]. Finally, in a web-based treatment for depression, those who received support from a therapist saw similar reductions in depressive symptoms, interpersonal problems, and improvements in quality of life compared with those who completed the web-based program without a therapist [35].

Other studies have varied the intensity and type of coaching that couples and individuals can receive and its effects on program outcomes and adherence. When comparing the OurRelationship program with 4 calls to the OurRelationship program with one call, those who received 4 calls were more likely to complete the program (66% vs 36%, respectively) and saw greater reductions in anxiety symptoms than those who had one call [37]. However, those who received 4 calls reported similar gains in relationship satisfaction and decreases in depressive symptoms compared with the one call group [37]. Furthermore, in a web-based intervention aimed at treating panic disorder that compared scheduled coach calls to on-demand coach calls, individuals who received scheduled coach calls saw larger reductions in panic and anxiety symptoms than those who received on-demand services; however, the 2 conditions saw similar reductions in depressive symptoms and perceived stress [41]. In contrast, in a web-based problem-solving intervention for depression and anxiety, those who received scheduled support did not experience differential program outcomes compared with those who received support on request or received support in the form of nonspecific chat or email [42].

Few studies have investigated whether baseline characteristics moderate the effect of different coaching levels. Of the 20 baseline moderators tested in the OurRelationship program, only 2 significant interactions with coaching level emerged. First, those with higher baseline levels of depressive symptoms were actually less likely to complete the program when receiving 4 coach calls compared with the stand-alone version of the program [32]. Second, those who identified as Hispanic were more likely to complete the program with 4 coach calls than in the stand-alone version. However, race, ethnicity, and household income did not moderate differences in program or treatment gains between one and 4 coach calls [37]. A similar pattern of findings emerged when investigating web-based interventions for individuals with stress and anxiety symptoms [39]. A host of candidate variables (eg, age, gender, level of education, occupation, computer expertise, time perspective, perceived treatment credibility, levels of internal or external motivation, and therapist bond) were examined to determine whether background variables moderated the effect of a coach in adherence to the intervention or treatment benefits; however, none of these baseline characteristics acted as between-group moderators [39].

This Study: Research Aims and Hypotheses

Given past research, this study has 3 aims. The first aim is to investigate how well we can predict the completion rates and changes in relationship satisfaction. As model evaluation has rarely been used in this area of research, no specific hypotheses have been posited. The second aim of this study is to document the most powerful predictors of treatment adherence and gains in relationship satisfaction within 3 different levels of coaching. More specifically, what are the most powerful predictors of treatment adherence and gains in relationship satisfaction in a full-coach condition (with 4 scheduled 15-minute phone calls), automated coach condition (where couples only receive emails), and a contingent coach condition (where couples only receive scheduled coach calls after displaying a pattern of nonadherence)? Although many of the findings in this area of research are inconclusive, 2 findings are relatively consistent: lower external stress and higher intrinsic motivation both predict treatment adherence and gains. Thus, we hypothesize that, regardless of coach assignment, lower external stress and higher intrinsic motivation will emerge as reliable predictors of better adherence to the web-based program and subsequent treatment gains. In the final aim of the study, we intend to use the information gathered in the first 2 steps to determine the most powerful predictors of between-group differences. More specifically, what baseline characteristics are indicative of a given couple's adherence or gains in relationship satisfaction to couples assigned to the full-coach program compared with automated coaching, contingent coaching, or the waitlist control

condition? As this area of research is relatively underdeveloped, no specific hypotheses will be posited.

Methods

Procedure

This study was funded by the US Department of Health and Human Services, ACF (grant number 90PD0309; see Multimedia Appendix 1 for peer reviews). The parent study was registered with ClinicalTrials.gov (NCT02806635). The analyses and project design for this study will be preregistered with the Open Science Framework to promote accountability. Data for this study come from a large (N=1248 couples; N=2496 individuals) web-based RCT with a Sequential Multiple Assignment Randomized Trial design [44]. Sequential Multiple Assignment Randomized Trial designs are experiments that allow researchers to develop adaptive interventions and reassign nonadherent participants [44]. This was done by varying the levels and types of coach contact that a couple receives. In this study, couples were initially assigned to one of five conditions: OurRelationship coach, OurRelationship automated (email only), ePREP coach, ePREP automated (email only), and the waitlist control condition. However, couples initially assigned to the no-coach condition that did not complete scheduled web-based activities for >2 weeks underwent a second randomization: to continue the program without a coach or to be assigned to a coach for the remainder of the program. Those who were randomized to continue without a coach were still allowed to access the program, complete the activities, and were still sent automated reminders. In contrast, those who were randomly reassigned to receive coach contact were emailed by a coach and invited to schedule a call. Couples in this contingent coach condition received up to 3 additional calls (for a maximum of 4 calls) depending on where in the program they were when they stopped making adequate progress. This full variability of possible coaching contact, all of which involved random assignment, will allow us to determine the most powerful predictors of which couples should receive 4 15-minute coach calls, those who should simply receive emails, and those who should receive contingent coach contact after displaying patterns of treatment nonadherence.

Inclusion and Exclusion Criteria

To be eligible for participation, couples had to live in the United States, be married, engaged, or living together for at least six months, report a household income >200% of the federal poverty line, and be between the ages of 18 and 64 years inclusive. In addition, couples had to agree not to seek help for their relationship for the next 6 months and needed to speak English or Spanish fluently. Couples were excluded if they reported severe IPV within the past 6 months (eg, choking, beating, threatening with a deadly weapon, or forced sex), did not have access to highspeed internet, or had previously participated in an ePREP or OurRelationship program.

Participants

A total of 226 couples were randomly assigned to the OurRelationship coach condition, 145 couples were assigned to the OurRelationship contingent coach condition, and 145 couples were assigned to the OurRelationship automated (ie, email only) condition. Similarly, 222 couples were assigned to the ePREP coach condition, 143 couples were assigned to the ePREP contingent coach condition, and 143 couples were assigned to the ePREP automated (ie, email only) condition. A total of 224 couples were assigned to the waitlist control condition. In total, 4 individuals from the OurRelationship coach condition, 2 from the OurRelationship contingent coach condition, and 2 from the OurRelationship automated condition asked to discontinue and have their data removed from the study. Furthermore, 3 individuals from the ePREP coach condition, 2 from the ePREP contingent coach condition, and 3 from the ePREP automated condition asked to discontinue and have their data removed from the study.

In total, 47.5% (1178/2480) of the sample identified as male, and 52.5% (1302/2480) of the sample identified as female. The average length of the relationship was 5.74 years (SD 5.18). Most of the participants reported belonging to an opposite-gender relationship (2318/2480, 93.47%), and a smaller percentage were in same-gender relationships (162/2480, 6.53%). Most participants identified as White non-Hispanic (1520/2480, 61.29%), fewer identified as Black (434/2480, 17.5%), White Hispanic (279/2480, 11.25%), Black Hispanic (28/2480, 1.13%), American Indian or Alaskan Native (23/2480, 0.93%), Asian (17/2480, 0.69%), Hawaiian or Pacific Islander (4/2480, 0.16%), and Biracial (86/2480; 3.47%); and 3.59% (89/2480) of participants belonged to a race that was not listed. Furthermore, 6.81% (169/2480) of participants did not have a degree or diploma, 12.3% (305/2480) had earned a general education diploma, 14.23% (353/2480) had completed high school, 8.23% (204/2480) had a technical or vocational certification, 22.54% (559/2480) had some college degree, 8.83% (219/2480) had graduated with an associate's degree, 10.69% (265/2480) had a bachelor's degree, and 2.38% (59/2480) had a master's or advanced degree.

Measures: Outcome Variables

Program Completion

The first outcome of interest in this study is whether a couple completes all the required activities in the program to which they are assigned. Couples that complete all (100%) the activities to which they are assigned will be coded as 1, whereas couples that do not complete all the program activities will be coded as 0.

Relationship Satisfaction

Relationship satisfaction will be measured using the Couples Satisfaction Index–4 [45]. The Couples Satisfaction Index was developed using item response theory and has better psychometric properties than much longer measures of relationship quality. The reliability of the current scale is excellent among low-income, help-seeking couples (Cronbach α=.92) [17]. Furthermore, this scale is highly correlated with past measures of relationship quality (r>.78) and positive communication (r>.75), providing evidence its validity [45].

Measures: Predictor Variables

Demographic Variables

Although support for demographic variables and their relationship to treatment adherence varies, a host of demographic variables will be included as candidate predictor variables. Predictor variables include race, ethnicity, household income, age, gender, as well as identifying as a same-gender couple.

Baseline Measures of Relationship and Individual Symptomology

In line with the consistencies in previous research and in addition to relationship satisfaction, several measures of relationship symptomology will be used as possible candidates to predict program completion and gains in relationship satisfaction.

Breakup Potential

Breakup potential will be assessed using a three-item Likert-style measure adapted from the Marital Instability Index (*The thought of ending my relationship has crossed my mind*), which has good internal consistency (Cronbach α=.83) in past RCTs involving low-income couples [17,46].

Relationship Commitment

To assess relationship commitment, this study plans to use a single-item Likert-style measure developed by the ACF (ie, *How much do you agree or disagree with this statement? I view our marriage/relationship as lifelong*).

Intensity of the Biggest Relationship Problem

The intensity of a couple's biggest relationship problem could be a powerful predictor of nonadherence. This construct was measured using a single item on a Likert-style scale (ie, *How big of a problem is the biggest problem (core issue) in your relationship?*).

Communication Conflict

This form of negative communication was measured using a Likert-style scale developed by the ACF (ie, *My partner/spouse was rude or mean to me when we disagreed*). Past RCTs using this measure have reported good internal consistency (Cronbach α=.89) [17].

Emotional Support

As another measure of baseline relationship symptomology, emotional support was measured using a five-item measure developed by the ACF. Past RCTs using this measure have reported good internal consistency (Cronbach α=.83) [17].

Intimate Partner Violence

Minor levels of IPV were assessed using 7 items created in consultation with the National Domestic Violence Hotline [17]. Among others, participants were asked to indicate how often their partner pushed, slapped, or punched them in the past month. Responses were recorded on a Likert-style scale. Internal consistency in past RCTs with low-income couples has been acceptable (Cronbach α=.78) [17].

Measures of External Stress

Overview

In addition to including predictors of relationship well-being, the inclusion of measures assessing external stress has been shown to be a consistent predictor of treatment adherence. In addition, as this is measured at the individual level, this may highlight within-relationship differences that may aid in the prediction of treatment nonadherence and satisfaction gains. This study intends to measure psychological distress and general health using the following measures:

Psychological Distress

To assess individual distress, this study intends to use the Kessler Psychological Distress Scale (*During the past 30 days, how often have you felt nervous*) [47]. This is a high-precision, 6-item, Likert-style measure developed using the item response theory. In a past RCT with a low-income sample, this scale had good internal consistency (Cronbach α=.86) [48]. Furthermore, this scale has excellent discrimination when attempting to detect severe cases of psychopathology, providing evidence of its validity [47].

Perceived Stress

To assess perceived distress, this study intends to use the Perceived Stress Scale, a 4-item Likert-style measure (*In the last 30 days, how often have you felt that you were unable to control the important things in your life?*) [49]. A past RCT has indicated that internal consistency was acceptable (Cronbach α=.74) [48].

Chaos

Another measure of external stress will include a single-item measure of chaotic events that an individual may experience in their relationship. This will be assessed using a check-all-that-apply item developed by the ACF; that is, *the following are a list of events that may cause stress for you and your partner. Check each thing (or similar thing) that has happened to you in the past month*. Some of the answers from this item include *changes in work schedule, changes in childcare, changes in family structure, or changes in finances*.

General Health

Impacts on the physical well-being (eg, a chronic illness) of one individual may prevent both members of the dyad from completing the program. To assess general health, this study intends to use a single-item measure of general well-being on a Likert-style scale developed by the ACF (ie, *In general, how would you describe your health*).

Measures of Motivation

A final category of predictors of treatment adherence is the motivation to complete the treatment. In line with the literature, motivation will be measured using grit and motivation to change.

Grit

One measure of motivation is grit or passion and perseverance for long-term goals under challenging circumstances [50]. Despite the challenges accompanying relationship distress, perseverance to complete the program regardless of these challenges may be an important indicator of treatment adherence

and gains. In the standardization sample, internal consistency ranged from acceptable to great (Cronbach α=.73-.83), and the measure was strongly correlated with conscientiousness (*r*=.73-.77), providing evidence of the scale's reliability and validity.

Motivation to Change

Participants' motivation to change will also be measured with the following item adapted for this study: *Which of the following statements best describes your view of your current relationship problems* [51]? Participants will respond on a four-point Likert-style scale ranging from *I don't think I have relationship problems and therefore nothing should be done about it* (coded as 0) to *I know I have relationship problems, and I am here to take action to work on them now*.

Data Analysis

In an effort to reduce computational complexity, rather than using individual responses, responses from both members of the couple will be combined in the average score for the couple for each of the continuous predictor variables listed above as well as the continuous outcome variable (ie, relationship satisfaction).

Data Analysis Plan for Aim 1: Examining the Prediction Accuracy of the Within-Group Models Using the Random Forest Algorithm

The first research question asks: how well can one predict program completion and anticipated gains within (1) the full-coach condition, (2) the automated coach condition, and (3) the contingent coach condition? To ensure that the different programs do not account for a substantial portion of the variance when predicting program completion or changes in relationship satisfaction, a test will be performed where 2 models will be created and compared. In the first model, all predictors will be interacted with the level of coaching (full, contingent, and automated) and the program assignment (ie, OurRelationship and ePREP) resulting in Predictor×Treatment×Coaching interactions. However, the second model will maintain all predictors by coaching interactions but drop all program assignment interactions (ie, resulting in only Predictor×Coaching interactions). Next, the root mean square error (RMSE) between the 2 models will be compared. If the null hypothesis does not get rejected (H_0: $RMSE_{Model\ 1} = RMSE_{Model\ 2}$), program assignment will be ignored resulting in 3 conditions (full, contingent, and automated coaching), which will be used in the proceeding aims. If the interactions account for a significant portion of the variance ($H_a = RMSE_{Model\ 1} \neq RMSE_{Model\ 2}$), independent models will be built by treatment (ie, OurRelationship or ePREP) and coach condition (full, automated, and contingent) resulting in 6 models: OurRelationship full coach, OurRelationship automated coach, OurRelationship contingent coach, ePREP full coach, ePREP automated coach, and ePREP contingent coach, which will be used in the proceeding aims.

These models will be built using the random forest algorithm [52]. The random forest algorithm reduces overfitting by bootstrapping or fitting several different trees to subsets of the sample to inform the predictions (ie, bagging) [52]. Once the ensemble of trees is generated, the outputs from all the trees are aggregated, and the prediction is generated. Its ability to predict treatment outcomes for individuals and couples has been proven in several precision medicine studies [13,14]. Thus, in the first aim of this study, the random forest algorithm will be used to accurately predict the within-group likelihood that a couple completes the OurRelationship and ePREP programs in (1) the full-coach condition, (2) the automated coaching condition, and (3) the contingent coach condition as well as the magnitude of their gains in relationship satisfaction. The model characteristics address the model performance on the test data set. For binary outcomes (program completion), the model characteristics used to evaluate the validity of the model include sensitivity, specificity, positive predictive value, and negative predictive value of the model built on the test data set (Figure 1). Model sensitivity is measured by the percentage of true positives (ie, a/a+c). Model specificity is the percentage of true negatives (ie, d/d+b). A model's positive predictive value yields a positive test result and the probability that the participant will complete the program (ie, a/a+b). Finally, a model's negative predictive value yields negative test results and the probability that the participant will not complete the program (ie, d/d+c). Good models for binary outcomes include models whose sensitivity, specificity, positive predictive value, and negative predictive value are closest to 1. For continuous outcomes (ie, improvements in relationship satisfaction), model accuracy will be evaluated using the RMSE. The RMSE is a measure of absolute fit and is the square root of the variance of the residuals; smaller values indicate better fit.

Figure 1. A two-by-two table visually displaying model characteristics.

	Participant completes program	Participant drops out of program	
Model predicts program completion	True positive a	False positive b	Total predicted completers a+b
Model predicts program dropout	False negative c	True negative d	Total predicted dropouts c+d
	Total program completers a+c	Total program dropouts b+d	Total population a+b+c+d

Data Analysis Plan for Aim 2: What Are the Most Important Within-Group Predictors?

The second research question is: what are the most powerful predictors of treatment adherence and gains in relationship satisfaction within (1) the full-coach condition, (2) the automated coach condition, and (3) the contingent coach condition? If, in aim 1, the interaction terms result in a lower RMSE, better sensitivity, or better specificity, models will be constructed based on treatment assignment (ie, OurRelationship or ePREP) and coach assignment (ie, full, contingent, or automated). One statistically powerful way to test the most potent predictors of treatment adherence and gains is through the use of variable importance (VIMP). VIMP is a nonparametric approach within the random forest algorithm, which can help investigators identify which variables play a key role in predicting a binary (eg, program completion) or continuous (eg, improvements in relationship satisfaction) variable [53]. VIMP has been calculated in many ways in the past; however, one way that has shown promise has been through permutation (ie, Briemen–Cutler) importance [53]. This method randomly changes a given variable's out-of-bag data and compares and averages the permuted prediction error with the original error resulting in VIMP [53]. This process not only helps identify which variables play a key role in prediction but also overcomes issues of overtesting using bootstrapping. Recent studies have used these out-of-bag estimates to generate CIs to test whether a variable has a meaningful effect in predicting an outcome with great success [53]. Indeed, these studies have suggested that 95% CIs that do not include zero will be assumed to have reliable predictors [53]. After identifying the most powerful predictors using VIMP, a multiple regression model will be estimated using the reduced set of variables to aid in the interpretation of the main effects, helping clinicians identify predictors of treatment adherence and gains.

Data Analysis Plan for Aim 3: Predicting Between-Group Treatment Outcomes

Assuming that the models from the previous aim have levels of prediction accuracy, each of the within-group models will be used to generate predicted outcomes for each couple's likelihood of adhering to the program as well as their treatment gains, creating counterfactual estimates of program completion and treatment gains as if each couple in the data set completed each intensity and method of coach contact [14].

To do this, the within-group models built in aim 1 will be used to generate potential outcomes for each couple's likelihood of adhering as well as their gains in a (1) full coaching, (2) automated coaching, and (3) contingent coach conditions. If, in aim 1, the interaction terms result in a better RMSE, models will be constructed based on treatment assignment (ie, OurRelationship or ePREP) and coach assignment (ie, full, contingent, or automated). The estimates between the conditions for each couple's between-group treatment differences between the full and automated coaching conditions can be understood as:

where  is the between-group likelihood of treatment adherence or gains for couple x, $\hat{Y}(x, \textit{Full Coach})$ is the within-group likelihood of treatment adherence or gains for couple x in the full-coach condition, and $\hat{Y}(x, \textit{Contingent Coach})$ is the within-group likelihood of treatment adherence or gains for couple x in the contingent coach condition [14]. These hypothetical between-group outcomes will then serve as dependent variables in a second random forest to calculate VIMP, which will identify the most powerful predictors of between-group differences. After identifying the most powerful predictors using VIMP, a multiple regression model will be estimated using the reduced set of variables to aid in the interpretation of the main effects. This process will thereby help clinicians determine which couples should be assigned to which level of coach contact.

Missing Data

Finally, because missing data are anticipated, all missing data will be imputed using the miss-forest algorithm of Ishwaran and Kogalur randomForestSRC package in R (R Foundation for Statistical Computing) [54]. Miss-forest has been shown to robustly impute missing data without overfitting even if the types of data are mixed, there are interactions, or the data are high dimensional [55].

Results

Data collection was completed in October 2020 and data are being prepared to be analyzed. Overall, 63.8% (286/448) of individuals completed the material in the OurRelationship coach condition, 53.8% (155/288) of couples completed the OurRelationship contingent coach condition, and 54.5% (157/288) of individuals completed the OurRelationship automated (ie, email only) condition. Similarly, 69.4% (306/441) of couples completed the content in the ePREP coach condition, 74.2% (210/283) completed the content in the ePREP contingent coach condition, and 66.2% (188/284) of couples completed content in the ePREP automated (ie, email only) condition. Currently, no other outcomes except for completion rates have been analyzed. Given the large sample size within and between conditions, the current sample is large enough to identify potential predictor variables and evaluate their prediction accuracy. This study is expected to conclude in the summer of 2022.

Discussion

One of the direct benefits of this study will accrue to social services programs and program administrators of web-based relationship education. The results of this study will allow for more effective tailoring of coach contact to better meet the needs of unique low-income couples experiencing relationship distress. A second benefit is the improvement of web and evidence-based interventions. The federal government is increasing emphasis on delivering evidence-based interventions and, given the social distancing regulations put in place because of COVID-19, participation in web-based programs will likely increase either as an initial intervention or as a backup intervention in cases where in-person services are suspended. Thus, it is important that web-based federal services are as effective and accessible as possible. Overall, this study hopes to help practitioners by generating accurate predictions to match unique couples to the level of web-based programming that will help them to obtain the maximal benefit.

Conflicts of Interest

BDD is a coinventor of the intellectual property used in this study and an equity owner in OurRelationship LLC.

Multimedia Appendix 1
Peer-reviewer report from the Administration for Children & Families (USA).
[PDF File (Adobe PDF File), 157 KB - resprot_v10i11e33047_app1.pdf]

References

1. Whisman M, Beach S, Snyder D. Is marital discord taxonic and can taxonic status be assessed reliably? Results from a national, representative sample of married couples. J Consult Clin Psychol 2008;76(5):745-755 [FREE Full text] [doi: 10.1037/0022-006x.76.5.745] [Medline: 18837592]
2. Bramlett MD, Mosher WB. First marriage dissolution, divorce, and remarriage: United States. Advance Data - Centers for Disease Control and Prevention. 2001. URL: https://www.cdc.gov/nchs/data/ad/ad323.pdf [accessed 2021-09-24]
3. Lundquist E, Hsueh J, Lowenstein A, Faucetta K, Gubits D, Michalopoulos C, et al. A family strengthening program for low-income families: final impacts from the supporting healthy marriage evaluation. Office of Planning, Research and Evaluation, Administration for Children and Families, Washington, DC. 2014. URL: https://www.mdrc.org/sites/default/files/shm2013_30_month_impact_reportrev2.pdf [accessed 2021-09-24]
4. Jackson G, Krull J, Bradbury T, Karney B. Household income and trajectories of marital satisfaction in early marriage. J Marriage Fam 2017 Jun;79(3):690-704 [FREE Full text] [doi: 10.1111/jomf.12394] [Medline: 28603296]
5. Trail T, Karney B. What's (not) wrong with low‐income marriages. J Marriage Fam 2012 May 24;74(3):413-427. [doi: 10.1111/j.1741-3737.2012.00977.x]
6. Hatch SG, Le Y, Doss BD. Make up or break up? Charting the well-being of low-income help-seeking couples through the breakup process. J Fam Psychol 2021 May 13. [doi: 10.1037/fam0000859] [Medline: 33983755]
7. Gaubert JM, Gubits D, Alderson DP, Knox V. The supporting healthy marriage evaluation: final implementation findings. SSRN J 2012:2151081. [doi: 10.2139/ssrn.2151081]
8. Hawkins A, Erickson S. Is couple and relationship education effective for lower income participants? A meta-analytic study. J Fam Psychol 2015 Feb;29(1):59-68. [doi: 10.1037/fam0000045] [Medline: 25419911]
9. Cohen J. Statistical Power Analysis for the Behavioral Sciences. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988:1-567.
10. Christensen H, Mackinnon A. The law of attrition revisited. J Med Internet Res 2006 Sep 29;8(3):20-21 [FREE Full text] [doi: 10.2196/jmir.8.3.e20] [Medline: 17032636]
11. Eysenbach G. The law of attrition. J Med Internet Res 2005 Mar 31;7(1):e11 [FREE Full text] [doi: 10.2196/jmir.7.1.e11] [Medline: 15829473]
12. Mohr DC, Cuijpers P, Lehman K. Supportive accountability: a model for providing human support to enhance adherence to eHealth interventions. J Med Internet Res 2011 Mar 10;13(1):e30 [FREE Full text] [doi: 10.2196/jmir.1602] [Medline: 21393123]

13. Lamont A, Lyons M, Jaki T, Stuart E, Feaster D, Tharmaratnam K, et al. Identification of predicted individual treatment effects in randomized clinical trials. Stat Methods Med Res 2018 Jan;27(1):142-157 [FREE Full text] [doi: 10.1177/0962280215623981] [Medline: 26988928]
14. Lu M, Sadiq S, Feaster D, Ishwaran H. Estimating individual treatment effect in observational data using random forest methods. J Comput Graph Stat 2018;27(1):209-219 [FREE Full text] [doi: 10.1080/10618600.2017.1356325] [Medline: 29706752]
15. Doss B, Benson L, Georgia E, Christensen A. Translation of integrative behavioral couple therapy to a web-based intervention. Fam Process 2013 Mar;52(1):139-153 [FREE Full text] [doi: 10.1111/famp.12020] [Medline: 25408094]
16. Doss B, Cicila L, Georgia E, Roddy M, Nowlan K, Benson L, et al. A randomized controlled trial of the web-based our relationship program: effects on relationship and individual functioning. J Consult Clin Psychol 2016 Apr;84(4):285-296 [FREE Full text] [doi: 10.1037/ccp0000063] [Medline: 26999504]
17. Doss B, Knopp K, Roddy M, Rothman K, Hatch S, Rhoades G. Online programs improve relationship functioning for distressed low-income couples: Results from a nationwide randomized controlled trial. J Consult Clin Psychol 2020 Apr;88(4):283-294 [FREE Full text] [doi: 10.1037/ccp0000479] [Medline: 32134290]
18. Doss B, Roddy M, Nowlan K, Rothman K, Christensen A. Maintenance of gains in relationship and individual functioning following the online our relationship program. Behav Ther 2019 Jan;50(1):73-86 [FREE Full text] [doi: 10.1016/j.beth.2018.03.011] [Medline: 30661568]
19. Salivar EJ, Roddy M, Nowlan K, Doss B. Effectiveness of the online our relationship program for underserved couples. Couple Family Psychol 2018 Sep;7(3-4):212-226. [doi: 10.1037/cfp0000110]
20. Markman H, Stanley S, Blumberg S. Fighting for Your Marriage: Positive Steps for Preventing Divorce and Preserving a Lasting Love. San Francisco, California: Jossey Bass; Mar 13, 1996:1-352.
21. Braithwaite S, Fincham F. Eprep: computer based prevention of relationship dysfunction, depression and anxiety. J Soc Clin Psychol 2007 May;26(5):609-622 [FREE Full text] [doi: 10.1521/jscp.2007.26.5.609]
22. Braithwaite S, Fincham F. A randomized clinical trial of a computer based preventive intervention: replication and extension of ePREP. J Fam Psychol 2009 Feb;23(1):32-38 [FREE Full text] [doi: 10.1037/a0014061] [Medline: 19203157]
23. Braithwaite S, Fincham F. Computer-based dissemination: a randomized clinical trial of eprep using the actor partner interdependence model. Behav Res Ther 2011 Feb;49(2):126-131 [FREE Full text] [doi: 10.1016/j.brat.2010.11.002] [Medline: 21159326]
24. Braithwaite S, Fincham F. Computer-based prevention of intimate partner violence in marriage. Behav Res Ther 2014 Mar;54:12-21 [FREE Full text] [doi: 10.1016/j.brat.2013.12.006] [Medline: 24463577]
25. Hatch S, Knopp K, Le Y, Allen M, Rothman K, Rhoades G, et al. Online relationship education for help-seeking low-income couples: A Bayesian replication and extension of the OurRelationship and ePREP programs. Fam Process 2021 Aug 12:1-17. [doi: 10.1111/famp.12710] [Medline: 34383314]
26. Berger T, Caspar F, Richardson R, Kneubühler B, Sutter D, Andersson G. Internet-based treatment of social phobia: a randomized controlled trial comparing unguided with two types of guided self-help. Behav Res Ther 2011 Mar;49(3):158-169 [FREE Full text] [doi: 10.1016/j.brat.2010.12.007] [Medline: 21255767]
27. Button KS, Wiles NJ, Lewis G, Peters TJ, Kessler D. Factors associated with differential response to online cognitive behavioural therapy. Soc Psychiatry Psychiatr Epidemiol 2012 May 4;47(5):827-833. [doi: 10.1007/s00127-011-0389-1] [Medline: 21541696]
28. Christensen H, Griffiths KM, Farrer L. Adherence in internet interventions for anxiety and depression. J Med Internet Res 2009 Apr 24;11(2):e13 [FREE Full text] [doi: 10.2196/jmir.1194] [Medline: 19403466]
29. Farrer L, Christensen H, Griffiths K, Mackinnon A. Internet-based CBT for depression with and without telephone tracking in a national helpline: randomised controlled trial. PLoS One 2011;6(11):e28099 [FREE Full text] [doi: 10.1371/journal.pone.0028099] [Medline: 22140514]
30. Johansson O, Michel T, Andersson G, Paxling B. Experiences of non-adherence to internet-delivered cognitive behavior therapy: a qualitative study. Internet Interven 2015 May;2(2):137-142 [FREE Full text] [doi: 10.1016/j.invent.2015.02.006]
31. Melville K, Casey L, Kavanagh D. Dropout from internet ‐ based treatment for psychological disorders. Br J Clin Psychol 2010:455-471. [doi: 10.1348/014466509x472138]
32. Rothman K, Roddy M, Doss B. Completion of a stand ‐ alone versus coach ‐ supported trial of a web ‐ based program for distressed relationships. Fam Relat 2019 Aug 07;68(4):375-389 [FREE Full text] [doi: 10.1111/fare.12378]
33. Karyotaki E, Kleiboer A, Smit F, Turner D, Pastor A, Andersson G, et al. Predictors of treatment dropout in self-guided web-based interventions for depression: an ‘individual patient data’ meta-analysis. Psychol Med 2015 Apr 17;45(13):2717-2726 [FREE Full text] [doi: 10.1017/s0033291715000665]
34. Murray E, White IR, Varagunam M, Godfrey C, Khadjesari Z, McCambridge J. Attrition revisited: adherence and retention in a web-based alcohol trial. J Med Internet Res 2013 Aug 30;15(8):e162 [FREE Full text] [doi: 10.2196/jmir.2336] [Medline: 23996958]
35. Berger T, Hämmerli K, Gubser N, Andersson G, Caspar F. Internet-based treatment of depression: a randomized controlled trial comparing guided with unguided self-help. Cogn Behav Ther 2011;40(4):251-266 [FREE Full text] [doi: 10.1080/16506073.2011.616531] [Medline: 22060248]

36. Hirai M, Clum G. An internet-based self-change program for traumatic event related fear, distress, and maladaptive coping. J Trauma Stress 2005 Dec;18(6):631-636 [FREE Full text] [doi: 10.1002/jts.20071] [Medline: 16382433]
37. Roddy M, Rothman K, Doss B. A randomized controlled trial of different levels of coach support in an online intervention for relationship distress. Behav Res Ther 2018 Nov;110:47-54 [FREE Full text] [doi: 10.1016/j.brat.2018.09.002] [Medline: 30240874]
38. Lange A, Rietdijk D, Hudcovicova M, van de Ven J, Schrieken B, Emmelkamp P. Interapy: A controlled randomized trial of the standardized treatment of posttraumatic stress through the internet. J Consult Clin Psychol 2003;71(5):901-909 [FREE Full text] [doi: 10.1037/0022-006x.71.5.901]
39. Alfonsson S, Olsson E, Hursti T. Motivation and treatment credibility predicts dropout, treatment adherence, and clinical outcomes in an internet-based cognitive behavioral relaxation program: a randomized controlled trial. J Med Internet Res 2016 Mar 08;18(3):e52 [FREE Full text] [doi: 10.2196/jmir.5352] [Medline: 26957354]
40. Wangberg S, Bergmo T, Johnsen J. Adherence in internet-based interventions. Patient Prefer Adherence 2008 Feb 02;2:57-65 [FREE Full text] [Medline: 19920945]
41. Oromendia P, Orrego J, Bonillo A, Molinuevo B. Internet-based self-help treatment for panic disorder: a randomized controlled trial comparing mandatory versus optional complementary psychological support. Cogn Behav Ther 2016 Jun;45(4):270-286 [FREE Full text] [doi: 10.1080/16506073.2016.1163615] [Medline: 27007256]
42. Kleiboer A, Donker T, Seekles W, van Straten A, Riper H, Cuijpers P. A randomized controlled trial on the role of support in internet-based problem solving therapy for depression and anxiety. Behav Res Ther 2015 Sep;72:63-71 [FREE Full text] [doi: 10.1016/j.brat.2015.06.013] [Medline: 26188373]
43. Christensen H, Batterham P, Mackinnon A, Griffiths KM, Hehir KK, Kenardy J, et al. Prevention of generalized anxiety disorder using a web intervention, ichill: randomized controlled trial. J Med Internet Res 2014 Sep 02;16(9):e199 [FREE Full text] [doi: 10.2196/jmir.3507] [Medline: 25270886]
44. Collins LM, Murphy SA, Strecher V. The multiphase optimization strategy (most) and the sequential multiple assignment randomized trial (smart): new methods for more potent ehealth interventions. Am J Prev Med 2007 May;32(5 Suppl):112-118 [FREE Full text] [doi: 10.1016/j.amepre.2007.01.022] [Medline: 17466815]
45. Funk J, Rogge R. Testing the ruler with item response theory: increasing precision of measurement for relationship satisfaction with the Couples Satisfaction Index. J Fam Psychol 2007 Dec;21(4):572-583 [FREE Full text] [doi: 10.1037/0893-3200.21.4.572] [Medline: 18179329]
46. Booth A, Johnson D, Edwards J. Measuring marital instability. J Marriage Fam 1983 May;45(2):387-394 [FREE Full text] [doi: 10.2307/351516]
47. Bessaha M. Factor structure of the Kessler Psychological Distress Scale (K6) among emerging adults. Res Soc Work Pract 2015 Jul 06;27(5):616-624 [FREE Full text] [doi: 10.1177/1049731515594425]
48. Roddy M, Rhoades G, Doss B. Effects of ePREP and ourrelationship on low-income couples' mental health and health behaviors: a randomized controlled trial. Prev Sci 2020 Aug;21(6):861-871 [FREE Full text] [doi: 10.1007/s11121-020-01100-y] [Medline: 32108304]
49. Cohen S, Williamson G. Perceived stress in a probability sample of the United States. In: Spacapan S, Oskamp S, editors. The Social Psychology of Health: The Claremont Symposium on Applied Social Psychology. Thousand Oaks, California, United States: Sage Publications Inc; 1989:31-67.
50. Duckworth A, Quinn P. Development and validation of the Short Grit Scale (Grit-S). J Pers Assess 2009 Mar;91(2):166-174 [FREE Full text] [doi: 10.1080/00223890802634290] [Medline: 19205937]
51. Milstein D, Weinstein B. Effects of information sharing on follow-up after screening for older adults. J Acad Rehabil Audiol 2002;35:43-58 [FREE Full text]
52. Svetnik V, Liaw A, Tong C, Culberson J, Sheridan R, Feuston B. Random forest: a classification and regression tool for compound classification and QSAR modeling. J Chem Inf Comput Sci 2003;43(6):1947-1958 [FREE Full text] [doi: 10.1021/ci034160g] [Medline: 14632445]
53. Ishwaran H, Lu M. Standard errors and confidence intervals for variable importance in random forest regression, classification, and survival. Stat Med 2019 Feb 20;38(4):558-582 [FREE Full text] [doi: 10.1002/sim.7803] [Medline: 29869423]
54. Ishwaran H, Kogalur U. Random forests for survival, regression and classification (RF-SRC). R Package Version 1. URL: http://CRAN.R-project.org/package=randomForestSRC [accessed 2021-09-05]
55. Tang F, Ishwaran H. Random forest missing data algorithms. Stat Anal Data Min 2017 Dec;10(6):363-377 [FREE Full text] [doi: 10.1002/sam.11348] [Medline: 29403567]

Abbreviations

ACF: Administration for Children and Families
ePREP: web-based Prevention and Relationship Enhancement Program
IPV: intimate partner violence
RCT: randomized controlled trial
RMSE: root mean square error

VIMP: variable importance

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Protocol

The Efficacy of a Personalized mHealth Coaching Program During Pregnancy on Maternal Diet, Supplement Use, and Physical Activity: Protocol for a Parallel-Group Randomized Controlled Trial

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Abstract

Background: Adequate intake of macro- and micronutrients and adoption of an active lifestyle during pregnancy are essential for optimum maternal and fetal health and offspring development. Dietary counseling and advice regarding adequate physical activity are integral components of antenatal care. Personalized coaching through the use of mobile health (mHealth) that supports behavior modification is an innovative approach that needs exploration.

Objective: Our primary aim is to assess the efficacy of an mHealth program in improving diet, supplement use, and physical activity during pregnancy. Secondary objectives include evaluation of the program's effect on maternal and offspring health outcomes and assessment of its compliance and usability.

Methods: A randomized controlled trial was initiated at the Aga Khan University Hospital in Karachi, Pakistan, in January 2020. We aim to recruit 300 pregnant women in their first trimester who have smartphones, do not have comorbidities, and are not taking medications. The intervention group will be trained to use an mHealth app called *PurUmeed Aaghaz*. Through this app, the subjects will report information about their diet, supplement use, and physical activity and will receive personalized advice and three push messages as weekly reminders. The research assistant will obtain similar information from the control group via a paperless questionnaire; this group will receive standard face-to-face counseling regarding diet, supplement use, and physical activity. Data will be collected at enrollment and during four follow-up sessions scheduled 6 weeks apart. Primary study outcomes include improvements in diet (ie, change in mean dietary risk score from baseline to each follow-up), supplement use (ie, changes in mean supplement use score and biochemical levels of folic acid, iron, calcium, and vitamin D on a study subset), and mean duration of reported physical activity (minutes). Secondary study outcomes relate to maternal health (ie, gestational diabetes mellitus, gestational hypertension, pre-eclampsia, and gestational weight gain), newborn health (ie, birth weight and length and gestational age at delivery), and infant health (ie, BMI and blood pressure at 1 year of age). Compliance will be determined by the proportion of participants who complete the 6-month coaching program. Usability will be assessed based on features related to design, interface, content, coaching, perception, and personal benefit.

Results: The study was approved by the Ethics Review Committee of the Aga Khan University in 2017. The recruitment of study participants was completed in September 2021. All follow-ups and outcome assessments are expected to be completed by March 2023 and analysis is expected to be completed by June 2023. We expect the results to be published by the end of 2023.

Conclusions: This study will be an important step toward evaluating the role of mHealth in improving behaviors related to a healthy diet, supplement use, and promotion of physical activity during pregnancy, as well as in influencing maternal and offspring outcomes. If proven effective, mHealth interventions can be scaled up and included in antenatal care packages at tertiary care hospitals of low- and middle-income countries.

Trial Registration: ClinicalTrials.gov NCT04216446; https://clinicaltrials.gov/ct2/show/NCT04216446

International Registered Report Identifier (IRRID): DERR1-10.2196/31611

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KEYWORDS

coaching; compliance; diet; maternal health; mobile health; offspring health; physical activity; pregnancy; supplement use; usability

Introduction

Role of Maternal Diet and Micronutrient Supplement Use

Maternal diet serves as a critical prenatal modifiable factor that influences fetal growth and development. Inadequate consumption of macronutrients (ie, proteins, carbohydrates, and fats) and micronutrients, especially folic acid, iron, calcium, and vitamin D, may influence the programming of the offspring's organs with health consequences during the life course [1]. Evidence suggests strong associations between maternal undernutrition and fetal growth restriction [2]. Consumption of a Mediterranean-type diet rich in fruits and vegetables produces a remarkable decrease in the risk of preterm birth [3,4], hypertension [5], and gestational diabetes mellitus [6]. Adequate consumption of fish and folic acid has beneficial effects on the prevention of pre-eclampsia and gestational hypertension [7, 8].

Poor nutrition during the sensitive phase of the first trimester of pregnancy not only affects growth in the later trimesters and birth weight [9-11] but could also derange epigenetic programming, resulting in long-lasting health consequences [12]. Subtle variations in nutrition during pregnancy and lifestyle factors may influence the risk of noncommunicable diseases without affecting birth weight [13].

The association of micronutrient deficiencies with unfavorable maternal and fetal outcomes is well established. Maternal anemia accounts for low birth weight (12%), preterm births (19%), and perinatal mortality (18%) [14]. Low serum folate levels and absence of folic acid supplementation are associated with preterm births [15]. Similarly, vitamin D and calcium deficiencies are causally linked to pre-eclampsia, gestational diabetes mellitus, preterm delivery, and low birth weight [16].

Physical Activity During Pregnancy

In addition to diet and micronutrients, physical activity is also known to influence maternal and fetal outcomes. Regular physical activity is recommended during pregnancy for prevention of gestational diabetes and pre-eclampsia [17,18]. The American College of Obstetricians and Gynecologists (ACOG) recommends at least 150 minutes of moderate-intensity aerobic activity every week, or at least 30 minutes on most days of the week, for pregnant women [17,19]. Aerobic activities involve rhythmic movement of large body muscles, such as those in the legs and arms. Moderate intensity refers to moving enough to raise the heart rate and to sweat while being able to talk normally but not being able to sing [20].

Maternal Health Status in Pakistan

Women of reproductive age in Pakistan are facing a triple burden of malnutrition. A significant proportion of them are underweight (14.4%), overweight (24%), or obese (13.8%) [21]. In addition, there is a high prevalence of micronutrient deficiency, particularly regarding iron (18.2%), calcium (26.5%), and vitamin D (79.7%) [21]. There is also a substantial burden of high-risk pregnancies, causing such complications as gestational hypertension (6.5%) [22], pre-eclampsia (2.4%) [22], and gestational diabetes mellitus (3.3%-17.2%) [23,24]. Pakistan ranks 4th among the top 10 countries with regard to preterm births (16 per 100 live births) [25] and the prevalence of babies with low birth weight (22%) [26].

Of further concern are the suboptimal nutritional indicators for women living in urban areas, where only 42.2% of them have normal BMI compared to 48.5% in rural areas. A significant proportion of these women suffer from undernutrition (12%), overweight (26.5%), and obesity (17.2%) [21]. Also, vitamin D deficiency is more common in urban (83.6%) than in rural (77.1%) settings [21].

Lately, women in Pakistan, in addition to fulfilling their reproductive responsibilities, have started participating in economic activities to support their careers and families. About 17% of women are employed nationwide, and 21% of women who have ever been married are working in the province of Sindh [26]. When they enter pregnancy as nutritionally compromised, these women are found to further neglect their health due to work and other responsibilities [21]. Further, interventions for improving maternal nutrition in Pakistan have been mainly in the form of supplementation of folic acid, iron, multiple micronutrients, calcium, and iodine, as well as balanced protein-energy supplementation [27].

Given the significant magnitude of maternal undernutrition and adverse perinatal outcomes in Pakistan, there is a need to adopt innovative counseling strategies during the critical antenatal period that would regularly remind women to pay attention to their diet and physical activity needs. This would not only reduce the risk of maternal complications, such as pre-eclampsia, pregnancy-induced hypertension, and gestational diabetes, but

would also improve the immediate and long-term health of the newborn.

mHealth Interventions During Pregnancy

The antenatal period represents a major life event when self-motivation to improve diet and lifestyle is often high. This transition to parenthood provides an incredible opportunity, based on the theory of planned behavior [28], because of the willingness to adapt, keeping in mind the expected benefit of having a healthy baby [29]. Hence, communication strategies using mobile health (mHealth) can serve as an awareness tool for desired adjustment in diet and physical activity through positive reinforcement and by offering practical and evidence-based suggestions.

Smarter Pregnancy is one such mHealth intervention launched among the Dutch population in their local language [30]. It was introduced as an online, device-independent, web-based coaching platform for couples during their periconception and pregnancy periods for dietary improvement, folic acid use, and alcohol and smoking cessation [30]. The program consisted of 6 months of interactive coaching through tailored and personalized short text messages and emails; the program showed high compliance (65%) and usability (55%), as well as significant improvement in diet and lifestyle behaviors [30].

Emergence of mHealth in Pakistan

Being home to a population of over 220 million, Pakistan is experiencing an enormous increase in the digital landscape that parallels the global increase in internet access (45%) and mobile phone subscriptions (96%) [31]. Nationwide, the proportion of internet users has increased by 17% from 2019, reaching 76.38 million in 2020 [32]. According to the recent Digital Pakistan Policy, the Ministry of National Health Services has received support for the promotion of telemedicine and disease prevention information through information and communication tools [33]. With the potential to reach a great proportion of the population at a low cost [31,34], tailored health promotion messages through new delivery modes, such as the internet and mobile phones, have shown promising effects in improving nutrition, lifestyle, and compliance to medication [34-37].

mHealth-Related Interventions in Pakistan and the Existing Gap

Recently, a few mHealth initiatives have been introduced, such as the Baby+ app for pregnant women in urban areas [38]; the MotherCare app in Swat District [39]; Marham, a private initiative [40]; and Teeko, an Android-based app for improving childhood immunization in rural Sindh [41]. However, there has been no systematic assessment of any locally developed mHealth apps for pregnant women targeted toward improvement in diet, supplement use, and physical activity.

Using an mHealth platform, we intend to empower pregnant women and their health care providers to identify modifiable dietary and lifestyle inadequacies and to receive personalized coaching to address them.

Study Objectives

Primary Objective

Our primary objective is to assess the efficacy of an mHealth coaching intervention compared to standard face-to-face counseling in improving (1) maternal diet by 30%, (2) supplement use (ie, iron, folic acid, calcium, and vitamin D) by 30%, and (3) physical activity by 20%.

Secondary Objectives

Our secondary objectives are to conduct the following:

1. Investigate the efficacy of the intervention regarding the following:
   - Reducing incidence of gestational diabetes mellitus, gestational hypertension, and pre-eclampsia.
   - Improving mean gestational weight gain and mean weight, length, and gestational age at birth.
   - Improving mean BMI and blood pressure at 1 year of age.
2. Evaluate compliance (ie, completion of the 6-month program) and usability (ie, design and interface, content and coaching, and perception and personal benefit) of the mHealth app among women in the intervention group.

Methods

Target Population

Our target population is pregnant women in their first trimester from the urban area of Karachi, Pakistan.

Study Goal

Our study goal is to assess the role of the mHealth program in improving the behaviors of pregnant women related to diet, supplement use, and physical activity. In addition, we are interested in assessing whether the maternal, newborn, and infant outcomes differ between those who use the program compared to those who do not.

Study Hypothesis

We hypothesize that the mHealth coaching program will be effective in improving diet and supplement use among pregnant women by 30% and physical activity by 20% during the study period.

Study Design

This study is a parallel-group, randomized controlled superiority trial with two groups (ie, intervention and control) having an allocation ratio of 1:1. The trial was registered at ClinicalTrials.gov (NCT04216446) on January 2, 2020. The intervention to be tested is an mHealth program that was developed locally to collect dietary, supplement use, and physical activity information from pregnant women and to provide personalized counseling tailored to the screening information. The control group will receive standard counseling with similar content, but the content will not be personalized and will be delivered through face-to-face sessions.

Study Setting

The study is taking place at the Aga Khan University Hospital (AKUH) in Karachi, Pakistan. AKUH is a private, not-for-profit, tertiary care hospital, recognized for its trained health care professionals who specialize in providing high-quality compassionate care and for a full range of specialty services [42]. It is also certified by the Joint Commission International Accreditation. The study participants were recruited on a daily basis from the antenatal clinics that are run by trained obstetricians. Most obstetricians, on average, see 25 to 30 pregnant women every day in the clinic.

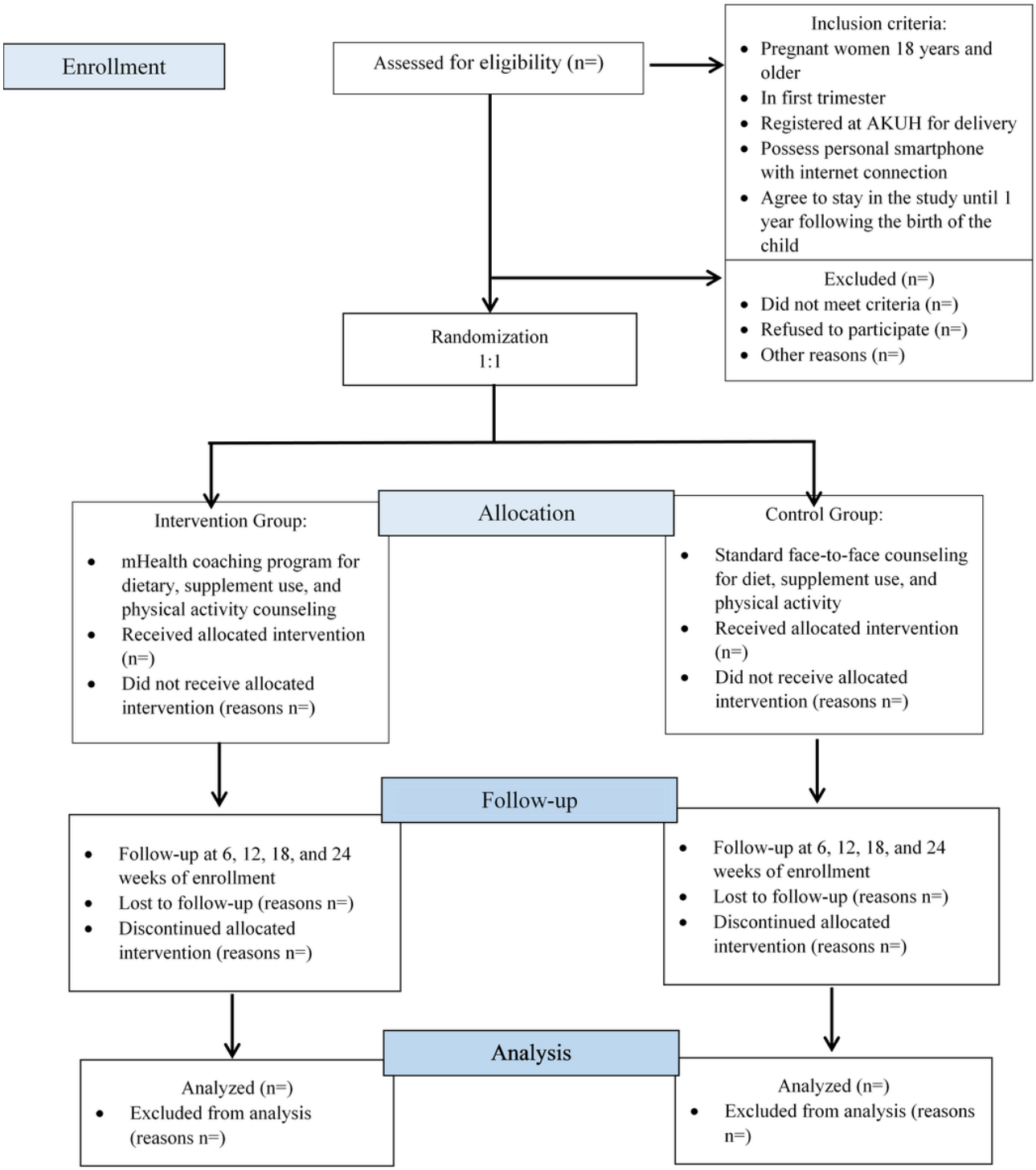
Enrollment Criteria

Pregnant women 18 years or older and in their first trimester are eligible to participate if they possess a personal smartphone with internet connection and agree to remain in the study until 1 year following the birth of their baby. Pregnant women on dietary control secondary to the diagnosis of diabetes mellitus; taking medications, such as antiplatelet aggregators, hypoglycemic drugs, or antihypertensive drugs; who have autoimmune, liver, or kidney disease; or who are unable to read and write due to a language barrier will be excluded from the study.

Sampling Strategy and Randomization

Participants were identified using a purposive sampling strategy and were randomly assigned to the study groups using simple block randomization (block size of 6). The Clinical Trials Unit at AKUH facilitated the computer-generated randomization and provided opaque, sealed envelopes to the research team to ensure concealment of the assignment (Figure 1).

Figure 1. CONSORT diagram of the study. AKUH: Aga Khan University Hospital; mHealth: mobile health.



Recruitment

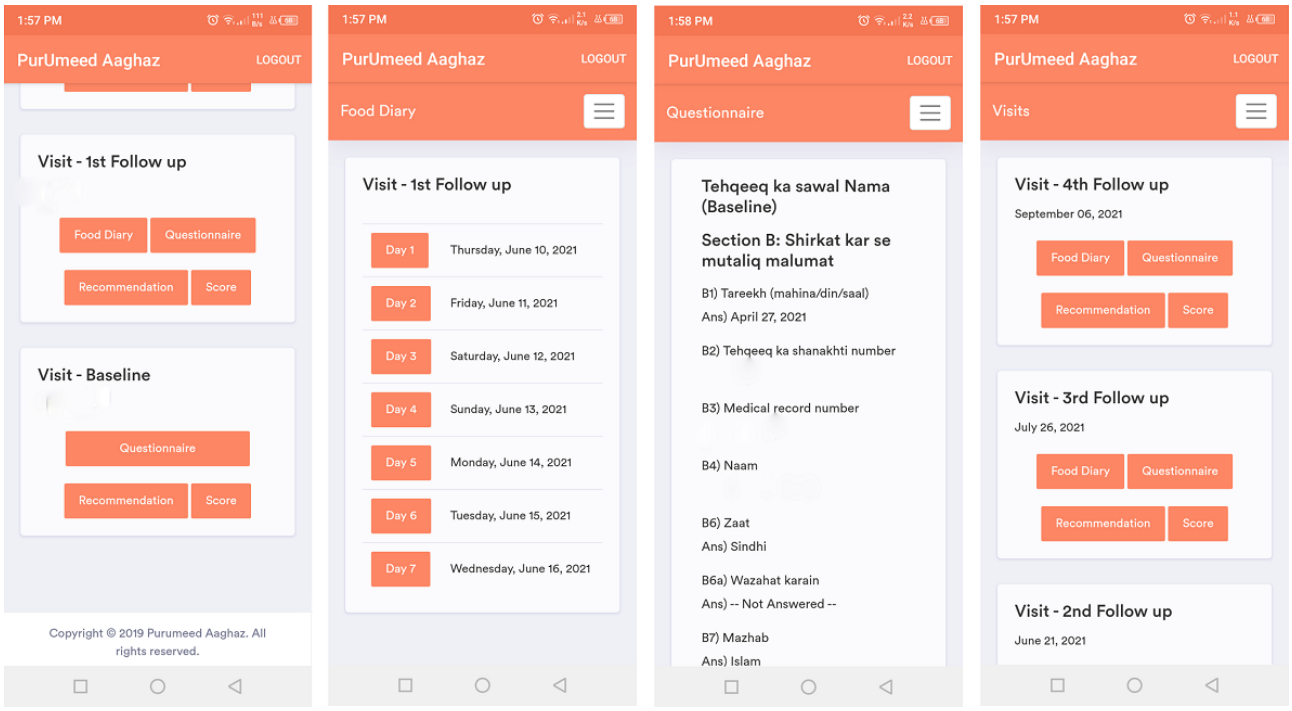
At the antenatal clinics, participants were approached to assess their eligibility and to obtain written informed consent. The data collector explained, in detail, the study's aims and procedures involved in order to facilitate women's participation and ensure compliance in the study. A signed copy of the consent form was provided to the participants. Enrolled participants were randomized to one of the two groups (Figure 1).

Web-Based mHealth Program: PurUmeed Aaghaz

The web-based mHealth program, called *PurUmeed Aaghaz* (a hopeful beginning), was designed and developed locally with the assistance of the Digital Health Resource Center (DHRC) of the Aga Khan Development Network. It is an online, device-dependent app designed to function on Android and iPhone operating systems. It was developed based on the scientific evidence of recommended dietary, supplement use, and physical activity guidelines during pregnancy. Moreover, the coaching platform takes into consideration the theory of planned behavior [43], the theory of self-efficacy [44], the Fogg

behavior model [45], and the transtheoretical model for behavior change [46]. Furthermore, the preference, availability, and consumption of locally available items from all the major food groups; supplement use (ie, folic acid, iron, calcium, and vitamin D); and physical activity were taken into account during the development of the app. Based on the participants' data, the app will generate tailored and personalized counseling messages and recommendations for the pregnant women regarding diet, supplement use, and physical activity. This app will be available to the participants who are randomized to the intervention group as a free subscription, starting from enrollment during their first trimester and for the entire duration of their pregnancy (Figure 2).

Figure 2. Screenshots of the *PurUmeed Aaghaz* app.



Features of the mHealth Program

The mHealth program has three main features, as discussed in the following three sections.

Personalized Recommendations and Dietary Risk Scores

Submission of completed questionnaires by the participants in the first trimester will generate recommendations based on an algorithm. This algorithm will compare participants' information with the recommended dietary [47], supplement use [48-50], and physical activity guidelines [19] for pregnant women as described in the Counseling for Diet, Supplement Use, and Physical Activity section below. In addition, individualized dietary risk scores for food quantity and diversity in diet will also be generated.

Push Messages

Content from the individual coaching sessions will be delivered three times a week in the form of short push messages containing tips and recommendations for diet, supplement use, and physical activity. These messages will be short, simple, and easy to comprehend. Women will be alerted to these messages through notifications on their phones, and these will be available in the app under the "advice" option.

Food Record Diary

A built-in food record diary will be available to document information about the food items consumed in a day for breakfast, lunch, dinner, and snacks, along with their portions. Women will be asked to complete the food record diary in their smartphones for a week before their next follow-up, so as to reduce the chance of recall bias. On the follow-up day, the diary will be synced with the data collection tool. Any missing information will be added during the interview.

Counseling for Diet, Supplement Use, and Physical Activity

Diet

Women randomized to the intervention group will receive dietary advice based on the World Health Organization (WHO) guidelines for healthy eating during pregnancy and breastfeeding [47]. We have also consulted guidelines by the WHO for healthy diet [51], the ACOG for nutrition during pregnancy [52], and the Food and Agriculture Organization of the United Nations [53] for the development of content for the push messages. In these messages, consumption of food from six main food groups will be encouraged as follows: bread, cereals, rice, and potato group (6-11 portions per day); vegetable group (at least 3 portions per day); fruit group (at least 2 portions per day); milk and dairy products group (3 portions per day); fish, poultry, meat, and beans group (2 portions per day); and butter, margarine, and oil group (less than 30% of total calories, preferably as unsaturated fats) [51]. In addition, women will be advised to consume three meals and two snacks per day to avoid prolonged periods of fasting and to consume monounsaturated fats, adequate protein, fiber-rich carbohydrates, and at least two

servings of omega-3–rich fish per week. Consumption of vitamin A will be encouraged from plant sources as beta carotene. Further, advice will be given to limit intake of carbohydrates with a high glycemic index (eg, fruit juices and sodas).

Supplement Use

WHO guidelines for micronutrient supplements during pregnancy will be used to counsel women. These will include daily oral supplements of folic acid (0.4 mg) [48], iron (30-60 mg) [49], calcium (1500-2000 mg) [49], and vitamin D (200 IU) [50].

Physical Activity

Based on ACOG guidelines [19], women will be advised to engage in moderate-intensity aerobic physical activity for at least 150 minutes over the week or 30 minutes on most days of the week. Moreover, they will be encouraged to limit prolonged periods of being sedentary [54].

Control Group

Women randomized to the control group will provide their dietary, supplement use, and physical activity information on a paperless questionnaire administered by the research assistant. Face-to-face counseling will follow, using the bilingual educational brochure from the AKUH on diet during pregnancy and ACOG guidelines for physical activity [19]. A copy of the educational brochure and a paper-based food record diary to be filled in a week prior to their next follow-up will also be provided to women in the comparison group.

Follow-Up

Follow-ups will be done four times, every 6 weeks: 6, 12, 18, and 24 weeks from the time of enrollment in the first trimester to monitor improvement, if any. For the intervention group, results of each follow-up and their comparison with the earlier one will be displayed on each participant's personal page of the app. A summary of the individual results will be able to be viewed at any moment by the participant and handed over or shared with their obstetrician by email for further assessment and care. The control group will receive face-to-face counseling at each follow-up.

Data Collection Tools

Screening Questionnaire

A comprehensive questionnaire has been developed to collect data from the participants on sociodemographic characteristics, general food information, anthropometric and blood pressure measurements, biochemical assessments, obstetrics history and supplement use, dietary consumption for the past 7 days recorded as quantity and quality of each food group, and physical activity history for the past 7 days. In addition, intake of savory and fast food, water, tea, coffee, carbonated beverages, and substances such as smoked and smokeless tobacco will be recorded. The questionnaire has been developed after consulting experts and reviewing various dietary assessment tools and programs, such as the 24-hour dietary recall [55], food frequency questionnaires [55], and the Smarter Pregnancy program [56]. The questionnaire has been pretested on 5% of the sample and has been further improved.

Food Record Diary

Information about the frequency and portions of food consumed from different food groups over 7 days before the participants' next follow-up will be collected in the food record diary. The intervention group will report this information in the *PurUmeed Aaghaz* app, while the control group will be required to record this information in a paper-based diary.

Biochemical Assessment of Micronutrient Status

In order to validate the information related to dietary intake, every 5th woman enrolled in the intervention and control groups—a subset of 30 women from each group—will undergo a free biochemical assessment of serum iron, ferritin, calcium, and vitamin D at baseline and at the end of the study at the AKUH laboratory. The specimens will be discarded once analyzed by the laboratory.

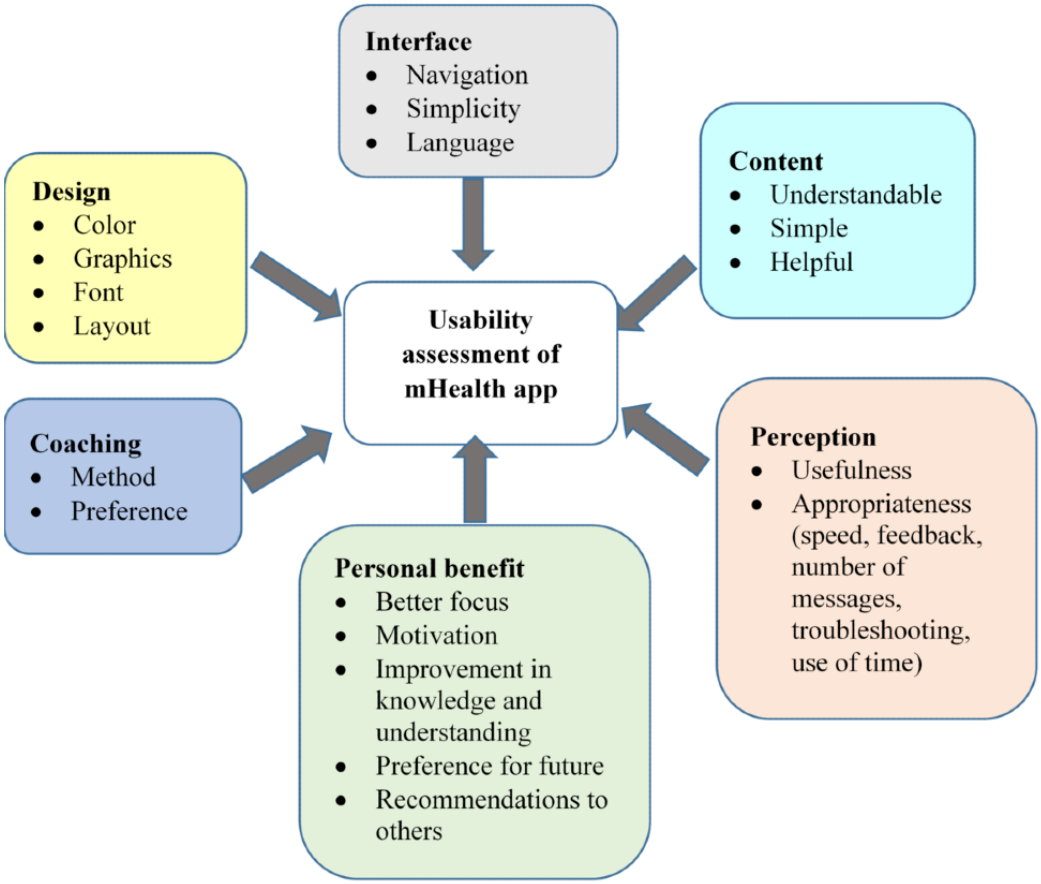
Outcome Assessment Questionnaire

A brief questionnaire has been developed to record information about the study outcomes. The data about maternal and newborn outcomes will be obtained from the medical records, while infant height, weight, and blood pressure will be measured by the trained research assistant.

Usability Assessment Questionnaire

A questionnaire containing 26 questions has been developed to assess the experience of using the mHealth program based on six domains: design, interface, content, coaching, perception, and personal benefit (Figure 3) [36].

Figure 3. Components of the usability assessment of the mobile health (mHealth) app.



Sample Size Calculation

Sample size has been calculated using OpenEpi (version 3.01). Based on assumptions of an α error of .05, a β error of .2, a 1:1 ratio of exposed to intervention to unexposed to intervention, and improvement in dietary intake and supplement use by 30% in the intervention group from a baseline of 20% [36], a sample size of 45 women in each group will be required. Based on the hypothesized 20% improvement in physical activity from a baseline of 36% [57], our sample size requirement increased to 107 women in each group. To reach 65% compliance [36], approximately 300 women will be needed for this study.

Expected Primary Outcomes

Dietary Intake: Quantity and Quality

Change in dietary intake between baseline and four subsequent follow-up visits 6 weeks apart will be assessed through a questionnaire. Based on consumption recorded in the food diary, data will be collected on the frequency and amount of all kinds of food consumed at each meal, including fruits and vegetables, red meat, white meat, legumes, nuts, eggs, dairy products, added table salt, and drinks (eg, carbonated drinks, fresh juices, and prepared juices). Averages will be calculated to determine the daily intake. Food sizes and amounts will be explained with the help of model utensils (ie, plate, bowl, and glass).

Dietary risk scores, ranging from 0 to 18, will be calculated based on the consumption of food items from six main food groups. Based on portions and diet quality, the score for each food group will be 0, 1.5, or 3 (Table 1) [58]. The total score will be the sum of individual food group scores. The higher the aggregate score, the poorer the dietary quantity and quality, and vice versa. Hence, a score of 18 indicates a highly inadequate dietary intake, a score of 9 indicates a nearly adequate dietary intake, and a score of 0 indicates an adequate diet [58].

Table 1. Dietary risk score for six food groups.

Food group and characteristics[a]	Dietary risk score		
	0	1.5	3
Bread, cereals, rice, and potato			
Quantity	6 portions	3 to <6 portions	<3 portions
Quality	≥50% of whole grains	25% to <50% of whole grains	<25% of whole grains
Fruits			
Quantity	≥2 portions	1 portion	<1 portion
Quality	Whole fruit consumption	<50% of whole fruits and >50% shakes or fruit juices	Juices and/or shakes only
Vegetables			
Quantity	≥3 portions	1.5 to <3 portions	<1.5 portions
Quality	>1/3 raw and <2/3 cooked	<1/3 raw and >2/3 cooked	Only in one form
Fish, poultry, meat, and beans			
Quantity	2 portions	1 portion	<1 portion
Quality	All sources (fish and meat 2 times/week; plant-based protein ≥4 times/week)	Fish >2 or <1 times/week; meat >2 or <1 times/week; plant-based protein 2 to <4 times/week	No fish, no plant-based protein, only meat
Milk and dairy products			
Quantity	3 portions	1.5 to <3 portions	<1.5 portions
Quality	Milk and dairy products	Milk or dairy products	None
Oils and fats			
Quantity	25% to 30% of total calories	30% to 35% of total calories	>35% of total calories
Quality	Polyunsaturated	Monounsaturated	Saturated

[a]The quantity and quality refer to the daily consumption.

Supplement Use

Supplement use will be assessed by recording the frequency of consumption of folic acid, iron, calcium, and vitamin D in the questionnaire. The frequency will be categorized as daily (7 days per week), often (4-6 days per week), and sometimes (1-3 days per week). Also, a total score ranging from 0 to 12 will be assigned, where use of each supplement will be scored 0 for daily use, 1.5 for less than daily use, and 3 for no consumption (Table 2). The total score will be the sum of each supplement use score and will be monitored at each follow-up.

Table 2. Scoring for use of each supplement.

Micronutrient supplement	Frequency of use by score		
	Adequate (0)	In between adequate and inadequate (1.5)	Inadequate (3)
Calcium (1.5-2 g)	Daily	Often or sometimes	Not consumed
Folic acid (0.4 mg)	Daily	Often or sometimes	Not consumed
Iron (30-60 mg)	Daily	Often or sometimes	Not consumed
Vitamin D (200 IU)	Daily	Often or sometimes	Not consumed

Physical Activity

Intensity and duration (minutes) of physical activity will be assessed through the questionnaire at baseline and at each follow-up. Walking slowly and household tasks, such as cooking, ironing, light physical work, driving, and washing dishes, will be categorized as mild-intensity activities [59]. Brisk walking; gardening; household chores, such as sweeping, washing, vacuuming, and mopping; actively playing with children; and carrying loads under 20 kg will be classified as moderate-intensity activities [60,61]. On the other hand, vigorous-intensity activities will include running, fast cycling, aerobics, swimming, sports games, or carrying loads over 20 kg [60,61].

Expected Secondary Outcomes

Maternal Health

The following four maternal conditions will be identified through the medical records.

Pre-eclampsia will be defined as new onset of hypertension after 20 weeks of gestation along with proteinuria (ie, a spot urine protein to creatinine ratio of ≥30 mg/mmol) and/or evidence of maternal acute kidney injury, liver dysfunction, neurological features, hemolysis or thrombocytopenia, and/or fetal growth restriction [62].

Gestational hypertension will be defined as new onset of hypertension (ie, blood pressure of ≥140 mm Hg systolic or ≥90 mm Hg diastolic at or after 20 weeks' gestation) [62].

Gestational diabetes will be defined as diagnosis made by a single-step 75-g oral glucose tolerance test conducted between 24 and 28 weeks of gestation or at any other time, with one or more of the following results: (1) fasting plasma glucose of 5.1 to 6.9 mmol/L (92-125 mg/dL), (2) 1-hour post–75-g oral glucose load of ≥10 mmol/L (180 mg/dL), and (3) 2-hour post–75-g oral glucose load of 8.5 to 11.0 mmol/L (153-199 mg/dL) [63].

Due to the expected low incidence of these conditions and given our small sample size, we shall pool these conditions as adverse maternal outcomes.

Gestational weight gain will be determined from weights recorded during the first, second, and third trimesters. Centiles and *z* scores will be assessed using the international gestational weight gain calculator based on the INTERGROWTH-21st (International Fetal and Newborn Growth Consortium for the 21st Century) Project standards for gestational weight gain [64,65].

Newborn Health

At birth, weight, height, and gestational age will be determined from medical records. Birth weight (in grams) will be the first weight of an infant measured soon after birth, ideally within the first hours before significant postnatal weight loss has occurred [66]. Length at birth will be measured from head to toe (in cm). Both weight and length will be adjusted for sex and gestational age at birth and compared with the INTERGROWTH-21st Project reference [67]. Preterm birth will be defined as spontaneous birth before completion of 37 weeks of gestation [68].

Infant Health

BMI will be assessed by measuring the weight and length of the infant at their first birthday using standardized equipment (seca 417 length scale and LAICA weight scale, model No. PS3001W1). BMI will be compared with the sex- and age-adjusted INTERGROWTH-21st reference [67]. At the same visit, resting blood pressure will be assessed using the Dinamap VS-900 vital signs monitor (Mindray), with an appropriate infant-sized cuff while the infant is in a state of calm. Two readings will be taken from the left arm, and an average will be calculated [69]. Mean systolic and diastolic blood pressure that is more than the height- and gender-based 90th centile will be considered high risk [70].

mHealth Outcomes

Compliance with the intervention will be defined by the percentage of participants who complete the 6-month program [36]. Usability of the mHealth program will be assessed through a usability questionnaire, where items are rated on a 5-point Likert scale with the following responses: 1 (always), 2 (often), 3 (sometimes), 4 (rarely), and 5 (never), or 1 (strongly agree), 2 (agree), 3 (neutral), 4 (disagree), and 5 (strongly disagree).

Type of Analysis

The data for the study participants will be analyzed based on the group to which they were initially assigned, irrespective of the intervention they received using the intention-to-treat approach [71]. This will preserve the benefits of randomization and will allow us to draw inferences regarding the efficacy of the intervention [71].

Statistical Analysis

Data will be entered and analyzed using Stata software (version 12; StataCorp LP). Data from the intervention group will be digitalized and uploaded to the app. Categorical variables will be reported as frequencies and percentages. Continuous variables will be reported as means and SDs or medians and IQRs, as appropriate. General characteristics, nutritional change in the form of dietary risk score, supplement use, maternal outcomes, gestational weight gain, birth weight and length, BMI, and blood pressure will be compared using chi-square tests for proportions and *t* tests and Mann-Whitney *U* tests for continuous variables. A mixed-model method will be used to take into account the repeated measurements and correlation while modeling the fraction that scores adequately at each of the follow-up time points. In order to minimize selection bias, we will use multiple imputation models to handle missing data from participants who prematurely leave the study. Possible confounding variables, such as age, BMI, parity, previous history of miscarriage, socioeconomic status, educational status of the women, and occupation, will be assessed and adjusted. Moreover, interactions will be reported if present in the model.

Data Management, Confidentiality, and Privacy Protection

The intervention group will add data via their smartphones to the mHealth app, which will be protected by log-in ID and password. The data from the program will be uploaded to the web server in real time. The server will be managed by the DHRC team, with access available to the primary person responsible for management of the mHealth program. The data will be handed over to the principal investigator (PI) when requested or upon study completion.

The data from the control group will be gathered on a database built using Microsoft Access. The file will be password protected and access will be limited to the PI and research assistant. The consent forms and the completed food record diaries will be saved in a locker, which will be secured by a lock and key.

Quality Assurance

To ensure the validity and accuracy of the trial implementation, hands-on training has been given to the research assistant for data collection and for use of the mobile app over the 5 training days using the manual of operations for data collection. Refresher trainings will be conducted every 3 months and as

needed. The data collected will be checked every day for possible errors and rectification will be made on the spot. In order to promote participant retention, they will be encouraged to ask any questions. The project PI will closely monitor the study and oversee its smooth implementation. Moreover, regular project meetings will be held for progress monitoring and troubleshooting. Since we do not anticipate changes in the indicators at interim periods of the trial, we intend to conduct intention-to-treat and full analyses at the end of the trial. No adverse events related to the intervention are anticipated.

Ethical Considerations

Approval for this study has been received from the Clinical Trials Unit and the Ethics Review Committee of the Aga Khan University. Written informed consent will be collected from the study subjects at recruitment. All data collected will be kept strictly confidential and analyzed anonymously. The data shall be used only for research purposes. In case of any changes to the protocol, the Ethics Review Committee will be notified and approval will be sought for amendments.

Limitations

There are few anticipated limitations of the study. Firstly, the randomization ensures that unknown variables and confounders are randomly distributed among the two groups; however, there could exist residual confounding if not enough data are collected for the confounder in question or if the categories formed are too broad or narrow. Secondly, there could be information bias given that the assessment of behaviors during pregnancy is subjective and, therefore, could lead to differential or nondifferential misclassification. For factors such as substance use and smoking, underreporting can be experienced since these are not socially desirable behaviors. Thirdly, participants may experience recall limitations during the assessment of diet, supplement use, and physical activity. However, in order to minimize the chances of recall bias, a food record diary will be provided to women to document accurate information. Fourthly, the study could experience attrition bias, due to multiple follow-ups and long duration. Fifthly, blinding was not possible owing to the behavioral nature of the intervention. Lastly, as the study will assess the efficacy of the intervention, generalizability will be limited.

Study Duration and Timeline

We have completed the recruitment and allocation of the participants. Each woman, once enrolled, is expected to remain in the study for a period of 18 months (Table 3).

Table 3. Study timeline.

Study steps, assessments, and outcomes	Study period and time point							
	Enrollment	Allocation	Postallocation					
	Baseline	Baseline	6 weeks	12 weeks	18 weeks	24 weeks	Delivery	1 year of birth
Enrollment and allocation								
Eligibility screen	X[a]							
Informed consent	X							
Randomization		X						
Allocation		X						
Allocated interventions								
mHealth[b] coaching[c]		X	X	X	X	X		
Standard face-to-face counseling		X	X	X	X	X		
Assessment of independent variables								
Sociodemographics, general food information, and obstetrics history		X						
Biochemical assessment information		X	X	X	X	X		
Diet, supplement use, and physical activity		X	X	X	X	X		
Measurement of outcomes								
Diet: dietary risk score		X	X	X	X	X		
Supplement use: biochemical assessment		X				X		
Physical activity: change in duration		X	X	X	X	X		
Maternal gestational diabetes			X	X	X	X		
Maternal gestational hypertension			X	X	X	X		
Maternal pre-eclampsia			X	X	X	X		
Maternal weight gain		X		X		X		
Newborn preterm birth							X	
Newborn birth weight and length							X	
Infant BMI and blood pressure								X
mHealth program compliance and usability						X		

[a]X indicates that the item took place or was measured at this time point.

[b]mHealth: mobile health.

[c]The mHealth coaching intervention occurs continuously over the study period and not just at the specific time points.

Results

The screening questionnaire was pretested in 2020 on 15 pregnant women (5% of the sample). We completed the study recruitment in September 2021. Of the 300 recruited participants, 22.0% (n=66) were lost to follow-up due to miscarriage, change of hospital, refusal by family to continue, or migration to another part of the country. Of these 66 participants, 64% (n=42) belonged to the intervention group. Of the 234 participants who remained in the study, 72.6% (n=170) have completed their four follow-up sessions. The maternal and newborn outcomes have been assessed for 64.1% (n=150) of the participants, and the infant assessment has been

conducted for 2.6% (n=6) of the participants. We plan to complete all follow-ups and outcome assessments by March 2023 and analysis by June 2023. Results are expected to be published by the end of 2023. Trial results will be disseminated through publications and conference proceedings.

Discussion

Maternal undernutrition and inadequate physical activity in Pakistan pose a serious public health threat. Pregnancy is a critical period when these behaviors directly affect fetal growth and development and influence maternal health in terms of pregnancy-related complications. Considering pregnancy as a window of opportunity, identification and rectification of dietary and lifestyle risk factors could not only provide awareness to women but could also lead to self-actualization leading to behavior change. Addressing dietary insufficiencies is significant not only during pregnancy but also for the health of the offspring throughout the life course. Dietary, supplement use, and physical activity counseling through mHealth has the potential to change behavior by providing tailored and personalized advice. This study will provide the opportunity to test the influence of cost-effective and rapidly evolving mHealth technology on maternal and offspring health in the local context. If proven effective, mHealth will open avenues for improving maternal and child health in Pakistan.

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Authors' Contributions

RN contributed to the conceptualization and design of the project and is currently supervising the project execution. KBAV contributed to the design of the project and project execution. NM contributed to the conceptualization and design of the project. SS contributed to the development of the mHealth app. All authors participated in the manuscript preparation and approved the final document for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review comments from the funding source.
[PDF File (Adobe PDF File), 236 KB - resprot_v10i11e31611_app1.pdf]

References

1. Barger MK. Maternal nutrition and perinatal outcomes. J Midwifery Womens Health 2010;55(6):502-511. [doi: 10.1016/j.jmwh.2010.02.017] [Medline: 20974412]
2. Wu G, Bazer FW, Cudd TA, Meininger CJ, Spencer TE. Maternal nutrition and fetal development. J Nutr 2004 Sep;134(9):2169-2172. [doi: 10.1093/jn/134.9.2169] [Medline: 15333699]
3. Khoury J, Henriksen T, Christophersen B, Tonstad S. Effect of a cholesterol-lowering diet on maternal, cord, and neonatal lipids, and pregnancy outcome: A randomized clinical trial. Am J Obstet Gynecol 2005 Oct;193(4):1292-1301. [doi: 10.1016/j.ajog.2005.05.016] [Medline: 16202717]
4. Mikkelsen TB, Osterdal ML, Knudsen VK, Haugen M, Meltzer HM, Bakketeig L, et al. Association between a Mediterranean-type diet and risk of preterm birth among Danish women: A prospective cohort study. Acta Obstet Gynecol Scand 2008;87(3):325-330 [FREE Full text] [doi: 10.1080/00016340801899347] [Medline: 18307073]
5. Timmermans S, Steegers-Theunissen RPM, Vujkovic M, Bakker R, den Breeijen H, Raat H, et al. Major dietary patterns and blood pressure patterns during pregnancy: The Generation R Study. Am J Obstet Gynecol 2011 Oct;205(4):337.e1-337312 [FREE Full text] [doi: 10.1016/j.ajog.2011.05.013] [Medline: 21855845]
6. Schoenaker DAJM, Mishra GD, Callaway LK, Soedamah-Muthu SS. The role of energy, nutrients, foods, and dietary patterns in the development of gestational diabetes mellitus: A systematic review of observational studies. Diabetes Care 2016 Jan;39(1):16-23. [doi: 10.2337/dc15-0540] [Medline: 26696657]
7. Wang Y, Zhao N, Qiu J, He X, Zhou M, Cui H, et al. Folic acid supplementation and dietary folate intake, and risk of preeclampsia. Eur J Clin Nutr 2015 Oct;69(10):1145-1150 [FREE Full text] [doi: 10.1038/ejcn.2014.295] [Medline: 25626412]

8. Ikem E, Halldorsson TI, Birgisdóttir BE, Rasmussen MA, Olsen SF, Maslova E. Dietary patterns and the risk of pregnancy-associated hypertension in the Danish National Birth Cohort: a prospective longitudinal study. BJOG 2019 Apr;126(5):663-673. [doi: 10.1111/1471-0528.15593] [Medline: 30675768]
9. Jaddoe VWV, de Jonge LL, Hofman A, Franco OH, Steegers EAP, Gaillard R. First trimester fetal growth restriction and cardiovascular risk factors in school age children: Population based cohort study. BMJ 2014 Jan 23;348:g14 [FREE Full text] [doi: 10.1136/bmj.g14] [Medline: 24458585]
10. Mook-Kanamori DO, Steegers EAP, Eilers PH, Raat H, Hofman A, Jaddoe VWV. Risk factors and outcomes associated with first-trimester fetal growth restriction. JAMA 2010 Feb 10;303(6):527-534. [doi: 10.1001/jama.2010.78] [Medline: 20145229]
11. van Uitert EM, Exalto N, Burton GJ, Willemsen SP, Koning AHJ, Eilers PHC, et al. Human embryonic growth trajectories and associations with fetal growth and birthweight. Hum Reprod 2013 Jul;28(7):1753-1761. [doi: 10.1093/humrep/det115] [Medline: 23569080]
12. Crispi F, Bijnens B, Figueras F, Bartrons J, Eixarch E, Le Noble F, et al. Fetal growth restriction results in remodeled and less efficient hearts in children. Circulation 2010 Jun 08;121(22):2427-2436. [doi: 10.1161/CIRCULATIONAHA.110.937995] [Medline: 20497977]
13. Gale CR, Jiang B, Robinson SM, Godfrey KM, Law CM, Martyn CN. Maternal diet during pregnancy and carotid intima-media thickness in children. Arterioscler Thromb Vasc Biol 2006 Aug;26(8):1877-1882. [doi: 10.1161/01.ATV.0000228819.13039.b8] [Medline: 16728657]
14. Rahman MM, Abe SK, Rahman MS, Kanda M, Narita S, Bilano V, et al. Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: Systematic review and meta-analysis. Am J Clin Nutr 2016 Feb;103(2):495-504. [doi: 10.3945/ajcn.115.107896] [Medline: 26739036]
15. Greenberg JA, Bell SJ, Guan Y, Yu Y. Folic acid supplementation and pregnancy: More than just neural tube defect prevention. Rev Obstet Gynecol 2011;4(2):52-59. [Medline: 22102928]
16. Hacker AN, Fung EB, King JC. Role of calcium during pregnancy: Maternal and fetal needs. Nutr Rev 2012 Jul;70(7):397-409. [doi: 10.1111/j.1753-4887.2012.00491.x] [Medline: 22747842]
17. Borodulin KM, Evenson KR, Wen F, Herring AH, Benson AM. Physical activity patterns during pregnancy. Med Sci Sports Exerc 2008 Nov;40(11):1901-1908 [FREE Full text] [doi: 10.1249/MSS.0b013e31817f1957] [Medline: 18845974]
18. Nascimento SL, Surita FG, Cecatti JG. Physical exercise during pregnancy: A systematic review. Curr Opin Obstet Gynecol 2012 Dec;24(6):387-394. [doi: 10.1097/GCO.0b013e328359f131] [Medline: 23014142]
19. Committee on Obstetric Practice. Physical activity and exercise during pregnancy and the postpartum period: ACOG Committee Opinion, Number 804. Obstet Gynecol 2020 Apr;135(4):e178-e188 [FREE Full text] [doi: 10.1097/AOG.0000000000003772] [Medline: 32217980]
20. American College of Obstetricians and Gynecologist. Exercise during pregnancy. American College of Obstetricians and Gynecologists. 2019. URL: https://www.acog.org/patient-resources/faqs/pregnancy/exercise-during-pregnancy [accessed 2021-10-16]
21. National Nutrition Survey 2018 - Key Findings Report. Islamabad, Pakistan: UNICEF Pakistan; 2019. URL: https://www.unicef.org/pakistan/media/1951/file/Final%20Key%20Findings%20Report%202019.pdf [accessed 2021-10-16]
22. Magee LA, Sharma S, Nathan HL, Adetoro OO, Bellad MB, Goudar S, CLIP Study Group. The incidence of pregnancy hypertension in India, Pakistan, Mozambique, and Nigeria: A prospective population-level analysis. PLoS Med 2019 Apr;16(4):e1002783 [FREE Full text] [doi: 10.1371/journal.pmed.1002783] [Medline: 30978179]
23. Riaz M, Nawaz A, Masood S, Fawwad A, Basit A, Shera A. Frequency of gestational diabetes mellitus using DIPSI criteria, a study from Pakistan. Clin Epidemiol Glob Health 2019 Jun;7(2):218-221. [doi: 10.1016/j.cegh.2018.06.003]
24. Fatima SS, Rehman R, Alam F, Madhani S, Chaudhry B, Khan TA. Gestational diabetes mellitus and the predisposing factors. J Pak Med Assoc 2017 Feb;67(2):261-265 [FREE Full text] [Medline: 28138182]
25. Maternal and Newborn Health Disparities: Pakistan. New York, NY: UNICEF; 2019. URL: https://data.unicef.org/resources/maternal-newborn-health-disparities-country-profiles/ [accessed 2021-10-16]
26. National Institute of Population Studies - NIPS/Pakistan and ICF. Pakistan Demographic and Health Survey 2017-18. Islamabad, Pakistan, and Rockville, MD: NIPS and ICF; 2019. URL: https://dhsprogram.com/publications/publication-fr354-dhs-final-reports.cfm [accessed 2021-10-15]
27. Bhutta ZA, Das JK, Rizvi A, Gaffey MF, Walker N, Horton S, Lancet Nutrition Interventions Review Group, the Maternal and Child Nutrition Study Group. Evidence-based interventions for improvement of maternal and child nutrition: What can be done and at what cost? Lancet 2013 Aug 03;382(9890):452-477. [doi: 10.1016/S0140-6736(13)60996-4] [Medline: 23746776]
28. Ajzen I. The theory of planned behavior. Organ Behav Hum Decis Process 1991 Dec;50(2):179-211. [doi: 10.1016/0749-5978(91)90020-T]
29. Bassett-Gunter RL, Levy-Milne R, Naylor PJ, Symons Downs D, Benoit C, Warburton DER, et al. Oh baby! Motivation for healthy eating during parenthood transitions: A longitudinal examination with a theory of planned behavior perspective. Int J Behav Nutr Phys Act 2013 Jul 06;10:88 [FREE Full text] [doi: 10.1186/1479-5868-10-88] [Medline: 23829582]

30. van Dijk MR, Oostingh EC, Koster MPH, Willemsen SP, Laven JSE, Steegers-Theunissen RPM. The use of the mHealth program Smarter Pregnancy in preconception care: Rationale, study design and data collection of a randomized controlled trial. BMC Pregnancy Childbirth 2017 Jan 26;17(1):46 [FREE Full text] [doi: 10.1186/s12884-017-1228-5] [Medline: 28125970]
31. The World in 2013: ICT Facts and Figures. Geneva Switzerland: International Telecommunication Union; 2013. URL: https://www.itu.int/en/ITU-D/statistics/Documents/facts/ICTFactsFigures2013-e.pdf [accessed 2021-10-16]
32. Kemp S. Digital 2020: Pakistan. DataReportal. 2020 Feb 18. URL: https://datareportal.com/reports/digital-2020-pakistan [accessed 2021-10-16]
33. Digital Pakistan Policy. Islamabad, Pakistan: Ministry of IT & Telecom; 2019. URL: https://phkh.nhsrc.pk/sites/default/files/2019-06/Digital%20Pakistan%20Policy%20MoIT.pdf [accessed 2021-10-27]
34. Free C, Phillips G, Watson L, Galli L, Felix L, Edwards P, et al. The effectiveness of mobile-health technologies to improve health care service delivery processes: A systematic review and meta-analysis. PLoS Med 2013;10(1):e1001363 [FREE Full text] [doi: 10.1371/journal.pmed.1001363] [Medline: 23458994]
35. Bennett GG, Glasgow RE. The delivery of public health interventions via the internet: Actualizing their potential. Annu Rev Public Health 2009;30:273-292. [doi: 10.1146/annurev.publhealth.031308.100235] [Medline: 19296777]
36. Van Dijk MR, Huijgen NA, Willemsen SP, Laven JS, Steegers EA, Steegers-Theunissen RP. Impact of an mHealth platform for pregnancy on nutrition and lifestyle of the reproductive population: A survey. JMIR Mhealth Uhealth 2016 May 27;4(2):e53 [FREE Full text] [doi: 10.2196/mhealth.5197] [Medline: 27234926]
37. Free C, Phillips G, Galli L, Watson L, Felix L, Edwards P, et al. The effectiveness of mobile-health technology-based health behaviour change or disease management interventions for health care consumers: A systematic review. PLoS Med 2013;10(1):e1001362 [FREE Full text] [doi: 10.1371/journal.pmed.1001362] [Medline: 23349621]
38. Sajjad U, Shahid S. Baby+: A mobile application to support pregnant women in Pakistan. In: Proceedings of the 18th International Conference on Human-Computer Interaction with Mobile Devices and Services Adjunct. 2016 Presented at: 18th International Conference on Human-Computer Interaction with Mobile Devices and Services Adjunct; September 6-9, 2016; Florence, Italy p. 667-674. [doi: https://doi.org/10.1145/2957265.2961856]
39. Khalil MAT, Jan S, Ali W, Khan A. MotherCare app for expectant mothers in interior parts of Pakistan. In: Umair S, Shah MY, editors. Mobile Devices and Smart Gadgets in Human Rights. Hershey, PA: IGI Global; 2019:132-152.
40. Ittefaq M, Iqbal A. Digitization of the health sector in Pakistan: Challenges and opportunities to online health communication: A case study of MARHAM social and mobile media. Digit Health 2018;4:1-13 [FREE Full text] [doi: 10.1177/2055207618789281] [Medline: 30057774]
41. Zaidi S, Shaikh SA, Sayani S, Kazi AM, Khoja A, Hussain SS, et al. Operability, acceptability, and usefulness of a mobile app to track routine immunization performance in rural Pakistan: Interview study among vaccinators and key informants. JMIR Mhealth Uhealth 2020 Feb 13;8(2):e16081 [FREE Full text] [doi: 10.2196/16081] [Medline: 32053115]
42. Main Campus, Karachi. The Aga Khan University Hospital. URL: https://hospitals.aku.edu/pakistan/karachi/pages/default.aspx [accessed 2021-10-15]
43. Conner M. Theory of planned behavior. In: Tenenbaum G, Eklund RC, editors. Handbook of Sport Psychology. 4th edition. Hoboken, NJ: John Wiley & Sons, Inc; 2020:1-18.
44. Bandura A. Self-efficacy. In: The Corsini Encyclopedia of Psychology. Hoboken, NJ: John Wiley & Sons, Inc; 2010:1-3.
45. Fogg BJ. A behavior model for persuasive design. In: Proceedings of the 4th International Conference on Persuasive Technology. 2009 Presented at: 4th International Conference on Persuasive Technology; April 26-29, 2009; Claremont, CA p. 1-7. [doi: 10.1145/1541948.1541999]
46. Velicer W, Prochaska J, Fava J, Norman G, Redding C. Smoking cessation and stress management: Applications of the transtheoretical model of behavior change. Homeost Health Dis 1998;38(5-6):216-233 [FREE Full text]
47. Healthy Eating During Pregnancy and Breastfeeding: Booklet for Mothers. Geneva, Switzerland: World Health Organization; 2001. URL: https://apps.who.int/iris/bitstream/handle/10665/108425/E73182.pdf?sequence=1&isAllowed=y [accessed 2021-10-15]
48. Daily iron and folic acid supplementation during pregnancy. World Health Organization. 2018. URL: https://www.who.int/elena/titles/guidance_summaries/daily_iron_pregnancy/en/ [accessed 2021-10-16]
49. WHO Recommendations on Antenatal Care for a Positive Pregnancy Experience. Geneva, Switzerland: World Health Organization; 2016 Nov 28. URL: https://www.who.int/publications/i/item/9789241549912 [accessed 2021-10-27]
50. WHO Antenatal Care Recommendations for a Positive Pregnancy Experience: Nutritional Interventions Update: Vitamin D Supplements During Pregnancy. Geneva, Switzerland: World Health Organization; 2020 Jul 29. URL: https://www.who.int/publications/i/item/9789240008120 [accessed 2021-10-27]
51. Healthy Diet. Cairo, Egypt: WHO Regional Office for the Eastern Mediterranean; 2019. URL: https://apps.who.int/iris/bitstream/handle/10665/325828/EMROPUB_2019_en_23536.pdf?sequence=1&isAllowed=y [accessed 2021-10-16]
52. FAQs: Nutrition during pregnancy. American College of Obstetricians and Gynecologists. 2020. URL: https://www.acog.org/womens-health/faqs/nutrition-during-pregnancy [accessed 2021-10-16]

53. Paracha PI, Anis N. Pakistan Dietary Guidelines for Better Nutrition. Rome, Italy, and Islamabad, Pakistan: Food and Agriculture Organization of the United Nations and Ministry of Planning Development and Reform, Government of Pakistan; 2018. URL: https://www.fao.org/documents/card/en/c/CA1868EN/ [accessed 2021-10-27]
54. Physical activity. World Health Organization. 2020 Nov 26. URL: https://www.who.int/news-room/fact-sheets/detail/physical-activity [accessed 2021-10-16]
55. Dietary Assessment: A Resource Guide to Method Selection and Application in Low Resource Settings. Rome, Italy: Food and Agriculture Organization of the United Nations; 2018. URL: https://www.fao.org/3/i9940en/I9940EN.pdf [accessed 2021-10-27]
56. Smarter Pregnancy: For couples who are or wish to get pregnant. Slimmer Zwanger. Rotterdam, the Netherlands: Erasmus MC; 2019. URL: https://www.slimmerzwanger.nl/ [accessed 2021-10-16]
57. Hoodbhoy Z, Qureshi RN, Iqbal R, Muhabat Q. Household chores as the main source of physical activity: Perspectives of pregnant Pakistani women. J Pak Med Assoc 2018 Apr;68(4):565-569 [FREE Full text] [Medline: 29808046]
58. van Dijk MR, Koster MPH, Oostingh EC, Willemsen SP, Steegers EAP, Steegers-Theunissen RPM. A mobile app lifestyle intervention to improve healthy nutrition in women before and during early pregnancy: Single-center randomized controlled trial. J Med Internet Res 2020 May 15;22(5):e15773 [FREE Full text] [doi: 10.2196/15773] [Medline: 32412417]
59. Examples of moderate and vigorous physical activity. Harvard TH Chan School of Public Health. 2021. URL: https://www.hsph.harvard.edu/obesity-prevention-source/moderate-and-vigorous-physical-activity/ [accessed 2021-10-27]
60. Prosch N. Light, moderate, and vigorous activity. South Dakota State University Extension. 2019 Dec 18. URL: https://extension.sdstate.edu/light-moderate-and-vigorous-activity [accessed 2021-10-27]
61. General physical activities defined by level of intensity. Centers for Disease Control and Prevention. URL: https://www.cdc.gov/nccdphp/dnpa/physical/pdf/pa_intensity_table_2_1.pdf [accessed 2021-10-27]
62. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. Hypertension 2018 Jul;72(1):24-43. [doi: 10.1161/HYPERTENSIONAHA.117.10803] [Medline: 29899139]
63. Hod M, Kapur A, Sacks DA, Hadar E, Agarwal M, Di Renzo GC, et al. The International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: A pragmatic guide for diagnosis, management, and care. Int J Gynaecol Obstet 2015 Oct 08;131:S173-S211. [doi: 10.1016/s0020-7292(15)30033-3]
64. Cheikh Ismail L, Bishop DC, Pang R, Ohuma EO, Kac G, Abrams B, et al. Gestational weight gain standards based on women enrolled in the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project: A prospective longitudinal cohort study. BMJ 2016 Feb 29;352:i555 [FREE Full text] [doi: 10.1136/bmj.i555] [Medline: 26926301]
65. Ohadike C, Cheikh-Ismail L, Ohuma E, Giuliani F, Bishop D, Kac G, et al. Systematic review of the methodological quality of studies aimed at creating gestational weight gain charts. Adv Nutr 2016 Mar;7(2):313-322 [FREE Full text] [doi: 10.3945/an.115.010413] [Medline: 26980814]
66. Cutland CL, Lackritz EM, Mallett-Moore T, Bardají A, Chandrasekaran R, Lahariya C, Brighton Collaboration Low Birth Weight Working Group. Low birth weight: Case definition & guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine 2017 Dec 04;35(48 Pt A):6492-6500 [FREE Full text] [doi: 10.1016/j.vaccine.2017.01.049] [Medline: 29150054]
67. Villar J, Cheikh Ismail L, Victora CG, Ohuma EO, Bertino E, Altman DG, International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). International standards for newborn weight, length, and head circumference by gestational age and sex: The Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet 2014 Sep 06;384(9946):857-868. [doi: 10.1016/S0140-6736(14)60932-6] [Medline: 25209487]
68. Preterm birth. World Health Organization. 2018 Feb 19. URL: https://www.who.int/news-room/fact-sheets/detail/preterm-birth [accessed 2021-10-16]
69. Bansal NA, Ayoola OO, Gemmell I, Vyas A, Koudsi A, Oldroyd J, et al. Effects of early growth on blood pressure of infants of British European and South Asian origin at one year of age: The Manchester children's growth and vascular health study. J Hypertens 2008 Mar;26(3):412-418. [doi: 10.1097/HJH.0b013e3282f3168e] [Medline: 18300849]
70. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. Pediatrics 2011 Dec;128 Suppl 5:S213-S256 [FREE Full text] [doi: 10.1542/peds.2009-2107C] [Medline: 22084329]
71. McCoy E. Understanding the intention-to-treat principle in randomized controlled trials. West J Emerg Med 2017 Oct;18(6):1075-1078 [FREE Full text] [doi: 10.5811/westjem.2017.8.35985] [Medline: 29085540]

Abbreviations

ACOG: American College of Obstetricians and Gynecologists
AKUH: Aga Khan University Hospital
DHRC: Digital Health Resource Center

INTERGROWTH-21st: International Fetal and Newborn Growth Consortium for the 21st Century
mHealth: mobile health
PI: principal investigator
URC: University Research Council
WHO: World Health Organization

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Protocol

Empowering Dementia Carers With an iSupport Virtual Assistant (e-DiVA) in Asia-Pacific Regional Countries: Protocol for a Pilot Multisite Randomized Controlled Trial

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Abstract

Background: Dementia is a global public health priority with an estimated prevalence of 150 million by 2050, nearly two-thirds of whom will live in the Asia-Pacific region. Dementia creates significant care needs for people with the disease, their families, and carers. iSupport is a self-help platform developed by the World Health Organization (WHO) to provide education, skills training, and support to dementia carers. It has been adapted in some contexts (Australia, India, the Netherlands, and Portugal). Carers using the existing adapted versions have identified the need to have a more user-friendly version that enables them to identify solutions for immediate problems quickly in real time. The iSupport virtual assistant (iSupport VA) is being developed to address this gap and will be evaluated in a randomized controlled trial (RCT).

Objective: This paper reports the protocol of a pilot RCT evaluating the iSupport VA.

Methods: Seven versions of iSupport VA will be evaluated in Australia, Indonesia, New Zealand, and Vietnam in a pilot RCT. Feasibility, acceptability, intention to use, and preliminary impact on carer-perceived stress of the iSupport VA intervention will be assessed.

Results: This study was funded by the e-ASIA Joint Research Program in November 2020. From January to July 2023, we will enroll 140 dementia carers (20 carers per iSupport VA version) for the pilot RCT. The study has been approved by the Human Research Committee, University of South Australia, Australia (203455).

Conclusions: This protocol outlines how a technologically enhanced version of the WHO iSupport program—the iSupport VA—will be evaluated. The findings from this intervention study will provide evidence on the feasibility and acceptability of the iSupport VA intervention, which will be the basis for conducting a full RCT to assess the effectiveness of the iSupport VA. The study will be an important reference for countries planning to adapt and enhance the WHO iSupport program using digital health solutions.

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KEYWORDS

Dementia; informal carer; iSupport; virtual assistant; digital health

Introduction

Dementia is a global public health priority, and its global prevalence is growing exponentially [1], tripling from 46.8 million in 2015 to approximately 150 million by 2050 [2]. The fastest growth is occurring in the Asia-Pacific region, where 70 million people are estimated to be living with dementia by 2050 [3]. Dementia is among the leading causes of disability and dependency in older people, creating significant care needs for people with dementia, their families, and carers, affecting social, health, well-being, and economic dimensions [1,2]. In 2018, dementia was estimated to cost US $1 trillion worldwide, and the cost is predicted to rise to US $2 trillion by 2030 [2]. The catastrophic costs of long-term care drive many families of people with dementia into poverty, strain health and social systems, and is a significant impost on government budgets [1].

Approximately 60% of people with dementia live in low- and middle-income countries (LMICs) and the costs of care are mostly borne by family members [2]. Health and social care systems in LMICs are often not well-developed or well-funded, resulting in unmet care needs for people with dementia and their carers [3,4]. In high-income countries (HICs), most people with dementia also live at home and receive care from their families [3,5]. Health and social care systems in HICs are often fragmented and unable to meet all the needs of people with dementia, especially people from culturally and linguistically diverse (CALD) groups [6]. For example, care arrangements and family carer input are disproportionately high for CALD people with dementia in Australia [7] and Māori families in New Zealand [6], which result in them experiencing more psychological and economic burdens associated with care.

Provision of unpaid care often exposes family carers to pronounced stress, resulting in mental and physical health deterioration, and loss of productivity and income [1,3]. Women, who provide the bulk of family care, are disproportionately affected [8]. In LMICs where aged care facilities and other formal support services are underdeveloped, such impacts can be devastating [9]. Supporting family carers through low-cost and sustainable nonpharmacological approaches is much needed to avoid potentially dangerous alternatives with limited efficacy, such as prescribing psychotropic medications, hospitalization, and institutionalization**.** Providing practical support for carers of people with dementia is viewed as an essential part of national dementia plans to maintain the health and well-being of people with dementia, reduce costs related to dementia, and relieve burden on the health and social care systems [10].

Emerging web-based training and support programs have shown positive effects on improving dementia carers' mental health outcomes with considerable potential for scaling up [11]. To provide practical support for carers, the World Health Organization (WHO) developed "iSupport for Dementia," a self-learning evidence-based web-based skills training and support program for informal dementia carers, which can be adapted for use in different countries [12]. iSupport offers education, skills training, and support for carers, using problem-solving and cognitive behavioral therapy techniques. The web-based program contains 23 lessons within five modules: (1) what is dementia; (2) being a carer; (3) self-care; (4) providing care; and (5) dealing with behavior changes. Each lesson comprises interactive exercises, and carers receive immediate feedback to their answers, as well as certification when lessons are completed.

The discontinuation of services that has resulted from COVID-19 and its impact on carers of people with dementia (eg, increased social isolation and caregiving burden) emphasizes the need for concise, easy-to-read tips for dementia family carers. This need led the WHO to develop iSupport Lite [13]. Carer feedback from an Australian iSupport adaptation study also demonstrated the need for iSupport enhancement with a more user-friendly version, mechanisms for real-time support, and provision of peer support [14]. They also identified the need to adapt iSupport for CALD communities given their different care needs [14]. iSupport has not been adapted for use in most countries in the Asia-Pacific Region (APR). The exception includes India, where study findings underscored the need to pay close attention to cultural adaptations of the program

to improve its acceptability and accessibility [15]. However, cultural adaptation of the iSupport program requires resources, which may not be achievable in many LMICs in the APR. International collaboration is much needed to address the resource issues.

A dearth of scientific evidence on effective cultural adaptation is significant impediments for the uptake of iSupport in many APR countries grappling with the public health challenges of dementia. The e-ASIA funded e-DiVA project addresses these gaps by (1) developing and evaluating an iSupport virtual assistant (VA) to support dementia carers through a partnership among four APR countries: Australia, Indonesia, New Zealand, and Vietnam; and (2) building capacity of researchers and nongovernment organization (NGO) partners to support this development and evaluation. This paper reports the protocol of a pilot randomized control trial (RCT) evaluating the iSupport VA.

Methods

Methodological Approaches

This study will operationalize the UK Medical Research Council guidelines for developing and evaluating complex interventions and will focus on the first two stages of this guide: (1) development and (2) feasibility and piloting [16]. A co-design approach will be applied to involve carers in the design process, focusing on the challenges and issues from their perspective and designing solutions to enhance desirability, acceptability, and usability of the intervention [17]. This work will culminate in the development of the iSupport VA comprising a website and a smart device app that will allow carers to search topics of their choice using text or voice commands and provide video instruction to support them in their caring role. Feasibility, acceptability, intention to use, and preliminary impact on carer perceived stress of the iSupport VA will be conducted via a pilot RCT using established approaches [18,19].

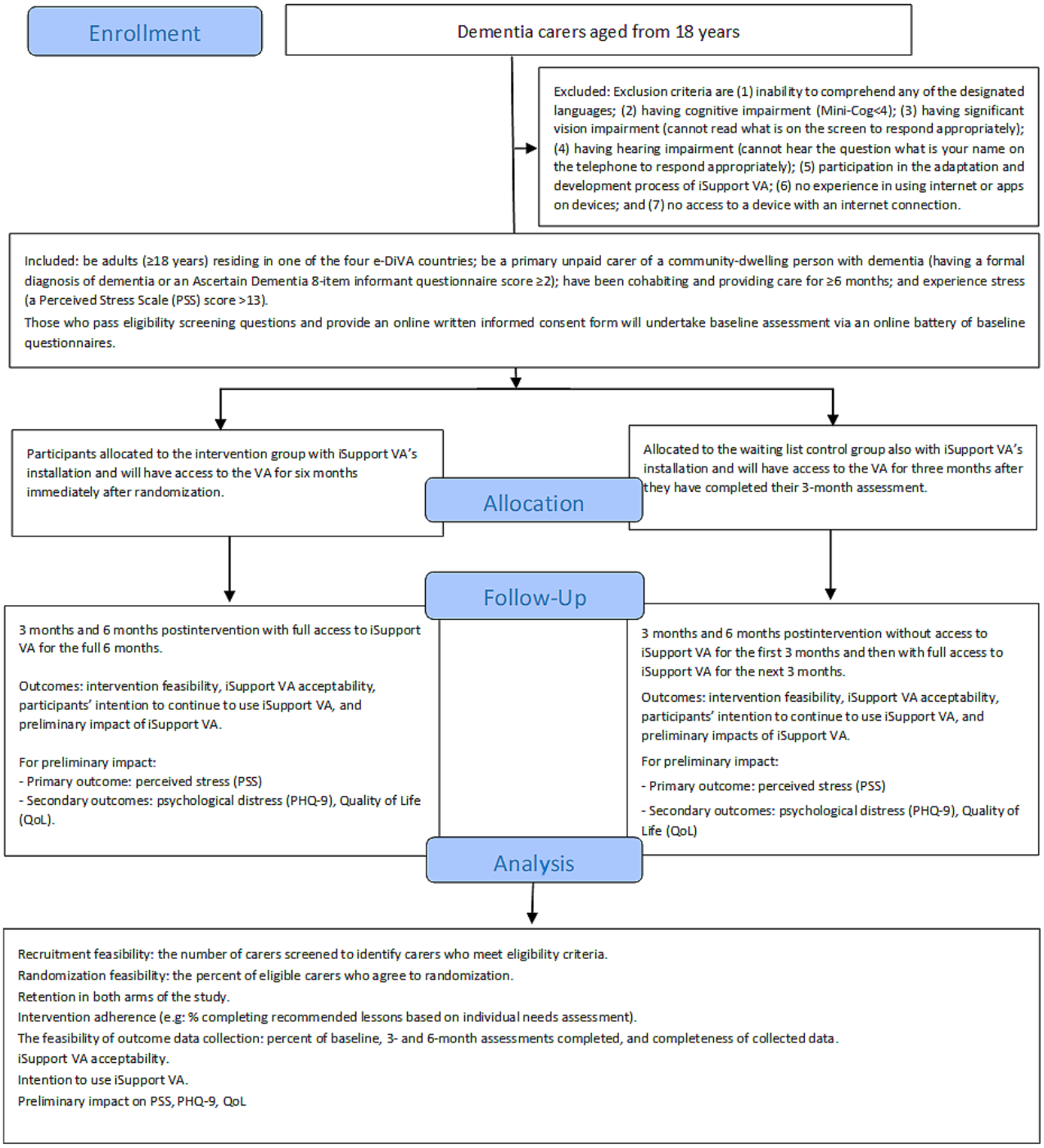
Theoretical Approach

Guided by the Stress/Health model [20], this study proposes to address the identified gaps through a 3-year research program, which uses established theoretical and methodological approaches to culturally and contextually adapt WHO iSupport for use in the aforementioned 4 countries [21]. The Stress/Health model provides a theoretical framework for understanding multidimensional stressors (primary stressors: care recipients' changed behavior and disability; secondary stressors: family conflict and work difficulty) and adaptive capacities (coping and social support) that collectively affect carer mental health or well-being [22]. iSupport is a multi-component intervention that builds carer skills for managing different stressors and improving adaptive capacities to improve carer mental health and well-being.

Study Design

A pilot, waitlist RCT will be used with 140 carers (20 carers for each of the 7 versions of iSupport VA (English, Bahasa, and Vietnamese in Australia; Vietnamese in Vietnam; Bahasa in Indonesia; and English and Maori in New Zealand). Carers will be randomized into (1) an intervention group (10 carers per version of iSupport VA) that will use the iSupport VA for 6 months immediately following randomization, or (2) a waiting list control group (10 carers/version) that will receive access to the iSupport VA 3 months after randomization (Figure 1). While pilot studies are not powered to examine effectiveness, this pilot RCT will provide data about acceptability, useability, and preliminary impact of the intervention, as well as the feasibility of the methods and procedures [18] for a fully powered RCT to test effectiveness.

Figure 1. Flow diagram of the pilot randomized controlled trial. PHQ-9: Patient Health Questionnaire, 9-item; VA: virtual assistant.



Inclusion Criteria

Participants eligible for the pilot RCT study will (1) be adults (≥18 years) residing in one of the aforementioned 4 countries (2) be a primary unpaid carer of a community-dwelling person with dementia (having a formal diagnosis of dementia as reported by the carer or an Ascertain Dementia 8-item Informant Questionnaires (AD-8) score of ≥2) [23], (3) have been cohabiting and providing care for ≥6 months, and (4) experience stress (a Perceived Stress Scale [PSS] score >13) [24].

Exclusion Criteria

Exclusion criteria are (1) inability to comprehend any of the designated languages, (2) having cognitive impairment (Mini-Cog < 4) [25], (3) having significant vision impairment (cannot read what is on the screen to respond appropriately), (4) having hearing impairment (cannot hear the question "What is your name?" on the telephone to respond appropriately), (5) participation in the adaptation and development process of iSupport VA, (6) having no experience in using the internet or apps on devices, and (7) having no access to a device with an internet connection.

Recruitment Procedure

Multiple recruitment strategies will be used. Our local NGO partners (eg, Dementia Australia [DA], Alzheimer's Indonesia [ALZI], and Alzheimers New Zealand) and local clinics and hospitals will announce the study on their website, social media pages, and newsletter. In Australia, study announcements will also be placed in memory and geriatric clinics managed by the Southern Adelaide Local Health Network, and Resthaven South Australia, the Step-Up for Dementia Research group in New South Wales and Western Australia, and the National Ageing Research Institute (NARI)'s CALD Research Engagement Network, the latter hosts a database of >1000 CALD community groups across Australia. We will leave brochures and posters in hospitals, clinics, senior centers that collaborate with ALZI in Indonesia, dementia services at local District Health Boards in New Zealand, and memory clinics and dementia units in hospitals in Vietnam. Treating clinicians of people with dementia will advise carers about the study during their consultations. All study announcements will refer to our e-DiVA project website, where carers interested in the study can register to participate. Potential participants will be contacted by telephone and email or text message via mobile phones and will receive study information and eligibility screening questions, and will be directed to the web-based written informed consent form. Carers who fulfil eligibility criteria and provide consent will receive a weblink to the internet-based battery of baseline questionnaires and will then be included in the study.

Randomization Procedure

After enrollment, carers will be randomized separately for each iSupport VA version to either intervention or waiting list control groups (1:1 ratio). A permuted block randomization of size 4 will be used to ensure an even balance of carers in each group throughout the study period. A central clinical trials service in Australia will undertake randomization for each iSupport version in the aforementioned 4 countries.

Interventions

Seven versions of the iSupport VA, comprising a web-based app, will be built from the content of the adapted iSupport. The VA will be designed to make the iSupport program easier and simpler to use on all device types including smart phones, tablets, and laptop and desktop computers. The VA will first ask individual carers in their respective languages to undergo an assessment of their key education and support needs. Using the finding of this initial need assessment, the algorithm of the VA will provide tailored interventions (ie, recommending specific modules or lessons in the iSupport program) to match each individual's need profiles. The VA will provide text or voice command search options (similar to Google Assistant). The search outcomes will be in text, picture, or video formats with detailed instructions. Users can choose specific modules or any part of the program simply by selecting a specific topic.

Weblinks for existing health and well-being, aged, and social care services for dementia and other important information (eg, first-aid tips, emergency contact numbers, etc) in each country will be incorporated in VA versions. With carers' consent, the VA will support web-based peer support groups. These peer support groups will enable sharing of experiences, practical tips, and peer support either in real time video or through text chats among logged in members, or through an asynchronous messaging system. The app will have the capability for a "Personal Diary" for users to write their action plans or scheduled medical appointments and will remind users to follow the scheduled plans and appointments.

Carers randomized to the intervention group will receive a weblink to the iSupport VA app together with the intervention login details, and they will have access to the intervention for 6 months immediately after randomization. Those in the waiting list control group will also receive the iSupport VA. However, they will be informed that they will receive login details for iSupport VA after completing the 3-month assessment. After completing their 3-month assessment, all waiting list control carers will have full access to iSupport VA for 3 months, which will increase the number of dementia carers to access the iSupport VA in this pilot RCT. Intervention dose will be defined as the percentage of lessons completed of the total lessons recommended by the iSupport VA at 3 months in the intervention group, based on the initial need assessment. Monthly phone contact with carers will be also conducted to assess their use of the intervention. Notes from these contacts will be recorded. A local research team member fluent in the country's appropriate language will be available and contactable by telephone or email if carers need technical assistance.

Outcomes

The intervention feasibility will be evaluated with reference to recruitment, randomization, retention, treatment adherence, and assessment processes [18]. At the end of the RCT, carers in the intervention group (10 per iSupport VA version) will undergo a 30-60–minute semi-structured exit interview to assess iSupport VA acceptability, including most and least relevant and helpful aspects, the main barriers and facilitators of using the VA, and recommended improvements. All 140 carers will be asked to complete a questionnaire to assess their intention to use the iSupport VA. The questionnaire will include one question: "How will you (dementia carer) use the iSupport VA in the coming six months?" Guided by the Unified Theory of Acceptance and Use of Technology (UTAUT) [19], the questionnaire will assess the direct determinants of intention. These are performance expectancy (the degree to which using the iSupport VA will provide benefits in performing caring role), effort expectancy (the degree of ease associated with the use of the VA), and social influence (the degree to which a carer perceives that others vital to them believe that they should use the VA).

Outcomes will be assessed within the iSupport web-based tool using encryption for data protection at baseline (t_0), post-intervention (3 months after baseline; t_1), and follow-up (6 months after baseline; t_2). For measuring the preliminary impact, the primary outcome will be change in perceived stress [24] at t_1. The secondary outcomes will include change in psychological distress [26] and global Visual Analogue Scale quality of life [27] at t_1. To account for a potential contamination of the control group owing to the availability of the generic version of WHO iSupport web-based program, at their 3-month assessment, carers in the control group will be asked if they

have accessed the WHO iSupport manual or generic web-based program. Where local-language versions are unavailable, study instruments will be translated and back-translated, followed by reconciliation and review by bilingual experts to develop local language versions. The baseline measures will include language version, characteristics of carers (age; sex; ethnicity; educational, occupational and economic attainments; cohabitation status; and relationship with the care recipient), and care recipients (age, sex, dementia duration, type, and severity [28], and behavioral and psychological symptoms [29]). Further analysis will include a comparison of change in outcomes in the 2 groups between t_0 and t_3. This will compare long-term use (6 months) of the tool versus short-term (3 months).

Analyses and Evaluation

Recruitment feasibility will be assessed on the basis of the number of carers screened to identify carers who meet eligibility criteria. Randomization feasibility will be assessed on the basis of the percentage of eligible carers who agree to randomization. Subject retention in both arms of the study will be evaluated. We will also track intervention adherence (eg, the rate of completing lessons recommended by the VA based on the initial carer need assessment). We will assess the feasibility of assessing study outcomes in terms of the percentage of the baseline, 3-, and 6-month assessments completed and the completeness of the collected data. The criteria for determining feasibility success will be as follows: (1) average of 3 carers per iSupport version per month (approximately 140 carers for 7 iSupport VA versions in the aforementioned 4 countries over 7 months) can be recruited; (2) at least 70% of all eligible carers can be recruited; (3) complete baseline and follow-up assessments by at least 70% of all recruited carers. iSupport VA acceptability will be analyzed thematically. The association between the UTAUT construct [19] and the intention to use iSupport VA will be assessed using logistic regression analyses. For preliminary impact assessment, linear mixed-effects modeling will be used to analyze changes in primary and secondary outcomes from baseline to 3 and 6 months. For dichotomous or noncontiguous outcome measures, appropriate generalized linear mixed-effects models will be applied. All analyses will be adjusted for the language version. One chief investigator of the project is a biostatistician, who will support the research and RCT from designing, collecting, analyzing, and presenting the data. A detailed statistical analysis plan will be developed before unbinding the data and any analyses.

Data Management and Monitoring

The data collection and management procedures have been approved by the human research ethics committee (The University of South Australia, approval number: 203455). All personal information on people with dementia and their carers will be retained in the pseudonymized data set using a unique participant ID, separate from the main data set, and will not be shared; these data will be accessible to only the project leader. All RCT data will be stored securely to protect confidentiality before, during, and after the trial. Data entry, coding, and analysis of the de-identified data will be conducted by trained and experienced researchers.

Any unexpected outcomes or serious adverse events will be discussed by the project executive committee. RCT progress will be updated in monthly meetings by the study's executive committee and country leaders. The committee will monitor the recruitment, intervention, and any concerns related to the study.

Ethics, Dissemination, and Protocol Amendment

Ethics

The study has been approved by the Human Research Ethics Committee (HREC) of the University of South Australia. Each study site also seeks their own local IRB approval. Informed consent material is available in local languages of Vietnamese, Bahasa, and Maori with the approved protocol.

Dissemination and Protocol Amendment

The primary RCT results will be submitted for publication to international, peer-reviewed journals, regardless of whether the results are positive, negative, or inconclusive with regard to the research aims and questions. Authorship eligibility will be based on the reviews and contributions among researchers. An annual project report will be submitted to the HREC. Any critical protocol amendments will be reported to the HREC in the annual report, updated in the Australian New Zealand Clinical Trials registry, and communicated in the preliminary RCT result reports.

Results

This study was funded by the e-ASIA Joint Research Program in November 2020, with funding from the National Health and Medical Research Council (Australia), the Ministry of Research and Technology/National Research and Innovation Agency (Indonesia), Health Research Council (New Zealand), and the Ministry of Science and Technology (Vietnam). The study brings together complementary expertise across multiple disciplines of 39 senior, early/midcareer and predoctoral researchers in the aforementioned 4 e-DiVA countries and NGO partners including DA, ALZI, Alzheimers New Zealand, Alzheimer's Disease International, and the WHO.

The WHO iSupport manual in English has been translated to Bahasa and Vietnamese, and the adaptation of these translated versions is being conducted prior to the production of video clips as content for the iSupport VA. From November 2021 to June 2022, the iSupport VA will be developed. The iSupport VA will enhance WHO iSupport web-based program by providing real-time supports for carers with additional interaction options of voice command and video instruction to make it more user-friendly, quicker, and easier to learn. The VA will then be tested by carers and health care professionals in 6 months from July 2022 to December 2022, and their feedback will be considered in an iterative process of refining the VA. From January to July 2023, we will enroll 140 dementia carers (20 carers per iSupport VA version) for the pilot RCT and follow them up for 6 months. This study is expected to conclude in June 2024.

Discussion

Expected Outcomes

Family carers of people with dementia face many challenges. Approximately 40% of family carers of people with dementia have clinically significant depression or anxiety [30]. When compared to the general population and carers of people with other chronic diseases, dementia carers have worse mental and physical health, more absences from work, and lower quality of life [31,32]. Carer burden, psychological distress, and perceived inability to provide care predict care recipient's institutionalization [33]. Educating, upskilling, and supporting carers to reduce the burden of care and improve their mental health and well-being through low-cost and sustainable nonpharmacological intervention has become one of the 7 priority areas of action in the WHO Global Action Plan on dementia [10].

Dementia carers who are supported in their caring role benefit from support, as does the person with dementia [34]. Most effective carer interventions are multimodal, incorporating education, skill-building to manage atypical behaviors, stress reduction, and referral to community resources [35]. One of the most comprehensive multi-component carer intervention is the REACH (Resources for Enhancing Alzheimer's Caregiver Health) model [20]. The REACH model was used in Vietnam with preliminary findings showing significant improvement for carer mental health and caregiving burden [22,36]. However, this model is resource-intensive with interventionists going to carers' home to deliver the intervention over 3 months. Additionally, while face-to-face interventions have demonstrated positive effects on carer mental health, many carers cannot attend support programs owing to lack of transport, finances, or being unable to leave the person for whom they provide care [37].

Carer interventions delivered on the internet via an app could be an effective solution to overcome these accessibility barriers and are a viable option in crises such as the COVID-19 pandemic when social restrictive policies are in place. Internet-based approaches may be perceived more acceptable because carers can access them at their own convenience and expense [11]. Via digital health solutions via smartphones, tablets, and computers, carers can learn in their own language and cultural context about dementia care [38]. Smartphone use is exponentially increasing in the APR; by 2025, 83% of the population (2.7 billion people) will be mobile internet users, thus making smartphone digital media a crucial platform to increase community education and understanding [39].

Over 2 million people have dementia in the aforementioned 4 countries in this study—a number that will triple by 2050. The vast majority live at home, are cared for by family members, and are mainly women. Recognizing the effects of long-term dementia care on carers' time, energy, income, health, and well-being, the e-DiVA study will test a digital solution to support dementia carers. Using co-design ensures iSupport VA's user friendliness and trustworthiness, the study's diverse settings ensure the cultural adaptability of iSupport VA across high-, middle-, and low-income settings. The COVID-19 pandemic has underscored the importance of and need for digital innovation for people with dementia and their carers. This study offers a solution to ensure quality care for people with dementia, no matter their location, income, or crises facing them.

To our knowledge, this is the first study using information technology solutions not only to adapt the WHO iSupport web-based program but also to enhance it by providing real-time support to carers with additional interaction options of voice command and video instruction to make it more user-friendly, quicker, and easier to learn. This is an important innovation, which will assist those with limited digital and general literacy to access information, although it will not be relevant for those carers who do not have access to the internet.

The e-DiVA study builds on our team's prior work and expertise, strengthens and expands existing collaborations between investigators in high-income countries (Australia and the United States) and Vietnam. These include our pilot iSupport adaptation study in Australia [14] and other studies to develop Vietnam's National Dementia Plan [40] and to support Vietnamese dementia family carers [41]. This project proposal keeps laying the continual foundation for extramural support for both research and capacity-building. The proposal directly responds to the priorities of our collaborating countries [40,42-44] and will create a multinational partnership between the NGO partners (ie, national Alzheimer/dementia associations, Alzheimer's Disease International, and the WHO) and researchers to optimize support for dementia carers. Our commitment to ongoing co-design and stakeholder engagement in every step of our research, along with our commitment to building capacity in our stakeholders and locally based researchers will support the successful translation and ownership of iSupport VA by the local Alzheimer and dementia associations. By the end of the project, we aim to have research-ready, stakeholder engaged, local champions to enable the final translation of iSupport VA nationally, as well as its ongoing development and increasing chances of having a longer-term impact, beyond the life of the project.

Trial Status

The trial is ongoing. Participants are not yet being enrolled. The protocol date and version are July 10, 2021, and 1.0, respectively. The trial has been registered on Australian New Zealand Clinical Trials Registry (identifier ACTRN12621001452886).

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Conflicts of Interest

HB has been an Advisory Board member or consultant for Nutricia Australia, Biogen, and Roche.

Multimedia Appendix 1
Peer-reviewer report from the Health Research Council of New Zealand.
[PDF File (Adobe PDF File), 408 KB - resprot_v10i11e33572_app1.pdf]

References

1. Dementia: a public health priority. World Health Organization. 2012. URL: https://apps.who.int/iris/handle/10665/75263 [accessed 2021-10-07]
2. World Alzheimer Report 2015. The Global Impact of Dementia: An Analysis of Prevalence, Incidence, Cost and Trends. Alzheimer's Disease International. 2015. URL: https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf [accessed 2021-10-07]
3. World Alzheimer Report 2016. Improving healthcare for people living with dementia: Coverage, Quality and Costs Now and in the Future. Alzheimer's Disease International. 2016. URL: https://www.alzint.org/u/WorldAlzheimerReport2016.pdf [accessed 2021-10-07]
4. Nguyen TA, Pham T, Vu HTT, Nguyen TX, Vu TT, Nguyen BTT, et al. Use of Potentially Inappropriate Medications in People With Dementia in Vietnam and Its Associated Factors. Am J Alzheimers Dis Other Demen 2018 Nov;33(7):423-432 [FREE Full text] [doi: 10.1177/1533317518768999] [Medline: 29642720]
5. Wimo A, Guerchet M, Ali G, Wu Y, Prina AM, Winblad B, et al. The worldwide costs of dementia 2015 and comparisons with 2010. Alzheimers Dement 2017 Jan;13(1):1-7 [FREE Full text] [doi: 10.1016/j.jalz.2016.07.150] [Medline: 27583652]
6. Dudley M, Menzies O, Elder H, Nathan L, Garrett N, Wilson D. Mate wareware: Understanding 'dementia' from a Māori perspective. N Z Med J 2019 Oct 04;132(1503):66-74. [Medline: 31581183]
7. Shanley C, Boughtwood D, Adams J, Santalucia Y, Kyriazopoulos H, Pond D, et al. A qualitative study into the use of formal services for dementia by carers from culturally and linguistically diverse (CALD) communities. BMC Health Serv Res 2012 Oct 09;12:354 [FREE Full text] [doi: 10.1186/1472-6963-12-354] [Medline: 23043332]
8. Prince M, 10/66 Dementia Research Group. Care arrangements for people with dementia in developing countries. Int J Geriatr Psychiatry 2004 Feb;19(2):170-177. [doi: 10.1002/gps.1046] [Medline: 14758582]
9. Hinton L, Kohrt BA, Kleinman A. Engaging families to advance global mental health intervention research. Lancet Psychiatry 2019 May;6(5):365-367 [FREE Full text] [doi: 10.1016/S2215-0366(19)30134-8] [Medline: 30954478]
10. Global action plan on the public health response to dementia 2017 - 2025. World Health Organization. 2017. URL: https://apps.who.int/iris/bitstream/handle/10665/259615/9789241513487-eng.pdf;jsessionid=D966B65FADA9448010C1A245A41EF564?sequence=1 [accessed 2021-10-07]
11. Egan KJ, Pinto-Bruno Á, Bighelli I, Berg-Weger M, van Straten A, Albanese E, et al. Online Training and Support Programs Designed to Improve Mental Health and Reduce Burden Among Caregivers of People With Dementia: A Systematic Review. J Am Med Dir Assoc 2018 Mar;19(3):200-206.e1. [doi: 10.1016/j.jamda.2017.10.023] [Medline: 29306605]
12. iSupport Manual for Dementia. World Health Organization. 2019 May 09. URL: https://www.who.int/mental_health/neurology/dementia/isupport_manual/en/ [accessed 2021-01-16]
13. WHO. iSupport lite: Public health messages to improve the mental health wellbeing of caregivers of people with dementia. In: https://www.who.int/teams/mental-health-and-substance-use/treatment-care/isupport. https://www.who.int/teams/mental-health-and-substance-use/treatment-care/isupport: World Health Organization; 2020.
14. Xiao LD, McKechnie S, Jeffers L, De Bellis A, Beattie E, Low LF, et al. Stakeholders' perspectives on adapting the World Health Organization iSupport for Dementia in Australia. Dementia (London) 2021 Jul;20(5):1536-1552. [doi: 10.1177/1471301220954675] [Medline: 32864991]
15. Baruah U, Varghese M, Loganathan S, Mehta KM, Gallagher-Thompson D, Zandi D, et al. Feasibility and preliminary effectiveness of an online training and support program for caregivers of people with dementia in India: a randomized controlled trial. Int J Geriatr Psychiatry 2021 Apr;36(4):606-617. [doi: 10.1002/gps.5502] [Medline: 33491811]
16. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M, Medical Research Council Guidance. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 2008 Sep 29;337:a1655 [FREE Full text] [doi: 10.1136/bmj.a1655] [Medline: 18824488]
17. Borgstrom E, Barclay S. Experience-based design, co-design and experience-based co-design in palliative and end-of-life care. BMJ Support Palliat Care 2019 Mar;9(1):60-66. [doi: 10.1136/bmjspcare-2016-001117] [Medline: 28209568]

18. Leon AC, Davis LL, Kraemer HC. The role and interpretation of pilot studies in clinical research. J Psychiatr Res 2011 May;45(5):626-629 [FREE Full text] [doi: 10.1016/j.jpsychires.2010.10.008] [Medline: 21035130]
19. Venkatesh V, Morris MG, Davis GB, Davis FD. User Acceptance of Information Technology: Toward a Unified View. MIS Quarterly 2003;27(3):425. [doi: 10.2307/30036540]
20. Schulz R, Martire LM. Family caregiving of persons with dementia: prevalence, health effects, and support strategies. Am J Geriatr Psychiatry 2004;12(3):240-249. [Medline: 15126224]
21. WHO, iSupport V. Adaptation and Implementation Guide. Geneva: World Health Organization; 2018.
22. Nguyen T, Nguyen H, Pham T, Nguyen TH, Hinton L. A cluster randomized controlled trial to test the feasibility and preliminary effectiveness of a family dementia caregiver intervention in Vietnam: The REACH VN study protocol. Medicine (Baltimore) 2018 Oct;97(42):e12553 [FREE Full text] [doi: 10.1097/MD.0000000000012553] [Medline: 30334942]
23. Galvin JE, Roe CM, Powlishta KK, Coats MA, Muich SJ, Grant E, et al. The AD8: a brief informant interview to detect dementia. Neurology 2005 Aug 23;65(4):559-564. [doi: 10.1212/01.wnl.0000172958.95282.2a] [Medline: 16116116]
24. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983 Dec;24(4):385-396. [Medline: 6668417]
25. Standardized Mini-Cog© Instrument. Mini-Cog©. URL: https://mini-cog.com/mini-cog-instrument/standardized-mini-cog-instrument/ [accessed 2021-09-20]
26. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001 Sep;16(9):606-613 [FREE Full text] [doi: 10.1046/j.1525-1497.2001.016009606.x] [Medline: 11556941]
27. de Boer A, van Lanschot J, Stalmeier P, van Sandick J, Hulscher J, de Haes J, et al. Is a single-item visual analogue scale as valid, reliable and responsive as multi-item scales in measuring quality of life? Qual Life Res 2004 Mar;13(2):311-320. [doi: 10.1023/B:QURE.0000018499.64574.1f] [Medline: 15085903]
28. Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. Am J Psychiatry 1982 Sep;139(9):1136-1139. [doi: 10.1176/ajp.139.9.1136] [Medline: 7114305]
29. Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. J Neuropsychiatry Clin Neurosci 2000;12(2):233-239. [doi: 10.1176/jnp.12.2.233] [Medline: 11001602]
30. Mahoney R, Regan C, Katona C, Livingston G. Anxiety and depression in family caregivers of people with Alzheimer disease: the LASER-AD study. Am J Geriatr Psychiatry 2005 Sep;13(9):795-801. [doi: 10.1176/appi.ajgp.13.9.795] [Medline: 16166409]
31. Gilhooly KJ, Gilhooly MLM, Sullivan MP, McIntyre A, Wilson L, Harding E, et al. A meta-review of stress, coping and interventions in dementia and dementia caregiving. BMC Geriatr 2016 May 18;16:106 [FREE Full text] [doi: 10.1186/s12877-016-0280-8] [Medline: 27193287]
32. Ory MG, Hoffman RR, Yee JL, Tennstedt S, Schulz R. Prevalence and impact of caregiving: a detailed comparison between dementia and nondementia caregivers. Gerontologist 1999 Apr;39(2):177-185. [doi: 10.1093/geront/39.2.177] [Medline: 10224714]
33. Coehlo DP, Hooker K, Bowman S. Institutional placement of persons with dementia: what predicts occurrence and timing? J Fam Nurs 2007 May;13(2):253-277. [doi: 10.1177/1074840707300947] [Medline: 17452605]
34. Selwood A, Johnston K, Katona C, Lyketsos C, Livingston G. Systematic review of the effect of psychological interventions on family caregivers of people with dementia. J Affect Disord 2007 Aug;101(1-3):75-89. [doi: 10.1016/j.jad.2006.10.025] [Medline: 17173977]
35. Walter E, Pinquart M. How Effective Are Dementia Caregiver Interventions? An Updated Comprehensive Meta-Analysis. Gerontologist 2020 Nov 23;60(8):609-619. [doi: 10.1093/geront/gnz118] [Medline: 33226434]
36. Hinton L, Nguyen H, Nguyen HT, Harvey DJ, Nichols L, Martindale-Adams J, et al. Advancing family dementia caregiver interventions in low- and middle-income countries: A pilot cluster randomized controlled trial of Resources for Advancing Alzheimer's Caregiver Health in Vietnam (REACH VN). Alzheimers Dement (N Y) 2020;6(1):e12063 [FREE Full text] [doi: 10.1002/trc2.12063] [Medline: 33532542]
37. Prina AM, Mayston R, Wu Y, Prince M. A review of the 10/66 dementia research group. Soc Psychiatry Psychiatr Epidemiol 2019 Jan;54(1):1-10 [FREE Full text] [doi: 10.1007/s00127-018-1626-7] [Medline: 30467589]
38. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. Lancet 2017 Dec 16;390(10113):2673-2734. [doi: 10.1016/S0140-6736(17)31363-6] [Medline: 28735855]
39. GSMA Report: The Mobile Economy Asia Pacific 2019. Telepin Software Systems Inc. 2019. URL: https://www.telepin.com/gsma-report-the-mobile-economy-asia-pacific-2019/ [accessed 2021-10-07]
40. Nguyen TA, Pham T, Dang TH, Hinton WL, Nguyen AT, Pham TL, et al. Towards the development of Vietnam's national dementia plan-the first step of action. Australas J Ageing 2020 Jun;39(2):137-141 [FREE Full text] [doi: 10.1111/ajag.12755] [Medline: 31814244]
41. Hinton L, Nguyen H, Nguyen HT, Harvey DJ, Nichols L, Martindale-Adams J, et al. Advancing family dementia caregiver interventions in low- and middle-income countries: A pilot cluster randomized controlled trial of Resources for Advancing Alzheimer's Caregiver Health in Vietnam (REACH VN). Alzheimers Dement (N Y) 2020;6(1):e12063 [FREE Full text] [doi: 10.1002/trc2.12063] [Medline: 33532542]

42. National Framework for Action on Dementia 2015–2019. Australian Government. Department of Health. 2015. URL: https://www.health.gov.au/resources/publications/national-framework-for-action-on-dementia-2015-2019 [accessed 2021-10-07]
43. New Zealand Framework for Dementia Care. New Zealand Ministry of Health. 2013. URL: https://www.health.govt.nz/system/files/documents/publications/new-zealand-framework-for-dementia-care-nov13.pdf [accessed 2021-10-07]
44. From Plan to Impact II: The urgent need for action. Alzheimer's Disease International. 2018. URL: https://www.alz.co.uk/adi/pdf/from-plan-to-impact-2019.pdf [accessed 2021-10-07]

Abbreviations

ALZI: Alzheimer's Indonesia
APR: Asia-Pacific Region
CALD: culturally and linguistically diverse
DA: Dementia Australia
HIC: high-income country
iSupport VA: iSupport virtual assistant
LMIC: low- and middle-income country
NARI: National Ageing Research Institute
NGO: nongovernment organization
NHMRC: National Health and Medical Research Council
PSS: Perceived Stress Scale
RCT: randomized controlled trial
REACH: Resources for Enhancing Alzheimer's Caregiver Health
UTAUT: Unified Theory of Acceptance and Use of Technology
WHO: World Health Organization

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Protocol

Evaluating the Efficacy of Automated Smoking Treatment for People With HIV: Protocol for a Randomized Controlled Trial

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Abstract

Background: Smoking prevalence rates among people with HIV are nearly 3 times higher than those in the general population. Nevertheless, few smoking cessation trials targeting smokers with HIV have been reported in the literature. Efforts to develop and evaluate sustainable, low-cost, and evidence-based cessation interventions for people with HIV are needed. Given the widespread proliferation of mobile phones, the potential of using mobile health apps to improve the reach and efficacy of cessation interventions is promising, but evidence of efficacy is lacking, particularly among people with HIV.

Objective: This study will consist of a 2-group randomized controlled trial to evaluate a fully automated smartphone intervention for people with HIV seeking cessation treatment.

Methods: Participants (N=500) will be randomized to receive either standard treatment (ST; 250/500, 50%) or automated treatment (AT; 250/500, 50%). ST participants will be connected to the Florida Quitline and will receive nicotine replacement therapy in the form of transdermal patches and lozenges. This approach, referred to as Ask Advise Connect, was developed by our team and has been implemented in numerous health systems. ST will be compared with AT, a fully automated behavioral treatment approach. AT participants will receive nicotine replacement therapy and an interactive smartphone-based intervention that comprises individually tailored audiovisual and text content. The major goal is to determine whether AT performs better in terms of facilitating long-term smoking abstinence than the more resource-intensive ST approach. Our primary aim is to evaluate the efficacy of AT in facilitating smoking cessation among people with HIV. As a secondary aim, we will explore potential mediators and moderators and conduct economic evaluations to assess the cost and cost-effectiveness of AT compared with ST.

Results: The intervention content has been developed and finalized. Recruitment and enrollment will begin in the fall of 2021.

Conclusions: There is a critical need for efficacious, cost-effective, and sustainable cessation treatments for people with HIV who smoke. The AT intervention was designed to help fill this need. If efficacy is established, the AT approach will be readily adoptable by HIV clinics and community-based organizations, and it will offer an efficient way to allocate limited public health resources to tobacco control interventions.

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KEYWORDS

smoking cessation; health disparities; HIV/AIDS; mHealth; mobile phone

Introduction

HIV and Cigarette Smoking

In the United States, the prevalence of cigarette smoking in the general population has dropped to 13.7% [1]; however, smoking rates among people with HIV remain quite high, with evidence suggesting that 34% to 42% are current smokers [2,3]. Thus, smoking among people with HIV is a leading cause of morbidity and mortality [4-7]. People with HIV who smoke are more likely to die of lung cancer than AIDS-related diseases, even after accounting for antiretroviral therapy adherence [8]. They are also at greater risk of experiencing various oral, renal, and cardiovascular diseases, decreased bone mineral density and fracture, pulmonary complications, tuberculosis, opportunistic and nonopportunistic infections, and poor quality of life [7,9-12]. Moreover, smoking negatively affects the response to antiretroviral therapies, resulting in poor viral and immunologic response [13]. Among people with HIV, the mortality rate for smokers is twice that of nonsmokers [5,14], and the estimated population-attributable risk of all-cause mortality associated with smoking ranges from 24% to 62% [4,6]. Notably, smoking-related morbidity and mortality appear to decline over time in former versus current smokers with HIV [5,15]. Effective smoking cessation treatment is critical for lowering HIV- and smoking-related morbidity, improving antiretroviral therapy response, and reducing overall mortality.

Smoking Cessation Treatment for HIV-Positive Smokers

Despite this need, few studies have evaluated the efficacy of smoking cessation interventions targeting people with HIV [15]. Studies have shown that people with HIV who smoke are interested in quitting and receptive to cessation interventions [2,16,17], and smoking treatment programs have been successfully implemented in HIV clinics [18]. Although a recent systematic review found that smoking cessation interventions for people with HIV were effective at short- and intermediate-term follow-up (ie, 3-month), limited evidence supports long-term (ie, 6- and 12-month) effectiveness [19]. The results from our prior work are in line with these conclusions. Most eligible people with HIV who smoked (roughly two-thirds) enrolled in treatment, and those randomized to receive our interventions (vs controls) had higher abstinence rates through the 3-month follow-up. However, long-term relapse rates were high, with treatment effects diminished by the 6-month follow-up [20,21]. Efforts are needed to elucidate the resources needed to engage people with HIV who smoke during treatment and facilitate long-term abstinence.

Quitline-Delivered Smoking Cessation Treatment in Vulnerable Populations

Our team developed an approach to link smokers in health care settings with evidence-based treatment delivered via state quitlines. This approach—Ask Advise Connect (AAC)—links smokers with treatment via an automated connection system. Results from efficacy trials revealed that AAC was associated with a 13- [22] to 30-fold [23] increase in treatment enrollment when compared with Ask Advise Refer, where smokers were offered a quitline referral and encouraged to call on their own. We have successfully implemented AAC in various settings (eg, safety-net hospitals and HIV clinics) throughout Texas and Oklahoma [24,25].

While the results are encouraging, several factors suggest that interventions such as AAC that depend on connecting smokers with quitlines may not be sufficient. First, in recent years, state quitlines have experienced significant budget cuts, and some states have temporarily eliminated quitlines altogether [26-28]. Moreover, while quitlines provide a cost-effective and evidence-based treatment option and have the potential to reach countless smokers [29], human-delivered phone counseling has limited appeal. In fact, national data suggest that quitlines reach only 1% to 2% of smokers [30]. Finally, results from a recent AAC implementation study indicated that self-reported abstinence was 18.7% among HIV clinic patients and 16.5% among non–HIV clinic patients; however, biochemically confirmed abstinence was considerably lower (4.2% and 4.5%, respectively) [24,25]. There is a critical need to improve the reach, efficacy, sustainability, and impact of smoking cessation treatment for people with HIV [31].

Mobile Technology and Smoking Cessation Treatment

Over the last 20 years, cell phone ownership has steadily increased. The Pew Research Center found that as of February 2021, 97% of adults living in the United States reported owning a cell phone [32]. Previous studies have used cell phones to administer text message–based smoking cessation interventions, and findings suggest excellent reach and efficacy in the general population [33-35] and among people with HIV who smoke [36]. Moreover, text message–based interventions are cost-effective [37,38] and affordable options for global tobacco control [39].

Compared with cell phones, smartphones have greater capability, as they can be used to access the internet, run apps, view and send graphic messages, and stream audio and video content. According to Pew, in 2021, 85% of US adults reported owning a smartphone [32]. Smartphone ownership is high among adults between the ages of 18 and 64 years (83%) and within underserved populations, such as racial or ethnic minorities (83%), individuals with less than a high school education (75%), and those with an annual household income of less than US $30,000 (76%). Notably, the proportion of individuals who depend on smartphones for all internet access is higher among racial and ethnic minority groups (vs White individuals), those with lower income and education, and individuals living in rural (vs urban and suburban) communities.

Current national trends indicate that US smartphone ownership is nearing ubiquity. Smartphone-delivered interventions are an ideal method for reaching underserved populations (eg, minority, low income, low education, and rural). Although numerous smartphone-delivered smoking cessation apps exist, few were

constructed using evidence-based practices, and there is little outcome data to support the efficacy of these treatments [40,41]. Theoretically grounded smartphone-based smoking cessation interventions have broad scalability and dissemination potential and are likely to be cost-effective. Efforts are needed to evaluate these treatments in underserved populations, particularly among people with HIV who smoke.

Objectives

This paper describes the protocol for a randomized controlled trial (RCT) that will assess the efficacy of a fully automated smartphone intervention for people with HIV who smoke. Participants will be randomized to receive either (1) standard treatment (ST) or (2) automated treatment (AT). ST participants will be connected to the Florida Quitline (AAC, which was developed and evaluated by our team) and will receive nicotine replacement therapy (NRT) in the form of transdermal patches and nicotine lozenges. ST will be compared with AT, a fully automated behavioral treatment approach. AT participants will receive NRT plus an interactive smartphone-based intervention that comprises individually tailored audiovisual and text content.

Our primary aim is to evaluate the efficacy of AT in facilitating smoking cessation among people with HIV. We expect that at 12 months postenrollment, smoking abstinence rates will be higher in the AT group than in the ST group. Regarding secondary aims, we will first explore potential mediators and moderators. We will compare the magnitude of the mediated effects via common mechanisms (ie, motivation, agency, and stress or negative affect) on smoking abstinence between the AT and ST treatment groups. We will also examine the role of HIV-specific moderators (ie, stigma, resilience, disease progression, and HIV symptom burden). Second, we will evaluate the cost and cost-effectiveness of AT versus ST. Through these aims, we will determine whether AT performs better in terms of facilitating long-term smoking abstinence (ie, 12 months postenrollment) than the more resource-intensive ST approach. If efficacy is established, the AT approach will be readily adoptable by various HIV clinics and community-based organizations and offer an efficient way to allocate limited public health resources to tobacco control interventions.

Methods

Design Overview

This study will use a 2-group RCT to compare ST with AT. We will enroll a total of 500 participants (250/500, 50% per group). An additional 20 participants (10 per group) will be enrolled in a 12-week pilot study before the implementation of the full trial. All participants will be recruited on the web from Florida. Participants will complete assessments on the web via the Research Electronic Data Capture (REDCap) platform (Vanderbilt University) hosted at H. Lee Moffitt Cancer Center and Research Institute [42,43] or over the phone at baseline and at 3, 6, and 12 months postenrollment. These assessments will take approximately 20 minutes to complete. Weekly 4-item smartphone assessments will be collected from all participants for 26 weeks.

Eligibility Criteria

The eligibility is determined based on inclusion and exclusion criteria (Textbox 1).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- At least 18 years of age
- Smoked at least 100 cigarettes in their lifetime
- Currently smoking at least five cigarettes a day
- Willing to make a quit attempt within 1 week of enrollment
- HIV-positive
- English or Spanish speaking
- Possess a smartphone with a data plan and operating system compatible with the project app
- Have a valid email address

Exclusion criteria

- Medical conditions that preclude the use of nicotine replacement therapy
- Current use of smoking cessation medications
- Enrollment in another cessation study
- Household members enrolled in the study
- Inadequate health literacy

Recruitment and Screening

Participants will be recruited from Florida using web-based advertisements. As of 2018, 116,689 Floridians were living with HIV [44]. On the basis of national data suggesting that 32% to 42% of US adults with HIV currently smoke [2,3], we expect that about 39,675 will be current smokers. Thus, our

recruitment goal of 500 participants should be achievable within the proposed 42-month recruitment period.

Web-based advertisements will describe the study and direct potential participants to a landing page, which will provide more information about the study. Interested participants will complete a short web-based prescreening questionnaire, and those who pass the prescreener will be automatically redirected to the study's eligibility questionnaire. Those who do not complete the self-administered web-based screening form will be contacted by the study staff and offered screening over the phone. Individuals who are eligible and interested in participating in the study will provide informed consent electronically or verbally over the phone and receive a copy of the informed consent document via email or mail. They will then provide HIV status documentation via a REDCap link. Once the documentation is verified, participants will be asked to complete a baseline assessment. The full list of measures to be completed for each assessment is shown in Table 1.

Table 1. Study measures and assessment schedule.

Measure	Assessment schedule				
	Baseline	Weekly	3-month	6-month	12-month
Demographics and smoking history [45,46]	✓				
Drug use history [47]	✓				
Alcohol history and follow-up [48]	✓		✓	✓	✓
Smoking status [49]		✓[a]	✓	✓	✓
Heaviness of smoking index [50]	✓				
Financial Strain Questionnaire [51]	✓		✓	✓	✓
Contemplation ladder [52]	✓	✓[a]	✓	✓	✓
Reasons for quitting (intrinsic and extrinsic motivation) [53]	✓				
Sense of control [54]	✓		✓	✓	✓
Self-efficacy Scale [55]	✓	✓[a]	✓	✓	✓
Perceived Stress Scale-4 [56]	✓	✓[a]	✓	✓	✓
Positive and Negative Affect Scale [57,58]	✓		✓	✓	✓
Patient Health Questionnaire-8 [59]	✓		✓	✓	✓
Client Satisfaction Questionnaire [60]			✓	✓	
Health utilities (EQ-5D-5L[b]) [61]	✓		✓	✓	✓
Antiretroviral therapy adherence [62]	✓		✓	✓	✓
HIV symptoms burden [63]	✓		✓	✓	✓
Brief Resilience Scale [64]	✓		✓	✓	✓
HIV stigma scale [65]	✓		✓	✓	✓
Clinical measures	✓				✓
USDA[c] household food insecurity survey [66]	✓		✓	✓	✓
CDC[d] healthy days core module [67,68]	✓		✓	✓	✓
Subjective social status [69]	✓		✓	✓	✓
Three-item Loneliness Scale [70]	✓		✓	✓	✓
Brief Everyday Discrimination Scale [71]	✓		✓	✓	✓
COVID-19 risk perception, testing, and vaccination history	✓		✓	✓	✓
PROMIS[e] global health items [72]	✓		✓	✓	✓
HPV[f] and hepatitis B vaccination	✓				✓
Cancer screenings (cervical, colorectal, lung)	✓				✓
Brief weekly survey		✓			
Cotinine survey			✓	✓	✓

[a]Denotes brief version.

[b]EQ-5D-5L: EuroQol Five Dimension Five Level Scale.

[c]USDA: United States Department of Agriculture.

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

[e]PROMIS: Patient-Reported Outcomes Measurement Information System.

[f]HPV: human papillomavirus.

Randomization

Following completion of the baseline assessment, the participants will be randomized to the treatment group (ST or AT) using stratified randomization. Sex assigned at birth, HIV disease stage, and nicotine dependence will be balanced.

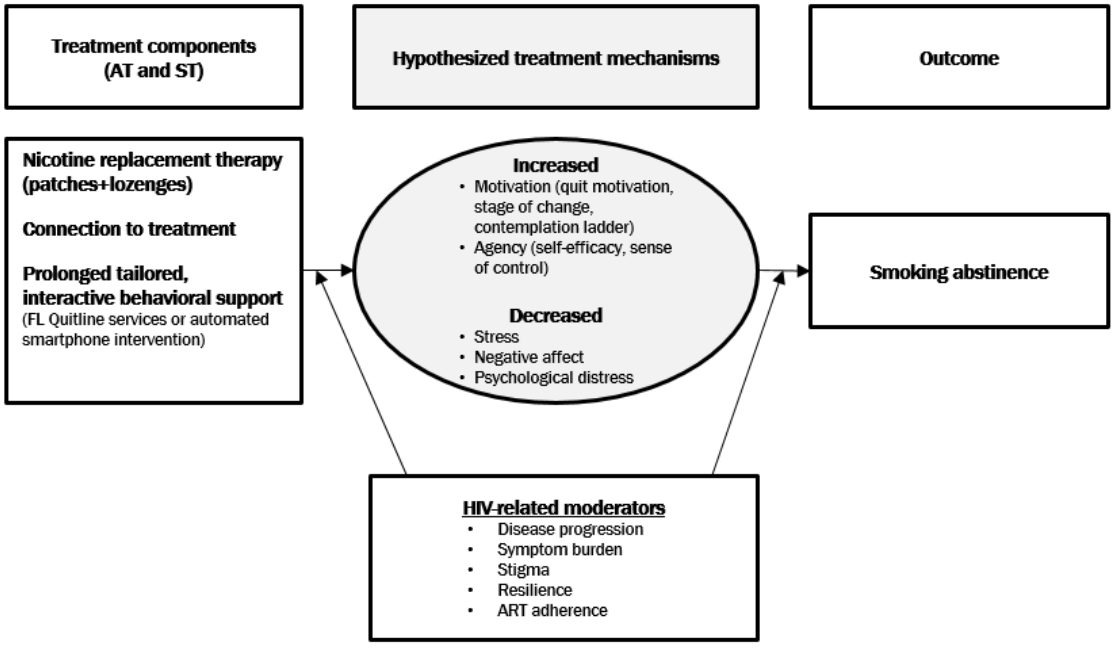
Participant Tracking, Compensation, and Retention Procedures

We will use various approaches to maximize follow-up rates. The baseline and the 3-, 6-, and 12-month assessments will be conducted on the web or over the phone at participants' convenience. Participants will be compensated for up to US $160 for completing these assessments (4 assessments × US $40 = US $160). Compensation for study-related smartphone use (ie, data, texting, and minutes) will be provided monthly for 26 weeks, based on the number of weekly assessments completed (26 weekly assessments × US $10 = US $260). We will also compensate participants for returning cotinine tests at 3, 6, and 12 months (3 tests × US $30 = US $90). Other procedures to reduce attrition will include (1) reminder phone calls/messages delivered via the app or by study staff before the follow-up assessments; (2) obtaining the names, addresses, and phone numbers of 3 collaterals (ie, relatives and friends) who can provide information on participants' whereabouts; and (3) using the Whitepages website to search for updated participant contact information on the web.

Conceptual Framework

Research and theory have identified motivation and agency as critical mechanisms underlying the decision to enroll in smoking cessation treatment, and motivation, agency, and stress or negative affect are established mechanisms underlying successful cessation [73-80]. As such, both ST and AT are designed to target these mechanisms. Although we hypothesize common mechanisms between ST and AT, we do not expect equivalent magnitudes of the effect. Thus, a secondary aim is to compare the magnitude of the mediated effects between AT and ST. For example, participants in ST (vs AT) may report higher quit motivation, whereas individuals in AT (vs ST) may report higher self-efficacy. See Figure 1 for the conceptual framework.

Figure 1. Hypothesized mechanisms underlying standard treatment and automated-treatment. ART: antiretroviral therapy; AT: automated treatment; FL: Florida; ST: standard treatment.



ST is intended to mirror a clinic-based AAC model, which involves delivery of brief advice to quit video followed by an invitation to enroll in treatment that mirrors standard proactive quitline-delivered phone counseling. AT is designed to function as a fully automated program capable of delivering cessation treatment via automated, smartphone-based treatment content that comprises an initial brief advice to quit video, followed by interactive messaging, images, and audiovisual clips. We have elected to extend AT over a 6-month period (vs a more conventional 3 months) to counter the high relapse rates among people with HIV who smoke observed in our previous studies [20,21]. All participants will receive NRT.

Motivation

Motivation refers to an individual's willingness and desire to make a specific change in their behavior [81]. Substantial evidence underscores the critical role of motivation in the process of decision-making regarding change and the likelihood of achieving and successfully maintaining change [73,74], as *stage of change* predicts both quit attempts and cessation success [73-75]. Notably, the motivation for change can fluctuate rapidly [82,83]. In fact, 41% of US smokers report that their motivation to quit smoking changes daily [84], and half or more quit attempts are unplanned [85,86], consistent with a model of smoking motivation that posits that motivation is characterized by frequent fluctuations [86]. After the initial change has been achieved, motivation for maintaining abstinence may weaken,

and ambivalence may increase as the individual is exposed to temptations and stressors [76]. Because empirical data indicate that motivation influences the initiation of a quit attempt, success in achieving cessation, and the maintenance of abstinence, efforts are needed to bolster individuals' motivation during the process of quitting [53,83,87]. A crucial focus of both interventions is to provide an appropriate therapeutic response to fluctuations in motivation throughout the change process.

Agency (Sense of Control and Self-efficacy)

Human agency reflects the ability to intentionally affect one's behavior or life situation; a sense of agency is determined both by personal resources and situational influences [88,89]. Agency includes constructs such as a sense of control and self-efficacy [89]. Sense of control refers to the learned expectation that outcomes depend on personal choices and actions rather than on chance, other people, or forces outside of one's control [54,90]. Self-efficacy is a form of agency that is dependent on context and behavior [90,91]. In the context of smoking, agency is reflected in greater self-efficacy when faced with situations that challenge one's ability to initiate or maintain abstinence. Self-efficacy is a strong predictor of cessation treatment outcomes [78,79,87,92]. Both AT and ST will target agency as a key mechanism.

Stress or Negative Affect or Psychological Distress

Stress/negative affect, measured in many ways, is associated with change. For example, Shiffman et al [80] found a strong dose-response relationship between smoking-related acute events and the severity of stress or negative affect. In addition, the magnitude and trajectory of stress or negative affect over time are powerful predictors of cessation [93,94], as are individual differences in affective vulnerability [95,96]. Results indicate that most smokers experience elevated levels of postcessation negative affect that continue for relatively long periods, regardless of NRT use [97]. Similarly, studies have shown that mood disorders, negative affect, and stress are associated with poorer treatment outcomes, including tobacco and alcohol relapse [92,98-101]. Given the multiple stressors (eg, medical, psychosocial, economical, and stigma) confronting people with HIV who smoke, we expect that addressing stress or negative affect in the context of smoking treatment will be crucial for this population [15,102].

Reciprocal Relations Among Mechanisms

Theory and data suggest reciprocal relationship among the key hypothesized mechanisms—motivation, self-efficacy, and stress or negative affect—targeted by the treatments (ST and AT) [76,92,103-105]. ST and AT are hypothesized to reduce stress or negative affect via the following mechanisms: (1) their impact on decreasing ambivalence and increasing motivation; (2) the application of coping skills training and problem solving to increase self-efficacy; and (3) the use of a holistic approach, where other life concerns and stressors will be addressed. Similarly, reductions in stress or negative affect are posited to increase motivation and agency.

HIV-Related Moderators

Our prior work and the extant literature suggest that several HIV-related variables may moderate the relationship between interventions and cessation outcomes. For example, we have observed higher quit rates and higher intention to quit among people with HIV with more advanced disease [106]. Conversely, we have observed lower cessation rates among people with HIV who report greater symptom burden and those with low adherence to antiretroviral therapies [107-109]. Finally, stigma is a risk factor for smoking among people with HIV, whereas resilience is associated with improved HIV-related outcomes [110,111].

Treatment Groups

ST Group

Following the baseline assessment and brief advice to quit video, participants randomized to ST will be given a 10-week supply of nicotine patches and lozenges. Nicotine patches provide a low, constant level of nicotine, which attenuates nicotine withdrawal symptoms after quitting (including physical symptoms and negative affect), while lozenges provide a fast-acting dose of nicotine that can be used as needed to combat cravings. When combined with behavioral treatment, NRT doubles the odds of successfully quitting [112]. ST participants will also be connected to Florida Quitline services and complete weekly 4-item smartphone assessments for 26 weeks. Weekly assessments will measure smoking status, motivation, self-efficacy, and perceived stress.

AT Group

Following the baseline assessment and brief advice to quit video, participants in AT will be given a 10-week supply of nicotine patches and lozenges (equivalent to ST). After randomization, they will be sent an email with a link to the smartphone app and instructions on how to use the app. AT will include (1) 12 proactive treatment videos (delivered weekly) that will be tailored to smoking status, motivation, agency, and negative affect or stress; (2) 26 weeks of on-demand access to treatment content; and (3) 26 weeks of text content.

As with participants in the ST group, AT participants will complete weekly 4-item smoking status, self-efficacy, motivation, and stress assessments for 26 weeks. An algorithm will use responses to these assessments to deliver brief, 2- to 6-minute, videos from an existing library of tailored content. Weekly topics are listed in Table 2. The AT app will deliver the most appropriate video each week, specifically tailored for each participant. During the first 12 weeks, videos will be proactively launched each week following the completion of the assessment. Throughout the entire 26-week treatment period, participants will also have the option to self-initiate treatment sessions. In addition, referrals to extra treatment resources will be available through the app. Resources will include phone numbers to substance abuse treatment centers, psychiatric services, HIV case management, and other services (eg, housing needs).

Table 2. Automated treatment session topic by study week.

Study week	Topic
Week 1	Preparing to quit
Week 2	Quit day
Week 3	What to do if you have a cigarette
Week 4	Nicotine patches and lozenges
Week 5	Smoking, stress, and mood
Week 6	Health benefits of quitting
Week 7	Smoking and your weight
Week 8	Staying on track
Week 9	Financial benefits of being a nonsmoker
Week 10	Taking care of yourself
Week 11	Social benefits of being a nonsmoker
Week 12	Life without cigarettes

The primary goal of the AT app is to function autonomously. It is designed to require minimal human involvement while being appropriate for implementation in various environments. This approach is expected to perform better than, yet share common mechanisms of action (eg, motivation, agency, and stress or negative affect) with, the behavioral standard of care (ie, quitline counseling). Underlying AT is a platform consisting of both a staff-facing dashboard and a mobile app. Videos were created with Adobe After Effects, an animation software package that is widely used in media campaigns.

On the basis of our prior work, as well as the growing literature supporting the efficacy of text messaging interventions for promoting smoking cessation, participants in the AT group will also receive smartphone-delivered text content [39,94]. This content will be delivered in the form of notifications generated by the app. Daily notifications will begin shortly before the scheduled quit date and continue through month 3. During months 4 to 6, the notification frequency will drop to once per week. The content of these notifications will be designed to target the hypothesized mechanisms and promote NRT adherence. Furthermore, the notifications will encourage participants to access additional on-demand content within the app. Participants will be referred to by first name within the notifications as a way of personalizing the treatment.

Measures and Assessment Strategy

Several considerations guided our assessment procedures. First, we attempted to include measures with established reliability and validity. If measures with established psychometric properties were not available, measures were required to at least have face validity. Second, assessments had to either (1) represent our hypothesized mechanisms, (2) empirically predict smoking behavior, or (3) describe the sample. Measures were informed by models of health behavior, theories of nicotine dependence, and existing data. To ensure that the study is available to a representative sample of the target population, we will recruit both English- and Spanish-speaking participants. Most of the measures have been translated and validated in Spanish. A certified translator will be used for measures that have not yet been translated.

The REDCap system will be used to administer the surveys. REDCap is a secure web-based app designed to support secure data capture for cleaning, storage, and analysis. Moffitt Cancer Center is a member of the REDCap Consortium.

Primary Outcomes

The main outcome is self-reported 7-day abstinence smoking status at the 12-month follow-up. Other definitions of abstinence, such as biochemically verified abstinence using salivary cotinine and self-reported 24-hour, 30-day, and continuous abstinence, will be examined as secondary outcomes. Participants who report 7-day abstinence will be mailed a cotinine kit with instructions for providing the cotinine sample. Study staff will be available by phone and email if participants have questions about the collection process. Participants will be asked to return cotinine samples using a prepaid envelope.

All participants (ST and AT) will complete brief smartphone-delivered assessments each week during the 26-week treatment period. These assessments will be delivered to AT participants through the app, while ST participants will receive their assessments through a REDCap link. Regardless of the treatment group, assessments will be identical and include current smoking status, motivation, agency, and stress or negative affect. Responses to the assessments will be used to select the appropriate treatment content for AT participants, as described above.

Assessment of Treatment Engagement–Related Variables in AT

An important focus of our evaluation of AT is to track and examine how frequently participants interact with the app and the duration of these interactions. Thus, each interaction will be date- and timestamped, and we will note how often specific features of the app are used. These data will allow us to examine the frequency and duration of participants' use of the various components of the app and the specific conditions under which

participants engage with the app components. This information will be used to help guide future refinements of the app.

Data Analysis Plan

Descriptive analyses will be conducted to determine which variables, if any, should be transformed before inferential analyses. In addition, descriptive statistics for demographic, smoking-related, and health-related variables will be used to characterize each sample. The samples will be compared to identify differences despite randomization, which may necessitate inclusion in models testing hypotheses. Descriptive statistics will also be used to summarize the participants' interactions with the app.

Primary Aim

The primary aim of this study is to evaluate the efficacy of AT in facilitating smoking cessation among people with HIV. We hypothesize that at 12 months postenrollment, smoking abstinence rates will be higher in the AT group than in the ST group. The primary outcome is self-reported 7-day point prevalence abstinence at 12 months. As is traditional in smoking cessation research, participants who do not complete a follow-up will be coded as smoking. Log-binomial regression will be used, with the intervention group (AT vs ST) as the primary predictor. Variables found to differ by group in preliminary analyses ($P<.10$) will be included as covariates. Differences in treatment effects as a function of sex assigned at birth will also be examined.

Additional analyses will evaluate the effects of the intervention on other definitions of smoking abstinence: biochemically verified abstinence using salivary cotinine and self-reported 24-hour, 30-day, and continuous abstinence. Outcomes from the 3- and 6-month follow-ups will also be considered. Repeated-measures analysis using generalized linear mixed models with a log-link function and the appropriate random-effect covariance structure will be used to analyze outcomes across all assessments with intervention, time, and their interaction as the primary model variables. Model fitting and diagnostics will follow the general approach described by McCullagh and Nelder [113] and McCulloch et al [114], when applicable. Adjustments for multiple comparisons will be made using the methods recommended by Westfall and Young [115].

Secondary Aim 1

The first secondary aim is to explore the role of potential mediators and moderators. Specifically, we will compare the magnitude of the mediated effects via common mechanisms (ie, motivation, agency, and stress or negative affect) on smoking abstinence between the AT and ST groups. We will also investigate the role of several established HIV-specific moderators (ie, stigma, resilience, disease progression, and HIV symptom burden). Furthermore, exploratory analyses will examine the associations of various AT treatment components with outcomes.

While we hypothesize common mechanisms of AT and ST, it is important to identify the relative strengths and weaknesses of the mechanisms on which each approach relies to facilitate cessation. Participants in ST (vs AT) may report higher levels of quit motivation, whereas those in AT (vs ST) may report higher self-efficacy. Such hypotheses can be tested via mediation analyses with the intervention group (AT vs ST) as the independent variable and smoking abstinence and the hypothesized mechanisms (ie, motivation, agency, and stress or negative affect) as potential mediators. Mediation will be evaluated using approaches developed by MacKinnon [116] and Preacher and Hayes [117-119]. We will also explore the role of HIV-specific moderators (ie, stigma, resilience, disease progression, and HIV-symptom burden) of these indirect effects on the outcome of smoking abstinence.

Secondary Aim 2

Our second secondary aim is to conduct economic evaluations from a societal perspective as well as a health system perspective to evaluate the cost and cost-effectiveness of AT versus ST. Although the societal perspective is recommended by the Second Panel on Cost-Effectiveness in Health and Medicine [120], we expect that a health system perspective will be of greater interest to decision makers in the public health sector who are responsible for making implementation decisions about smoking cessation programs. Conventional cost-effectiveness analysis will be used to summarize findings in terms of the incremental cost-effectiveness ratio (ICER) [120-122]. The ICER, calculated as the difference in mean costs between new (ie, AT) and ST divided by the difference in mean effectiveness between the two, estimates the additional resources needed to achieve an increase in one unit of effectiveness. We will use 2 commonly used effectiveness measures—number of quitters and years of life saved (YOLS) [123], to compare the ICER with other published cost-effectiveness analyses. The number of quitters in each arm will be retrieved from the 12-month self-reported abstinence assessment. We will extrapolate from abstinence to YOLS using a published algorithm that models YOLS per quitter [124]. The algorithm will be revised using current estimates of age-specific smoking-attributable deaths [125]. We will also include quality-adjusted life-years, which will be calculated based on a measure of health utilities, the EQ-5D-5L [61].

We will also use the net benefit approach [126,127], which transforms the ICER into a net benefit, defined as $NB(\lambda) = \lambda \times \Delta E - \Delta C$, where λ represents the societal willingness to pay, ΔC represents the incremental costs, and ΔE represents the incremental effectiveness. A benefit of the net benefit approach is that it can be incorporated into a regression framework to allow for covariate adjustments and the examination of interaction effects [128].

Moreover, we will assess the short- and long-term economic impact of the interventions. The short-term analysis will use the number of quitters and quality-adjusted life-years as the effectiveness measure and assess cost-effectiveness based on information collected at the 3-, 6-, and 12-month follow-ups. The long-term analysis will extrapolate the intervention effect to lifetime and use YOLS. A 3% discount rate will be applied to costs and outcomes accrued in the second year and forward. We will first perform a deterministic analysis, where point estimates of ICERs or cost differences will be calculated. To obtain the 95% CIs, we will apply nonparametric bootstrapping methods to the person-level data [129]. We will conduct

one-way sensitivity analyses to examine the impact of alternative measures of cost and outcomes. We will then apply the Bayesian approach to construct the cost-effectiveness acceptability curve and conduct a probabilistic sensitivity analysis [130,131]. We will conduct Bayesian analysis using WinBUGS (University of Cambridge) or STATA (StataCorp LLC), with costs modeled as a gamma or log-normal distribution and abstinence as a binomial distribution. Finally, we will apply a regression-based cost-effectiveness analysis. Individual-level net benefit will be regressed on covariates, plus a binary variable reflecting AT versus ST. The model will be analyzed using generalized linear mixed models to examine cost-effectiveness over time.

Missing Data and Dropouts

Although treating individuals lost to follow-up as presumed smoking is a widely used strategy in smoking cessation studies (ie, intention-to-treat), there are potential problems with this approach, especially when comparing interventions with differential dropout rates [132]. Therefore, we will conduct sensitivity analyses to test for treatment efficacy, assuming different missing data mechanisms. For example, we will consider a multiple imputation approach based on smoking-related participant characteristics at baseline, as well as demographics, to account for potential missing-at-random mechanisms. We will also explore pattern-mixture and selection models to account for potential missing-not-at-random mechanisms [133].

Power Considerations

Because an intention-to-treat approach will be used for our primary analysis, and participants lost to follow-up will be classified as smokers, our power calculation assumes a sample size of 500 (250/500, 50% per group). Power is based on the primary aim of comparing self-reported abstinence rates between AT and ST at the 12-month follow-up [134]. On the basis of findings from our AAC implementation study [24,25], we expect 5% abstinence in ST. Assuming a sample size of 250 per group, a 2-group large-sample normal approximation test of proportions with a 2-sided 0.05 significance level will have 80% power to detect an increase in abstinence of 7% in AT compared with ST. Simulation studies using similar and smaller samples have demonstrated that bootstrap resampling approaches are more powerful than other approaches for estimating indirect effects and conditional indirect effects [135-137]. Therefore, we expect to have sufficient power to detect effects.

Results

This study was funded in 2019 and approved by the institutional review board at Moffitt Cancer Center in 2019. The intervention content has been finalized, and participant recruitment and enrollment will begin in the fall of 2021.

Discussion

Implications of the Study

This project is designed to evaluate a fully automated smartphone intervention for people with HIV who smoke. Participants (N=500) will be randomized to receive either ST or AT. ST participants will be connected to the Florida Quitline and receive 10 weeks of NRT. ST (referred to as AAC) was developed by our team and has been successfully implemented in numerous health systems. ST will be compared with AT, a fully AT delivery approach. AT participants will receive 10 weeks of NRT plus an interactive smartphone-based intervention that comprises individually tailored audiovisual and text content. Our primary goal is to determine whether AT performs better in terms of facilitating long-term smoking abstinence (ie, 12 months postenrollment) than ST, the more resource-intensive approach. We will also explore potential mediators and moderators and conduct economic evaluations to assess the cost and cost-effectiveness of AT compared with ST. If successful, the AT intervention could be readily and cost-effectively disseminated to HIV care facilities and to a variety of outreach programs and community-based networks targeting people with HIV who smoke.

Several components of this project are novel. Despite the high smoking prevalence among people with HIV, efficacious and sustainable treatment choices are limited [19]. A consideration in the design of this study was the potential of the intervention to have a significant public health impact, while requiring relatively modest resources and removing treatment barriers. We will recruit participants using web-based advertisements, and participants will complete screening, baseline, and follow-up assessments either on the web or over the phone. Moreover, both interventions will be delivered remotely. ST will include smoking cessation treatment delivered by the Florida Quitline, and AT will consist of a fully automated smartphone intervention with proactive and user-initiated components. AT will make use of smartphone technology, including dynamically tailored audiovisual and text content, to boost treatment intensity, while enhancing accessibility, improving treatment engagement, and limiting participant burden. Finally, conducting an RCT to assess the efficacy of AT with a comprehensive economic evaluation alongside the RCT will contribute to future smoking cessation initiatives for people with HIV and the use of mobile health.

Limitations

This study has several limitations. First, participants will consist of people with HIV who smoke recruited from the state of Florida, which might limit the generalizability of our findings. Second, participants will be recruited using only web-based advertisements; however, we believe that using web-based (vs in-person) recruitment strategies will enhance study interest and participation, particularly during the pandemic. Third, eligible participants are required to have a smartphone with a data plan and operating system compatible with the project app. Thus, individuals who do not meet this criterion will not be included. As previously mentioned, about 85% of US adults report owning a smartphone [32], so we do not expect this to significantly affect generalizability. Moreover, we will compensate participants for costs accrued due to study-related smartphone use.

Conclusions

There is a critical need for efficacious, cost-effective, and sustainable smoking cessation treatments for people with HIV.

The AT intervention is designed to help fill this need. The scientific premise for this project is built on the following: (1) cigarette smoking among people with HIV is a pressing public health problem; (2) available cessation treatments may not be meeting the needs—in terms of reach, efficacy, sustainability, affordability, and impact—of people with HIV who smoke; (3) US smartphone ownership is almost ubiquitous; (4) smartphone treatments offer tremendous reach and may be an ideal modality for people with HIV who smoke; and (5) smartphone interventions offer great dissemination and sustainability potential owing to their widespread use.

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Authors' Contributions

All authors contributed to the design of this study and participated in the preparation and review of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer Review Report from the National Cancer Institute Special Emphasis Panel - Improving Smoking Cessation Interventions Among People Living with HIV (R01 and R21) AIDS (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 165 KB - resprot_v10i11e33183_app1.pdf]

References

1. Creamer MR, Wang TW, Babb S, Cullen KA, Day H, Willis G, et al. Tobacco product use and cessation indicators among adults - United States, 2018. MMWR Morb Mortal Wkly Rep 2019 Nov 15;68(45):1013-1019 [FREE Full text] [doi: 10.15585/mmwr.mm6845a2] [Medline: 31725711]
2. Frazier EL, Sutton MY, Brooks JT, Shouse RL, Weiser J. Trends in cigarette smoking among adults with HIV compared with the general adult population, United States - 2009-2014. Prev Med 2018 Jun;111:231-234. [doi: 10.1016/j.ypmed.2018.03.007] [Medline: 29550303]
3. Mdodo R, Frazier EL, Dube SR, Mattson CL, Sutton MY, Brooks JT, et al. Cigarette smoking prevalence among adults with HIV compared with the general adult population in the United States: cross-sectional surveys. Ann Intern Med 2015 Mar 03;162(5):335-344. [doi: 10.7326/M14-0954] [Medline: 25732274]
4. Helleberg M, Afzal S, Kronborg G, Larsen C, Pedersen G, Pedersen C, et al. Mortality attributable to smoking among HIV-1-infected individuals: a nationwide, population-based cohort study. Clin Infect Dis 2013 Mar;56(5):727-734. [doi: 10.1093/cid/cis933] [Medline: 23254417]
5. Helleberg M, May M, Ingle S, Dabis F, Reiss P, Fätkenheuer G, et al. Smoking and life expectancy among HIV-infected individuals on antiretroviral therapy in Europe and North America. AIDS 2015 Jan 14;29(2):221-229 [FREE Full text] [doi: 10.1097/QAD.0000000000000540] [Medline: 25426809]
6. Lifson AR, Neuhaus J, Arribas JR, van den Berg-Wolf M, Labriola AM, Read TR, INSIGHT SMART Study Group. Smoking-related health risks among persons with HIV in the Strategies for Management of Antiretroviral Therapy clinical trial. Am J Public Health 2010 Oct;100(10):1896-1903 [FREE Full text] [doi: 10.2105/AJPH.2009.188664] [Medline: 20724677]
7. Shirley DK, Kaner RJ, Glesby MJ. Effects of smoking on non-AIDS-related morbidity in HIV-infected patients. Clin Infect Dis 2013 Jul;57(2):275-282 [FREE Full text] [doi: 10.1093/cid/cit207] [Medline: 23572487]
8. Reddy KP, Kong CY, Hyle EP, Baggett TP, Huang M, Parker RA, et al. Lung cancer mortality associated with smoking and smoking cessation among people living with HIV in the United States. JAMA Intern Med 2017 Nov 01;177(11):1613-1621 [FREE Full text] [doi: 10.1001/jamainternmed.2017.4349] [Medline: 28975270]
9. Reynolds NR. Cigarette smoking and HIV: more evidence for action. AIDS Educ Prev 2009 Jun;21(3 Suppl):106-121 [FREE Full text] [doi: 10.1521/aeap.2009.21.3_supp.106] [Medline: 19537958]
10. Rahmanian S, Wewers ME, Koletar S, Reynolds N, Ferketich A, Diaz P. Cigarette smoking in the HIV-infected population. Proc Am Thorac Soc 2011 Jun;8(3):313-319 [FREE Full text] [doi: 10.1513/pats.201009-058WR] [Medline: 21653534]
11. Nahvi S, Cooperman NA. Review: the need for smoking cessation among HIV-positive smokers. AIDS Educ Prev 2009 Jun;21(3 Suppl):14-27 [FREE Full text] [doi: 10.1521/aeap.2009.21.3_supp.14] [Medline: 19537951]

12. van Zyl Smit RN, Pai M, Yew WW, Leung CC, Zumla A, Bateman ED, et al. Global lung health: the colliding epidemics of tuberculosis, tobacco smoking, HIV and COPD. Eur Respir J 2010 Jan;35(1):27-33 [FREE Full text] [doi: 10.1183/09031936.00072909] [Medline: 20044459]
13. Feldman JG, Minkoff H, Schneider MF, Gange SJ, Cohen M, Watts DH, et al. Association of cigarette smoking with HIV prognosis among women in the HAART era: a report from the women's interagency HIV study. Am J Public Health 2006 Jun;96(6):1060-1065. [doi: 10.2105/AJPH.2005.062745] [Medline: 16670229]
14. Crothers K, Griffith TA, McGinnis KA, Rodriguez-Barradas MC, Leaf DA, Weissman S, et al. The impact of cigarette smoking on mortality, quality of life, and comorbid illness among HIV-positive veterans. J Gen Intern Med 2005 Dec;20(12):1142-1145 [FREE Full text] [doi: 10.1111/j.1525-1497.2005.0255.x] [Medline: 16423106]
15. Ledgerwood DM, Yskes R. Smoking cessation for people living with HIV/AIDS: a literature review and synthesis. Nicotine Tob Res 2016 Dec;18(12):2177-2184 [FREE Full text] [doi: 10.1093/ntr/ntw126] [Medline: 27245237]
16. Pacek LR, Cioe PA. Tobacco use, use disorders, and smoking cessation interventions in persons living with HIV. Curr HIV/AIDS Rep 2015 Dec;12(4):413-420 [FREE Full text] [doi: 10.1007/s11904-015-0281-9] [Medline: 26391516]
17. Pacek LR, Crum RM. A review of the literature concerning HIV and cigarette smoking: morbidity and mortality, associations with individual- and social-level characteristics, and smoking cessation efforts. Addict Res Theory 2015 Feb;23(1):10-23 [FREE Full text] [doi: 10.3109/16066359.2014.920013] [Medline: 28529471]
18. Cropsey K, Jardin B, Burkholder G, Clark C, Raper J, Saag M. An algorithm approach to determining smoking cessation treatment for persons living with HIV/AIDS: results of a pilot trial. J Acquir Immune Defic Syndr 2015 Jul 01;69(3):291-298 [FREE Full text] [doi: 10.1097/QAI.0000000000000579] [Medline: 26181705]
19. Pool ER, Dogar O, Lindsay RP, Weatherburn P, Siddiqi K. Interventions for tobacco use cessation in people living with HIV and AIDS. Cochrane Database Syst Rev 2016 Jun 13(6):CD011120. [doi: 10.1002/14651858.CD011120.pub2] [Medline: 27292836]
20. Gritz E, Danysh H, Fletcher F, Tami-Maury I, Fingeret M, King R, et al. Long-term outcomes of a cell phone-delivered intervention for smokers living with HIV/AIDS. Clin Infect Dis 2013 Aug;57(4):608-615 [FREE Full text] [doi: 10.1093/cid/cit349] [Medline: 23704120]
21. Vidrine DJ, Marks RM, Arduino RC, Gritz ER. Efficacy of cell phone-delivered smoking cessation counseling for persons living with HIV/AIDS: 3-month outcomes. Nicotine Tob Res 2012 Jan;14(1):106-110 [FREE Full text] [doi: 10.1093/ntr/ntr121] [Medline: 21669958]
22. Vidrine JI, Shete S, Cao Y, Greisinger A, Harmonson P, Sharp B, et al. Ask-Advise-Connect: a new approach to smoking treatment delivery in health care settings. JAMA Intern Med 2013 Mar 25;173(6):458-464 [FREE Full text] [doi: 10.1001/jamainternmed.2013.3751] [Medline: 23440173]
23. Vidrine JI, Shete S, Li Y, Cao Y, Alford MH, Galindo-Talton M, et al. The Ask-Advise-Connect approach for smokers in a safety net healthcare system: a group-randomized trial. Am J Prev Med 2013 Dec;45(6):737-741 [FREE Full text] [doi: 10.1016/j.amepre.2013.07.011] [Medline: 24237916]
24. Bui D, Piñeiro B, Vidrine D, Wetter D, Frank-Pearce S, Vidrine J. Quitline treatment enrollment and cessation outcomes among smokers linked with treatment via ask-advise-connect: comparisons among smokers with and without HIV. Nicotine Tob Res 2020 Aug 24;22(9):1640-1643 [FREE Full text] [doi: 10.1093/ntr/ntz227] [Medline: 31811295]
25. Piñeiro B, Vidrine D, Wetter D, Hoover D, Frank-Pearce S, Nguyen N, et al. Implementation of Ask-Advise-Connect in a safety net healthcare system: quitline treatment engagement and smoking cessation outcomes. Transl Behav Med 2020 Feb 03;10(1):163-167 [FREE Full text] [doi: 10.1093/tbm/iby108] [Medline: 30476236]
26. Tobacco quitline calls it quits. NPR Illinois. 2015. URL: https://www.nprillinois.org/post/tobacco-quitline-calls-it-quits#stream/0 [accessed 2021-08-26]
27. Barry M, Saul J, Bailey L. U.S. quitlines at a crossroads: utilization, budget, and service trends 2005–2010. North American Quitline Consortium. 2010. URL: https://cdn.ymaws.com/www.naquitline.org/resource/resmgr/reports_2010/100407_executive-summary.pdf [accessed 2021-10-06]
28. Tobacco quitlines suffer from budget cuts. American Family Physician Community Blog. 2011. URL: http://afpjournal.blogspot.com/2011/07/tobacco-quitlines-suffer-from-budget.html [accessed 2021-08-26]
29. Fu SS, van Ryn M, Nelson D, Burgess DJ, Thomas JL, Saul J, et al. Proactive tobacco treatment offering free nicotine replacement therapy and telephone counselling for socioeconomically disadvantaged smokers: a randomised clinical trial. Thorax 2016 May;71(5):446-453 [FREE Full text] [doi: 10.1136/thoraxjnl-2015-207904] [Medline: 26931362]
30. Mann N, Nonnemaker J, Chapman L, Shaikh A, Thompson J, Juster H. Comparing the New York state smokers' quitline reach, services offered, and quit outcomes to 44 other state quitlines, 2010 to 2015. Am J Health Promot 2018 Jun;32(5):1264-1272. [doi: 10.1177/0890117117724898] [Medline: 28805074]
31. Reddy KP, Parker RA, Losina E, Baggett TP, Paltiel AD, Rigotti NA, et al. Impact of cigarette smoking and smoking cessation on life expectancy among people with HIV: a US-based modeling study. J Infect Dis 2016 Dec 01;214(11):1672-1681 [FREE Full text] [doi: 10.1093/infdis/jiw430] [Medline: 27815384]
32. Mobile fact sheet. Pew Research Center. 2021. URL: https://www.pewresearch.org/internet/fact-sheet/mobile/ [accessed 2021-08-26]

33. Scott-Sheldon LA, Lantini R, Jennings EG, Thind H, Rosen RK, Salmoirago-Blotcher E, et al. Text messaging-based interventions for smoking cessation: a systematic review and meta-analysis. JMIR Mhealth Uhealth 2016 May 20;4(2):e49 [FREE Full text] [doi: 10.2196/mhealth.5436] [Medline: 27207211]
34. Free C, Knight R, Robertson S, Whittaker R, Edwards P, Zhou W, et al. Smoking cessation support delivered via mobile phone text messaging (txt2stop): a single-blind, randomised trial. Lancet 2011 Jul 02;378(9785):49-55 [FREE Full text] [doi: 10.1016/S0140-6736(11)60701-0] [Medline: 21722952]
35. Whittaker R, McRobbie H, Bullen C, Rodgers A, Gu Y, Dobson R. Mobile phone text messaging and app-based interventions for smoking cessation. Cochrane Database Syst Rev 2019 Oct 22;10(10):CD006611 [FREE Full text] [doi: 10.1002/14651858.CD006611.pub5] [Medline: 31638271]
36. Tseng T, Krebs P, Schoenthaler A, Wong S, Sherman S, Gonzalez M, et al. Combining text messaging and telephone counseling to increase varenicline adherence and smoking abstinence among cigarette smokers living with HIV: a randomized controlled study. AIDS Behav 2017 Jul;21(7):1964-1974 [FREE Full text] [doi: 10.1007/s10461-016-1538-z] [Medline: 27605365]
37. Guerriero C, Cairns J, Roberts I, Rodgers A, Whittaker R, Free C. The cost-effectiveness of smoking cessation support delivered by mobile phone text messaging: Txt2stop. Eur J Health Econ 2013 Oct;14(5):789-797 [FREE Full text] [doi: 10.1007/s10198-012-0424-5] [Medline: 22961230]
38. Cobos-Campos R, Mar J, Apiñaniz A, de Lafuente AS, Parraza N, Aizpuru F, et al. Cost-effectiveness analysis of text messaging to support health advice for smoking cessation. Cost Eff Resour Alloc 2021 Feb 15;19(1):9 [FREE Full text] [doi: 10.1186/s12962-021-00262-y] [Medline: 33588885]
39. West R, Raw M, McNeill A, Stead L, Aveyard P, Bitton J, et al. Health-care interventions to promote and assist tobacco cessation: a review of efficacy, effectiveness and affordability for use in national guideline development. Addiction 2015 Sep;110(9):1388-1403 [FREE Full text] [doi: 10.1111/add.12998] [Medline: 26031929]
40. Abroms LC, Lee Westmaas J, Bontemps-Jones J, Ramani R, Mellerson J. A content analysis of popular smartphone apps for smoking cessation. Am J Prev Med 2013 Dec;45(6):732-736 [FREE Full text] [doi: 10.1016/j.amepre.2013.07.008] [Medline: 24237915]
41. Haskins BL, Lesperance D, Gibbons P, Boudreaux ED. A systematic review of smartphone applications for smoking cessation. Transl Behav Med 2017 Jun;7(2):292-299 [FREE Full text] [doi: 10.1007/s13142-017-0492-2] [Medline: 28527027]
42. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, REDCap Consortium. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019 Jul;95:103208 [FREE Full text] [doi: 10.1016/j.jbi.2019.103208] [Medline: 31078660]
43. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 Apr;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
44. Persons with an HIV diagnosis in Florida, 2019. Florida Health. URL: http://www.floridahealth.gov/diseases-and-conditions/aids/index.html [accessed 2021-10-06]
45. Reitzel LR, Mazas CA, Cofta-Woerpel L, Vidrine JI, Businelle MS, Kendzor DE, et al. Acculturative and neighborhood influences on subjective social status among Spanish-speaking Latino immigrant smokers. Soc Sci Med 2010 Mar;70(5):677-683 [FREE Full text] [doi: 10.1016/j.socscimed.2009.11.024] [Medline: 20044186]
46. McClure J, Westbrook E, Curry S, Wetter D. Proactive, motivationally enhanced smoking cessation counseling among women with elevated cervical cancer risk. Nicotine Tob Res 2005 Dec;7(6):881-889. [doi: 10.1080/14622200500266080] [Medline: 16298723]
47. Resource guide: screening for drug use in general medical settings. National Institute on Drug Abuse. URL: https://archives.drugabuse.gov/publications/resource-guide-screening-drug-use-in-general-medical-settings/nida-quick-screen [accessed 2021-08-26]
48. Alcohol use and alcohol use disorders in the United States: main findings from the 2012-2013 National Epidemiologic Survey on Alcohol and Related Conditions -III (NESARC-III). U.S. Alcohol Epidemiological Data Reference Manual. 2016. URL: https://pubs.niaaa.nih.gov/publications/NESARC_DRM3/NESARC3DRM.pdf [accessed 2021-10-29]
49. Hughes J, Keely J, Niaura R, Ossip-Klein D, Richmond R, Swan G. Measures of abstinence in clinical trials: issues and recommendations. Nicotine Tob Res 2003 Feb;5(1):13-25. [Medline: 12745503]
50. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. Br J Addict 1991 Sep;86(9):1119-1127. [doi: 10.1111/j.1360-0443.1991.tb01879.x] [Medline: 1932883]
51. Pearlin LI, Menaghan EG, Lieberman MA, Mullan JT. The stress process. J Health Soc Behav 1981 Dec;22(4):337-356. [doi: 10.2307/2136676]
52. Biener L, Abrams DB. The Contemplation Ladder: validation of a measure of readiness to consider smoking cessation. Health Psychol 1991;10(5):360-365. [doi: 10.1037//0278-6133.10.5.360] [Medline: 1935872]
53. Curry SJ, Wagner EH, Grothaus LC. Evaluation of intrinsic and extrinsic motivation interventions with a self-help smoking cessation program. J Consult Clin Psychol 1991 Apr;59(2):318-324. [doi: 10.1037//0022-006x.59.2.318] [Medline: 2030194]

54. Mirowsky J, Ross CE. Eliminating defense and agreement bias from measures of the sense of control: a 2 X 2 index. Soc Psychol Q 1991 Jun;54(2):127-145. [doi: 10.2307/2786931]
55. Velicer WF, Diclemente CC, Rossi JS, Prochaska JO. Relapse situations and self-efficacy: an integrative model. Addict Behav 1990;15(3):271-283. [doi: 10.1016/0306-4603(90)90070-e] [Medline: 2378287]
56. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983 Dec;24(4):385-396. [Medline: 6668417]
57. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988 Jun;54(6):1063-1070. [doi: 10.1037//0022-3514.54.6.1063] [Medline: 3397865]
58. Robles G, Paez F. Study of Spanish translation and psychometric properties of the Positive and Negative Affect Scales (PANAS). Salud Ment 2003;26(1):69-75 [FREE Full text]
59. Kroenke K, Strine TW, Spitzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord 2009 Apr;114(1-3):163-173. [doi: 10.1016/j.jad.2008.06.026] [Medline: 18752852]
60. Larsen DL, Attkisson C, Hargreaves WA, Nguyen TD. Assessment of client/patient satisfaction: development of a general scale. Eval Program Plann 1979;2(3):197-207. [doi: 10.1016/0149-7189(79)90094-6] [Medline: 10245370]
61. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011 Dec;20(10):1727-1736 [FREE Full text] [doi: 10.1007/s11136-011-9903-x] [Medline: 21479777]
62. Wilson IB, Lee Y, Michaud J, Fowler FJ, Rogers WH. Validation of a new three-item self-report measure for medication adherence. AIDS Behav 2016 Nov;20(11):2700-2708 [FREE Full text] [doi: 10.1007/s10461-016-1406-x] [Medline: 27098408]
63. Justice A, Holmes W, Gifford A, Rabeneck L, Zackin R, Sinclair G, Adult AIDS Clinical Trials Unit Outcomes Committee. Development and validation of a self-completed HIV symptom index. J Clin Epidemiol 2001 Dec;54 Suppl 1:S77-S90. [doi: 10.1016/s0895-4356(01)00449-8] [Medline: 11750213]
64. Smith BW, Dalen J, Wiggins K, Tooley E, Christopher P, Bernard J. The brief resilience scale: assessing the ability to bounce back. Int J Behav Med 2008;15(3):194-200. [doi: 10.1080/10705500802222972] [Medline: 18696313]
65. Wright K, Naar-King S, Lam P, Templin T, Frey M. Stigma scale revised: reliability and validity of a brief measure of stigma for HIV+ youth. J Adolesc Health 2007 Jan;40(1):96-98 [FREE Full text] [doi: 10.1016/j.jadohealth.2006.08.001] [Medline: 17185215]
66. Blair JM, Fagan JL, Frazier EL, Do A, Bradley H, Valverde EE, National Center for HIV/AIDS, Viral Hepatitis, STD,TB Prevention, CDC. Behavioral and clinical characteristics of persons receiving medical care for HIV infection - Medical Monitoring Project, United States, 2009. MMWR Suppl 2014 Jun 20;63(5):1-22. [Medline: 24941443]
67. Moriarty DG, Zack MM, Kobau R. The Centers for Disease Control and Prevention's Healthy Days Measures - population tracking of perceived physical and mental health over time. Health Qual Life Outcomes 2003 Sep 02;1:37 [FREE Full text] [doi: 10.1186/1477-7525-1-37] [Medline: 14498988]
68. Mielenz T, Jackson E, Currey S, DeVellis R, Callahan LF. Psychometric properties of the Centers for Disease Control and Prevention Health-Related Quality of Life (CDC HRQOL) items in adults with arthritis. Health Qual Life Outcomes 2006 Sep 24;4:66 [FREE Full text] [doi: 10.1186/1477-7525-4-66] [Medline: 16995955]
69. Adler NE, Epel ES, Castellazzo G, Ickovics JR. Relationship of subjective and objective social status with psychological and physiological functioning: preliminary data in healthy white women. Health Psychol 2000 Nov;19(6):586-592. [doi: 10.1037//0278-6133.19.6.586] [Medline: 11129362]
70. Hughes ME, Waite LJ, Hawkley LC, Cacioppo JT. A short scale for measuring loneliness in large surveys: results from two population-based studies. Res Aging 2004;26(6):655-672 [FREE Full text] [doi: 10.1177/0164027504268574] [Medline: 18504506]
71. Krieger N, Smith K, Naishadham D, Hartman C, Barbeau EM. Experiences of discrimination: validity and reliability of a self-report measure for population health research on racism and health. Soc Sci Med 2005 Oct;61(7):1576-1596. [doi: 10.1016/j.socscimed.2005.03.006] [Medline: 16005789]
72. Hays RD, Bjorner JB, Revicki DA, Spritzer KL, Cella D. Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. Qual Life Res 2009 Sep;18(7):873-880 [FREE Full text] [doi: 10.1007/s11136-009-9496-9] [Medline: 19543809]
73. Prochaska JO, DiClemente CC. Stages of change in the modification of problem behaviors. Prog Behav Modif 1992;28:183-218. [Medline: 1620663]
74. Prochaska JO, DiClemente CC, Norcross JC. In search of how people change. Applications to addictive behaviors. Am Psychol 1992 Sep;47(9):1102-1114. [doi: 10.1037//0003-066x.47.9.1102] [Medline: 1329589]
75. Sciamanna CN, Hoch JS, Duke GC, Fogle MN, Ford DE. Comparison of five measures of motivation to quit smoking among a sample of hospitalized smokers. J Gen Intern Med 2000 Jan;15(1):16-23 [FREE Full text] [doi: 10.1046/j.1525-1497.2000.11198.x] [Medline: 10632829]
76. Donovan DM. Relapse Prevention: Maintenance Strategies in the Treatment of Addictive Behaviors. 2nd edition. New York: Guilford Press; 2005.

77. Witkiewitz K, Marlatt GA. Relapse prevention for alcohol and drug problems: that was Zen, this is Tao. Am Psychol 2004;59(4):224-235. [doi: 10.1037/0003-066X.59.4.224] [Medline: 15149263]
78. DiClemente CC, Prochaska JO, Fairhurst SK, Velicer WF, Velasquez MM, Rossi JS. The process of smoking cessation: an analysis of precontemplation, contemplation, and preparation stages of change. J Consult Clin Psychol 1991 Apr;59(2):295-304. [doi: 10.1037//0022-006x.59.2.295] [Medline: 2030191]
79. Shiffman S, Balabanis MH, Paty JA, Engberg J, Gwaltney CJ, Liu KS, et al. Dynamic effects of self-efficacy on smoking lapse and relapse. Health Psychol 2000 Jul;19(4):315-323. [doi: 10.1037//0278-6133.19.4.315] [Medline: 10907649]
80. Shiffman S, Paty JA, Gnys M, Kassel JA, Hickcox M. First lapses to smoking: within-subjects analysis of real-time reports. J Consult Clin Psychol 1996 Apr;64(2):366-379. [doi: 10.1037//0022-006x.64.2.366] [Medline: 8871421]
81. Ajzen I. The theory of planned behavior. Organ Behav Hum Decis Process 1991 Dec;50(2):179-211. [doi: 10.1016/0749-5978(91)90020-t]
82. Hughes JR, Keely JP, Fagerstrom KO, Callas PW. Intentions to quit smoking change over short periods of time. Addict Behav 2005 May;30(4):653-662. [doi: 10.1016/j.addbeh.2004.08.011] [Medline: 15833571]
83. Hopkins PD, Spears CA, Hoover DS, Li L, Cambron C, Potter LN, et al. Trajectories of motivation and self-efficacy during a smoking quit attempt: an ecological momentary assessment study. Psychol Addict Behav 2021 Aug 26:- (forthcoming). [doi: 10.1037/adb0000734] [Medline: 34435832]
84. Werner J, Lovering A, Herzog TA. Measuring time frames for intentions to quit smoking. In: Proceedings of the 11th annual meeting of the Society for Research on Nicotine and Tobacco. 2004 Presented at: 11th annual meeting of the Society for Research on Nicotine and Tobacco; 2004; Scottsdale, AZ URL: https://cdn.ymaws.com/srnt.site-ym.com/resource/resmgr/Conferences/Past_Annual_Meetings/2004_Annual_Meeting_Abstract.pdf
85. Larabie LC. To what extent do smokers plan quit attempts? Tob Control 2005 Dec;14(6):425-428 [FREE Full text] [doi: 10.1136/tc.2005.013615] [Medline: 16319368]
86. West R. Theory of Addiction. 1st edition. Hoboken, New Jersey: John Wiley & Sons; 2006.
87. Adamson SJ, Sellman JD, Frampton CM. Patient predictors of alcohol treatment outcome: a systematic review. J Subst Abuse Treat 2009 Jan;36(1):75-86. [doi: 10.1016/j.jsat.2008.05.007] [Medline: 18657940]
88. Bandura A. Toward a psychology of human agency. Perspect Psychol Sci 2006 Jun;1(2):164-180. [doi: 10.1111/j.1745-6916.2006.00011.x] [Medline: 26151469]
89. Bandura A. Self-efficacy mechanism in human agency. Am Psychol 1982;37(2):122-147. [doi: 10.1037/0003-066X.37.2.122]
90. Mirowsky J, Ross CE. Education, health, and the default American lifestyle. J Health Soc Behav 2015 Sep;56(3):297-306. [doi: 10.1177/0022146515594814] [Medline: 26272989]
91. Ross CE, Wu C. The links between education and health. Am Soc Rev 1995 Oct;60(5):719-745. [doi: 10.2307/2096319]
92. Cinciripini PM, Wetter DW, Fouladi RT, Blalock JA, Carter BL, Cinciripini LG, et al. The effects of depressed mood on smoking cessation: mediation by postcessation self-efficacy. J Consult Clin Psychol 2003 Apr;71(2):292-301. [doi: 10.1037/0022-006x.71.2.292] [Medline: 12699023]
93. Burgess ES, Brown RA, Kahler CW, Niaura R, Abrams DB, Goldstein MG, et al. Patterns of change in depressive symptoms during smoking cessation: who's at risk for relapse? J Consult Clin Psychol 2002 Apr;70(2):356-361 [FREE Full text] [doi: 10.1037//0022-006x.70.2.356] [Medline: 11952193]
94. Piasecki TM, Jorenby DE, Smith SS, Fiore MC, Baker TB. Smoking withdrawal dynamics: I. Abstinence distress in lapsers and abstainers. J Abnorm Psychol 2003 Feb;112(1):3-13. [Medline: 12653409]
95. Glassman AH, Helzer JE, Covey LS, Cottler LB, Stetner F, Tipp JE, et al. Smoking, smoking cessation, and major depression. JAMA 1990 Sep 26;264(12):1546-1549. [Medline: 2395194]
96. Wetter DW, Kenford SL, Smith SS, Fiore MC, Jorenby DE, Baker TB. Gender differences in smoking cessation. J Consult Clin Psychol 1999 Aug;67(4):555-562. [doi: 10.1037//0022-006x.67.4.555] [Medline: 10450626]
97. Piasecki TM, Fiore MC, Baker TB. Profiles in discouragement: two studies of variability in the time course of smoking withdrawal symptoms. J Abnorm Psychol 1998 May;107(2):238-251. [doi: 10.1037//0021-843x.107.2.238] [Medline: 9604553]
98. Borrelli B, Bock B, King T, Pinto B, Marcus BH. The impact of depression on smoking cessation in women. Am J Prev Med 1996;12(5):378-387. [Medline: 8909649]
99. Niaura R, Britt D, Borrelli B, Shadel W, Abrams D, Goldstein M. History and symptoms of depression among smokers during a self-initiated quit attempt. Nicotine Tob Res 1999 Sep;1(3):251-257. [doi: 10.1080/14622299050011371] [Medline: 11072422]
100. Ziedonis D, Hitsman B, Beckham JC, Zvolensky M, Adler LE, Audrain-McGovern J, et al. Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. Nicotine Tob Res 2008 Dec;10(12):1691-1715. [doi: 10.1080/14622200802443569] [Medline: 19023823]
101. Piper ME, Smith SS, Schlam TR, Fleming MF, Bittrich AA, Brown JL, et al. Psychiatric disorders in smokers seeking treatment for tobacco dependence: relations with tobacco dependence and cessation. J Consult Clin Psychol 2010 Feb;78(1):13-23 [FREE Full text] [doi: 10.1037/a0018065] [Medline: 20099946]

102. Balfour L, Wiebe SA, Cameron WD, Sandre D, Pipe A, Cooper C, et al. An HIV-tailored quit-smoking counselling pilot intervention targeting depressive symptoms plus Nicotine Replacement Therapy. AIDS Care 2017 Jan;29(1):24-31. [doi: 10.1080/09540121.2016.1201195] [Medline: 27435835]
103. Piasecki T, Fiore M, McCarthy D, Baker T. Have we lost our way? The need for dynamic formulations of smoking relapse proneness. Addiction 2002 Sep;97(9):1093-1108. [doi: 10.1046/j.1360-0443.2002.00216.x] [Medline: 12199822]
104. Crittenden KS, Manfredi C, Cho YI, Dolecek TA. Smoking cessation processes in low-SES women: the impact of time-varying pregnancy status, health care messages, stress, and health concerns. Addict Behav 2007 Jul;32(7):1347-1366 [FREE Full text] [doi: 10.1016/j.addbeh.2006.09.009] [Medline: 17097815]
105. Siahpush M, Borland R, Taylor J, Singh GK, Ansari Z, Serraglio A. The association of smoking with perception of income inequality, relative material well-being, and social capital. Soc Sci Med 2006 Dec;63(11):2801-2812. [doi: 10.1016/j.socscimed.2006.07.015] [Medline: 16971030]
106. Vidrine D, Frank S, Savin M, Waters A, Li Y, Chen S, et al. HIV care initiation: a teachable moment for smoking cessation? Nicotine Tob Res 2018 Aug 14;20(9):1109-1116 [FREE Full text] [doi: 10.1093/ntr/ntx218] [Medline: 29059424]
107. Vidrine DJ, Arduino RC, Gritz ER. The effects of smoking abstinence on symptom burden and quality of life among persons living with HIV/AIDS. AIDS Patient Care STDS 2007 Sep;21(9):659-666. [doi: 10.1089/apc.2007.0022] [Medline: 17919093]
108. Aigner CJ, Gritz ER, Tamí-Maury I, Baum GP, Arduino RC, Vidrine DJ. The role of pain in quitting among human immunodeficiency virus (HIV)-positive smokers enrolled in a smoking cessation trial. Subst Abus 2017;38(3):249-252 [FREE Full text] [doi: 10.1080/08897077.2017.1291466] [Medline: 28328303]
109. King RM, Vidrine DJ, Danysh HE, Fletcher FE, McCurdy S, Arduino RC, et al. Factors associated with nonadherence to antiretroviral therapy in HIV-positive smokers. AIDS Patient Care STDS 2012 Aug;26(8):479-485 [FREE Full text] [doi: 10.1089/apc.2012.0070] [Medline: 22612468]
110. Gamarel KE, Neilands TB, Dilworth SE, Taylor JM, Johnson MO. Smoking, internalized heterosexism, and HIV disease management among male couples. AIDS Care 2015 Dec;27(5):649-654 [FREE Full text] [doi: 10.1080/09540121.2014.991269] [Medline: 25506724]
111. Lyons A, Heywood W, Rozbroj T. Psychosocial factors associated with resilience in a national community-based cohort of Australian gay men living with HIV. AIDS Behav 2016 Aug;20(8):1658-1666. [doi: 10.1007/s10461-016-1338-5] [Medline: 26884311]
112. Fiore M, Bailey W, Cohen S, Dorfman S, Goldstein M, Gritz E. Treating Tobacco Use and Dependence: Clinical Practice Guideline. Rockland, MD: US Department of Health and Human Services, Public Health Service; 2000:1587630079.
113. McCullagh P, Nelder J. Generalized Linear Models. 2nd edition. Boca Raton, FL: Chapman and Hall/CRC; 1989.
114. McCulloch C, Searle S, Neahaus J. Generalized, Linear, and Mixed Models. New York, NY: John Wiley & Sons; 2008.
115. Westfall P, Young S. Resampling-Based Multiple Testing: Examples and Methods for p-Value Adjustment. New York: John Wiley & Sons; 1993.
116. MacKinnon D. Introduction to Statistical Mediation Analysis. New York, NY: Routledge; 2008.
117. Hayes AF. Beyond Baron and Kenny: statistical mediation analysis in the new millennium. Commun Monographs 2009 Dec;76(4):408-420. [doi: 10.1080/03637750903310360]
118. Preacher KJ, Hayes AF. SPSS and SAS procedures for estimating indirect effects in simple mediation models. Behav Res Methods Instrum Comput 2004 Nov;36(4):717-731. [doi: 10.3758/BF03206553]
119. Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods 2008 Aug;40(3):879-891. [doi: 10.3758/brm.40.3.879] [Medline: 18697684]
120. Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. JAMA 2016 Sep 13;316(10):1093-1103. [doi: 10.1001/jama.2016.12195] [Medline: 27623463]
121. Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. Methods for the Economic Evaluation of Health Care Programmes. 3rd ed. New York: Oxford University Press; 2005.
122. Neumann PJ, Ganiats TG, Russell L, Sanders GD, Siegel JE. Cost-Effectiveness in Health and Medicine. New York, NY: Oxford University Press; 2016.
123. Ronckers ET, Groot W, Ament A. Systematic review of economic evaluations of smoking cessation: standardizing the cost-effectivenes. Med Decis Making 2016 Sep 05;25(4):437-448. [doi: 10.1177/0272989x05278431]
124. Oster G, Huse D, Delea T, Colditz G. Cost-effectiveness of nicotine gum as an adjunct to physician's advice against cigarette smoking. JAMA 1986 Sep 12;256(10):1315-1318. [Medline: 3091857]
125. Holford TR, Meza R, Warner KE, Meernik C, Jeon J, Moolgavkar SH, et al. Tobacco control and the reduction in smoking-related premature deaths in the United States, 1964-2012. JAMA 2014 Jan 08;311(2):164-171 [FREE Full text] [doi: 10.1001/jama.2013.285112] [Medline: 24399555]
126. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. Med Decis Making 1998;18(2 Suppl):S68-S80. [doi: 10.1177/0272989X98018002S09] [Medline: 9566468]
127. Tambour M, Zethraeus N, Johannesson M. A note on confidence intervals in cost-effectiveness analysis. Int J Technol Assess Health Care 1998;14(3):467-471. [doi: 10.1017/s0266462300011442] [Medline: 9780533]

128. Hoch JS, Briggs AH, Willan AR. Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis. Health Econ 2002 Jul;11(5):415-430. [doi: 10.1002/hec.678] [Medline: 12112491]
129. Glick HA, Doshi JA, Sonnad SS, Polsky D. Economic Evaluation in Clinical Trials. New York: OUP Oxford; 2014.
130. O'Hagan A, Stevens JW. The probability of cost-effectiveness. BMC Med Res Methodol 2002 Mar 11;2(1):5 [FREE Full text] [doi: 10.1186/1471-2288-2-5] [Medline: 11914138]
131. Shih YT. Bayesian approach in pharmacoeconomics: relevance to decision-makers. Expert Rev Pharmacoecon Outcomes Res 2003 Jun;3(3):237-250. [doi: 10.1586/14737167.3.3.237] [Medline: 19807372]
132. Nelson D, Partin M, Fu S, Joseph A, An L. Why assigning ongoing tobacco use is not necessarily a conservative approach to handling missing tobacco cessation outcomes. Nicotine Tob Res 2009 Jan;11(1):77-83. [doi: 10.1093/ntr/ntn013] [Medline: 19246444]
133. Little R, Rubin D. Statistical Analysis with Missing Data. 2nd edition. New York, NY: John Wiley & Sons; 2014.
134. Velicer WF, Prochaska JO, Rossi JS, Snow MG. Assessing outcome in smoking cessation studies. Psychol Bull 1992 Jan;111(1):23-41. [doi: 10.1037/0033-2909.111.1.23] [Medline: 1539088]
135. Preacher KJ, Rucker DD, Hayes AF. Addressing moderated mediation hypotheses: theory, methods, and prescriptions. Multivariate Behav Res 2007;42(1):185-227. [doi: 10.1080/00273170701341316] [Medline: 26821081]
136. Fritz MS, Mackinnon DP. Required sample size to detect the mediated effect. Psychol Sci 2007 Mar 04;18(3):233-239 [FREE Full text] [doi: 10.1111/j.1467-9280.2007.01882.x] [Medline: 17444920]
137. Creedon PJ, Hayes AF. Small sample mediation analysis: how far can we push the bootstrap. In: Proceedings of the Annual conference of the Association for Psychological Science. 2015 Presented at: Annual conference of the Association for Psychological Science; 2015; New York URL: https://www.psychologicalscience.org/convention/program_2015/pdf/Poster Session X.pdf

Abbreviations

AAC: Ask Advise Connect
AT: automated treatment
ICER: incremental cost-effectiveness ratio
NRT: nicotine replacement therapy
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
ST: standard treatment
YOLS: years of life saved

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Protocol

Effective Treatment Strategies for the Removal of Antibiotic-Resistant Bacteria, Antibiotic-Resistance Genes, and Antibiotic Residues in the Effluent From Wastewater Treatment Plants Receiving Municipal, Hospital, and Domestic Wastewater: Protocol for a Systematic Review

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Abstract

Background: The widespread and unrestricted use of antibiotics has led to the emergence and spread of antibiotic-resistant bacteria (ARB), antibiotic-resistance genes (ARGs), and antibiotic residues in the environment. Conventional wastewater treatment plants (WWTPs) are not designed for effective and adequate removal of ARB, ARGs, and antibiotic residues, and therefore, they play an important role in the dissemination of antimicrobial resistance (AMR) in the natural environment.

Objective: We will conduct a systematic review to determine the most effective treatment strategies for the removal of ARB, ARGs, and antibiotic residues from the treated effluent disposed into the environment from WWTPs that receive municipal, hospital, and domestic discharge.

Methods: We will search the MEDLINE, EMBASE, Web of Science, World Health Organization Global Index Medicus, and ProQuest Environmental Science Collection databases for full-text peer-reviewed journal articles published between January 2001 and December 2020. We will select only articles published in the English language. We will include studies that measured (1) the presence, concentration, and removal rate of ARB/ARGs going from WWTP influent to effluent, (2) the presence, concentration, and types of antibiotics in the effluent, and (3) the possible selection of ARB in the effluent after undergoing treatment processes in WWTPs. At least two independent reviewers will extract data and perform risk of bias assessment. An acceptable or narrative synthesis method will be followed to synthesize the data and present descriptive characteristics of the included studies in a tabular form. The study has been approved by the Ethics Review Board at the International Centre for Diarrhoeal Disease Research, Bangladesh (protocol number: PR-20113).

Results: This protocol outlines our proposed methodology for conducting a systematic review. Our results will provide an update to the existing literature by searching additional databases.

Conclusions: Findings from our systematic review will inform the planning of proper treatment methods that can effectively reduce the levels of ARB, ARGs, and residual antibiotics in effluent, thus lowering the risk of the environmental spread of AMR and its further transmission to humans and animals.

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KEYWORDS

antimicrobial resistance; antimicrobial-resistant bacteria; antibiotic-resistant bacteria; antimicrobial-resistance genes; antibiotic-resistance genes; antibiotics; antibiotic residues; wastewater treatment plant; effluent; systematic review

Introduction

The role of the environment in contributing to the spread of antimicrobial resistance (AMR) is being recognized on a global scale due to the growing threat it poses to public health. The rapid increase in AMR is rendering even the last generation of antibiotics as useless to treat common infections [1,2]. This has resulted in increased rates of mortality, prolonged hospitalization, and increased health care costs [3]. The widespread and unrestricted use of antibiotics in humans and animals has led to the emergence of antibiotic-resistant bacteria (ARB) and antibiotic-resistance genes (ARGs) by the release of antibiotic residues in the environment through untreated fecal waste [4].

Wastewater serves as one of the largest reservoirs of ARB, ARGs, and antibiotic residues, which have originated from humans, animals, and environments [5,6]. In high-income countries, wastewater resulting from domestic sewage and agricultural runoff is collected at wastewater treatment plants (WWTPs), which are designed to treat wastewater depending on the contaminants in the influent and guidelines for effluent quality [7-9]. Some low-income countries, such as Nigeria, Ethiopia, and South Sudan, do not have WWTPs [10-12]. Low- and middle-income countries (LMICs) usually have WWTPs; however, functionality concerns are common. For example, in India, 54% of WWTPs are operating poorly [12]. LMICs are only able to treat around 28% of the generated wastewater, whereas high-income countries can treat around 70% [13]. WWTPs present in LMICs have often not been designed for the proper removal of ARB, ARGs, and antibiotics [10,14], as evident from ARB and ARGs being detected in wastewater effluent [15,16]. Fecal sludge generated during wastewater treatment is also a major source of ARB, such as extended-spectrum β-lactamase–producing *Escherichia coli* [17]. Discharge of wastewater effluent and fecal sludge containing ARB, ARGs, and antibiotic residues into the environment allows for the dissemination of AMR to other bacteria present in the natural environment. This process is known as horizontal gene transfer, where genetic information is exchanged between neighboring bacteria, leading to increased levels of AMR among populations [15,18].

In addition, wastewater discharged from pharmaceutical industries contains a complex array of contaminants, including antibiotic residues, hormones, toxic substances, and organic compounds, that require novel treatment methods, such as the recent membrane-integrated hybrid technology, which has proven more effective than conventional technologies [19]. However, many pharmaceutical companies around the world continue to conceal the nature and extent of the toxicity of the substances they generate, thus escaping regulations and disposing hazardous waste into the environment [19]. On-site treatment of pharmaceutical waste before release into the sewer system requires technologies that are expensive [10]. In addition to the lack of financial resources and adequate treatment facilities, pharmaceutical companies in LMICs exploit the absence of proper regulatory enforcement and are thus unwilling to employ such methods [20].

Antibiotic residues have been found in greater concentrations in the raw influent of WWTPs in Asian countries, including Japan, China, South Korea, India, Taiwan, Hong Kong, Thailand, Malaysia, Singapore, and Vietnam, compared with European and North American countries [21]. At least nine commonly used antibiotic classes, such as beta-lactams, lincosamides, tetracycline family, vancomycin, chloramphenicol, sulfonamides, fluoroquinolones, macrolides, and trimethoprim, were found in WWTP influent [21]. Antibiotic concentrations found in both influent and effluent from WWTPs reached or exceeded the predicted no-effect concentrations required for resistance selection [21]. A study conducted in India in 2007 found that the effluent from a WWTP receiving waste streams from 90 drug manufacturing companies released a quantity of ciprofloxacin in a single day that was equivalent to the amount sufficient to treat the entire population of Sweden for 5 days [22]. The presence of antibiotics in lethal or sublethal concentrations creates a selective pressure among the bacterial communities present in wastewater, allowing them to acquire resistance through horizontal gene transfer [23].

Conventional wastewater treatment processes combine physical, chemical, and biological treatment levels for the removal of solids and organic matter. The primary sedimentation tank releases effluent for secondary treatment using aerobic biological processes, such as activated sludge processes, trickling filters or biofilters, oxidation ditches, and rotating biological contactors [24]. Afterward, wastewater effluent undergoes tertiary treatment through a disinfection process. One of the most common disinfection methods used at WWTPs is chlorination [25]. These treatment methods have various limitations, including feasibility, efficiency, reliability, environmental impact, sludge production, operation difficulty, pretreatment

requirements, and the formation of potentially toxic by-products [26]. High chlorination, treatment costs, long treatment periods, and lack of availability of large areas for WWTP setup are some of the limitations of many chemical-based and biological treatment processes [27]. Inability to remove contaminants, such as ARB, ARGs, and antibiotic residues, poses additional challenges for these conventional processes, proving their effectiveness to be limited in the last 20 years [28].

Therefore, new and additional wastewater treatment technologies have been introduced and have been evaluated for their level of effectiveness in the reduction of ARB/ARGs and antibiotic residues from effluent [29]. Some of these novel processes include membrane filtration systems, UV radiation, ozonation, automatic variable filtration, advanced oxidation processes, and nanotechnology with improved membranes providing efficient energy recovery systems [28,30]. A study comparing the ARB/ARG removal efficiency between chlorination and UV disinfection of wastewater found that consecutive treatment with UV followed by chlorination resulted in a significant reduction in ARGs, in contrast with the application of either method alone [31], whereas, for drinking water treatment, either method led to the effective inactivation of bacterial cells [32]. No single technology alone can obliterate ARB, ARGs, and antibiotic residues in WWTPs [27,33]. To date, many articles have examined the presence or abundance of ARB, ARGs, and antibiotics in the effluent of WWTPs that receive municipal, domestic, hospital, and industrial discharge [33-38]. However, to the best of our knowledge, no study has investigated effective treatment strategies for the removal of ARB, ARGs, and antibiotic residues in WWTPs that simultaneously receive municipal, domestic, and hospital discharge. A knowledge gap also persists in the prevalence of antibiotic residues in wastewater effluents that create selective pressure for bacteria to acquire resistance, which we aim to address through this review.

Therefore, our objective is to compare the efficiency of different new and conventional wastewater treatment methods for reducing the level of ARB/ARGs in effluent and to assess the presence, concentration, and types of antibiotic residues that are released in effluent from WWTPs receiving municipal, domestic, and hospital wastewater. Through the findings of this review, we aim to determine the rate of removal of ARB, ARGs, and antibiotic residues via various wastewater treatment methods, which will eventually allow us to compare the efficiencies of the different methods. The findings will also provide insights into the extent of contamination of ARB, ARGs, and antibiotic residues in water bodies receiving treated wastewater effluent that may pose health risks to humans exposed to those sites. In addition, we aim to determine if wastewater treatment processes in WWTPs promote the selection of ARB despite an effective decrease in the total number of bacteria. Furthermore, a review of the existing level of efficacy of WWTPs will inform future design guidelines for improving wastewater treatment methods in WWTPs that can adequately eliminate ARB, ARGs, and antibiotic residues before environmental release.

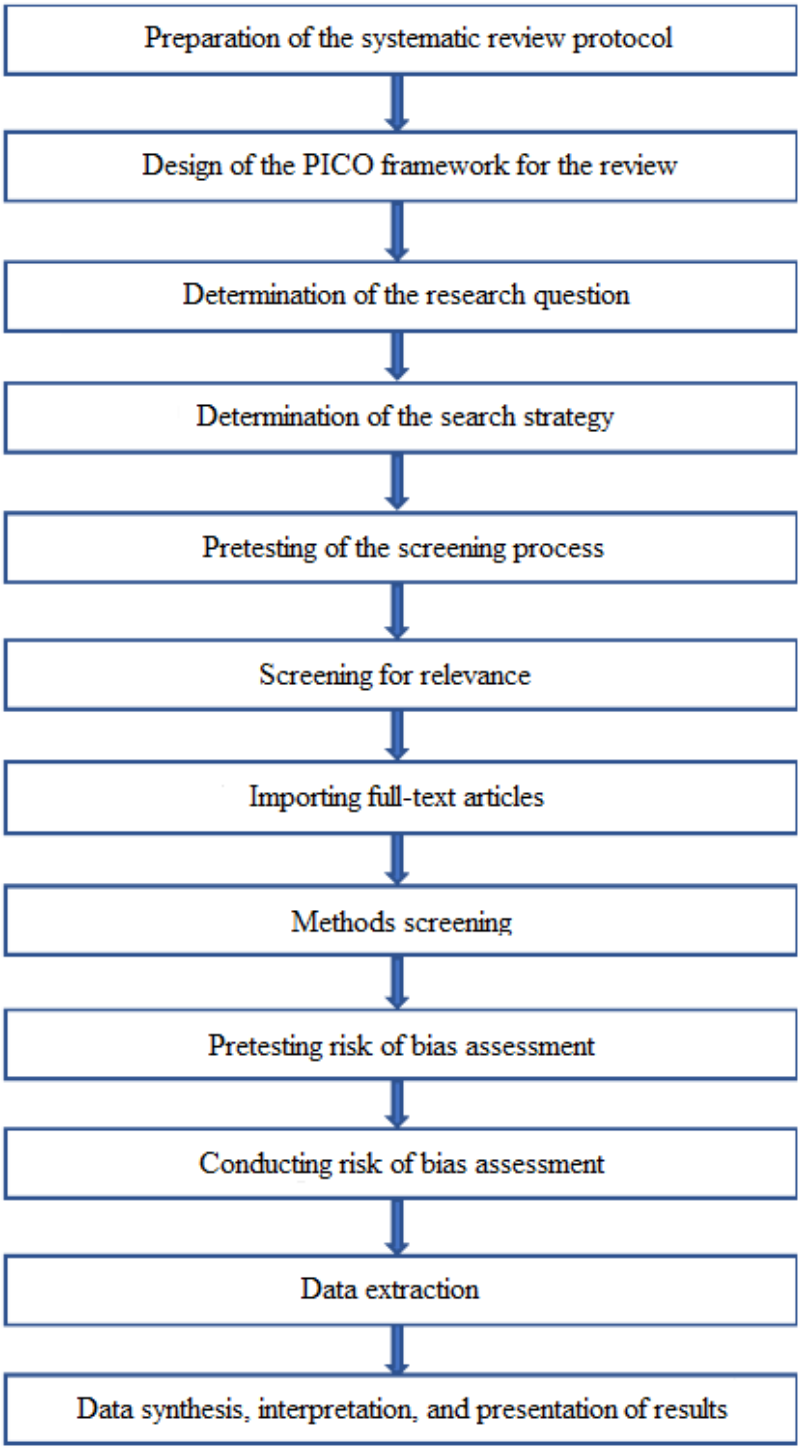
Methods

Overview

This systematic review will identify and evaluate various treatment methods in WWTPs that receive municipal, hospital, and domestic discharge with regard to the extent of removal of ARB, ARGs, and antibiotic residues in the effluent released to the environment. We will screen articles for eligibility, perform quality assessment of the studies, extract data, and synthesize the evidence from the published scientific literature (Figure 1).

Textbox 1 outlines the objectives, eligibility criteria, and data sources to be used for the review. The research objectives have been designed following the PICO (population, intervention, comparison, and outcome) framework [39]. Furthermore, we aim to conduct the systematic review by following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist [40].

Figure 1. Flow diagram of the steps for conducting the systematic review. PICO: population, intervention, comparison, and outcome.



Textbox 1. Eligibility protocol for the systematic review.

Research Question

What are the most effective wastewater treatment strategies in wastewater treatment plants (WWTPs) for the removal of antibiotic-resistant bacteria (ARB), antibiotic-resistance genes (ARGs), and antibiotic residues in the resulting effluent?

Objectives

- To determine the removal rate of ARB/ARGs in WWTPs that receive municipal, hospital, and domestic wastewater and compare between conventional treatment strategies and new/alternative treatment strategies (eg, presence or absence of disinfection process)

- To assess the presence, concentration, and types of antibiotics in the effluent of WWTPs

- To determine if wastewater treatment processes in WWTPs promote the selection of ARB despite an effective decrease in the total number of bacteria

Search Strategy

Inclusion Criteria

- Relation of various WWTP treatment methods with antimicrobial resistance

- Estimation of the rate of removal of ARB/ARGs

- Presence and concentration of ARB/ARGs in the influent and effluent from WWTPs that receive municipal, hospital, and domestic discharge

- Presence and concentration of antibiotic residues

- Types of antibiotic residues in the effluent from WWTPs that receive municipal, hospital, and domestic discharge

- Full-text article from a peer-reviewed journal, and other grey materials

- English language

Exclusion Criteria

- No inclusion of wastewater treatment methods

- No assessment of ARB or ARGs in the influent and effluent from WWTPs that receive municipal, hospital, and domestic discharge

- No assessment of the presence/concentration of antibiotics in the effluent of WWTPs

- Involvement of WWTPs that receive wastewater from agricultural or industrial/commercial origin, discharge from animal farms or slaughter houses, and only municipal, domestic, or hospital wastewater

- No mention of the types of wastewater that were received by the WWTP

- Collection of pretreated influent samples

- Sample collection during a high epidemic situation

- Pilot/lab-scale studies, books, reviews, guidelines, and survey studies

Time Frame

January 2001 to December 2020

Data Sources

Peer-reviewed Articles

Ovid MEDLINE, Ovid EMBASE, Web of Science, World Health Organization Global Index Medicus, and ProQuest Environmental Science Collection

Grey Literature

Google Scholar and Trove

Population

The population of interest will not be specific to any groups, categories, or locations. Studies that assess the presence and/or abundance of ARB, ARGs, and antibiotic residues in treated WWTP effluent in any population will be included.

Interventions

Interventions will include the wastewater treatment methods employed at WWTPs that receive municipal, hospital, and domestic wastewater, with respect to the removal of ARB/ARGs and antibiotic residues from the effluent that is discharged into receiving water bodies from the treatment plant.

Comparison

We will compare conventional and new wastewater treatment strategies to assess the efficiency of different wastewater treatment methods in reducing the levels of ARB, ARGs, and antibiotic residues from effluent. We consider conventional treatment methods as a combination of processes, including physical, chemical, and biological methods for removing solids and organic matter, and new/additional treatment methods as those that provide integrational alternatives for the treatment of wastewater for reducing contaminants.

Outcomes

The main outcomes to be explored in this systematic review are as follows: (1) The removal rate of ARB/ARGs from WWTPs that receive 3 types of wastewater, and comparison between conventional treatment strategies and new/additional treatment strategies (eg, presence or absence of disinfection processes); (2) The presence, concentration, and types of antibiotic residues in the effluent; and (3) Whether wastewater treatment processes in WWTPs promote the selection of ARB despite an effective decrease in the total number of bacteria.

Sources of Information

The research team will search several scientific electronic databases for peer-reviewed articles and grey literature to identify published articles according to the search terms for the review.

Databases will include Ovid MEDLINE, Ovid EMBASE, Web of Science, World Health Organization Global Index Medicus (WHO GIM), and ProQuest Environmental Science Collection. Searches for grey literature will be conducted through Google Scholar and Trove. The reference lists of all the included studies will also be searched manually by the researchers to identify any relevant articles for inclusion in the review and for improving the comprehensiveness of the search. Since the review will be based on samples from influent and effluent generated from WWTPs to determine the removal rate of ARB, ARGs, and antibiotic residues, which will help us to determine the treatment methodologies that have a comparative advantage, we will not include any existing review articles on the relevant topic.

Studies that have been published or accepted for publication will be included since limited data from conference proceedings may not allow an in-depth assessment of the studies [41,42] and will be limited to those that have been published within the years 2001-2020. The time frame limitation has been added since studies related to AMR published prior to 2001 did not have an environmental focus. The review will also be limited to English articles that are available in international databases and on websites. However, a certain level of bias may be introduced due to the language restriction, although few studies claim that excluding non-English literature does not have a large effect on systematic reviews and meta-analyses [43,44].

Search Strategy

The search strategy used for the Ovid MEDLINE database has been shown in Table 1. For the other databases, the search strategy will be adjusted according to the instructions of each database.

Table 1. Search strategy used for the MEDLINE database.

Number	Search[a]	Results, n
1	Antibiotic residue$.mp.	1052
2	Antibiotic resistan$ bacteria.mp.	3338
3	antibiotic resistance gene$.mp.	5460
4	antimicrobial resistan$ organism$.mp.	161
5	antimicrobial resistan$ pathogen$.mp.	267
6	ARB selection.mp.	2
7	Anti-Microbial Agent$.mp.	399
8	Wastewater treat$.mp.	23,724
9	Graywater treat$.mp.	9
10	Greywater treat$.mp.	92
11	wastewater treat$ plant$.mp.	10,628
12	wastewater treatment method$.mp.	105
13	conventional wastewater treatment process$.mp.	69
14	new wastewater treatment process$.mp.	11
15	effluent.mp.	29,387
16	influent.mp.	7430
17	Antimicrobial resistance gene$.mp.	1566
18	antimicrobial resistan$.mp.	25,483
19	antibiotic resistan$.mp.	45,671
20	plasmid$.mp.	184,995
21	Sewage treatment.mp.	3861
22	1 or 2 or 3 or 4 or 5 or 6 or 7 or 17 or 18 or 19 or 20	245,158
23	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 21	52,791
24	22 and 23	1397
25	limit 24 to yr="2001 -Current"	1324
26	limit 25 to english language	1296

[a]In the search, mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, and synonyms.

Data Management

The articles retrieved from database searching will be imported to EndNote X9 to identify and remove duplicates. Remaining entries will be evaluated using the inclusion and exclusion criteria. The list of retrieved full-text articles will be exported from EndNote to the web-based application Rayyan QCRI, which will be used for carrying out the screening process [45]. Following the PRISMA guidelines, we will select articles in 4 phases following the flow of the diagram as follows: (1) identification, (2) screening, (3) eligibility, and (4) inclusion [46].

Study Selection

During the study selection process, titles and abstracts of the articles will be screened to shortlist them according to relevance to the objectives under the research question. Two reviewers will screen titles and abstracts independently. The decision for including or excluding articles will be finalized by the 2 reviewers, after reaching a common level of understanding for each article, and a third reviewer will provide approval and resolve disagreements, should any arise. The shortlisted articles will be screened for eligibility in order to determine if they fulfill the objectives of the review, and critical appraisal will be conducted subsequently.

We will use a standardized set of questions that have been adapted from previous studies [42,47,48] for selecting articles to include or exclude for the systematic review. The questions for screening studies for relevance are as follows: (1) Does the abstract refer to primary research published in a peer-reviewed journal or as grey literature (eg, thesis)? (2) Does the study assess the presence, abundance, or concentration of ARB, ARGs, or antibiotic residues in the influent and effluent of WWTPs? (3) Does the study report the removal rate of ARB, ARGs, or antibiotic residues going from influent to effluent? (4) Were the samples collected from the effluent of WWTPs that received municipal, domestic, and hospital discharge?

Articles for which the answer is “Yes” to any of the questions from 1 through 3 and “Yes” for question 4 will be shortlisted from the relevance screening phase for full-text review. Articles for which the answer is “No” for question 4 will be excluded and will not be considered for additional review. Literature for which the answer to the first 3 questions cannot be determined through screening of the abstracts and titles will be considered for further full-text screening. These articles will be classified as “maybe” in Rayyan QCRI software for further discussion among the reviewers in order to reach a mutual decision regarding inclusion. After finalizing the list of articles from the relevance screening phase, we will screen the methods of the included studies against the objectives of the review for data extraction.

Data Extraction

To increase the reliability of the process, data extraction will be carried out by at least two reviewers who will collaboratively work on the selected articles. Findings extracted will be inputted into a standardized data extraction form on MS Excel spreadsheet (Microsoft Corp) that will be piloted before use. The form will include key points, findings, and a summary of the included studies based on the review objectives. The extracted data will be grouped into the following categories: (1) characteristics of the study (location, study design, and sample size), (2) type of source (location and characteristics of WWTPs), (3) type of sample (quality of samples, ARB or ARGs analyzed, and effluent or influent analyzed), and (4) comparators (types of treatment methods analyzed, and the removal rate, presence, and concentration of ARB/ARGs/antibiotics for each method).

Quality Assessment

We will perform risk of bias assessment at the study design level through adapting the previously published tool by Williams-Nguyen et al [47]. The risk of bias in each domain will be categorized as “low,” “high,” and “unclear” according to the Cochrane Collaboration Risk of Bias Tool [49]. Two reviewers will independently assess the quality of the included studies. Before the full assessment, the risk of bias tool (Table 2) will be pretested by both reviewers on several included papers to improve interpretation agreement and ensure consistency of data entry. Discrepancies will be resolved by discussion, and a third reviewer will be consulted if necessary.

Table 2. Risk of bias tool.

Bias domain	Assessment question	Criteria
Sample selection bias	Were sample locations and sampling methods implementing such that sampling did not introduce systematic differences depending on the value of the exposure variable for each sample (in the case of continuous exposure data) or between the comparison groups (in the case of categorical exposure measures)?	1. Criteria for the judgement of "Yes" (low risk): • Method for determining the sampling locations is identical and independent of exposure status (ie, sample taken from the influent and final effluent of the WWTP[a]) • The WWTP receives only municipal, hospital, and domestic wastewater regardless of differences in treatment methods or treatment stages (primary, secondary, or tertiary) • Influent wastewater does not have any form of pretreatment before being discharged in the WWTP • The time between sampling at all sites is sufficiently close to render the outcomes measured at these sites comparable for the sample type in question • Collection of 24-h composite samples • The authors describe the frequency of sampling (daily, weekly, monthly, etc) at each site • The authors describe the volume of collected samples from the influent and effluent of the WWTP 2. Criteria for the judgement of "No" (high risk): • Sampling locations are selected differently (eg, samples taken from the effluent of the grit chamber, aeration tank, and secondary clarifier) • The WWTP does not receive municipal, hospital, and domestic wastewater regardless of differences in treatment methods or treatment stages (primary, secondary, or tertiary) • Influent wastewaters have some form of pretreatment before being discharged in the WWTP • Time between sampling at all sites is not sufficiently close • Collection of grab samples • Collection of grab samples • The authors do not describe the frequency of sampling (daily, weekly, monthly, etc) at each site • The authors do not describe the volume of collected samples 3. Risk of bias will be considered "unclear" if there is not enough information to judge sample selection bias criteria as either "yes" or "no." For example, if methods for determining sampling locations are not described in enough detail.
Information bias	Were outcome ascertainment methods (ie, methods for antibiotic-resistance gene, antibiotic-resistant bacteria, and antibiotic or bacterial measurements) conducted in a way that ensures the same accuracy regardless of wastewater sample type?	1. Criteria for the judgement of "Yes" (low risk): • Identical microbiological methods are applied to all samples (ie, influent and effluent samples) for ARB[b], ARG[c], and antibiotic detection (eg, culture, polymerase chain reaction, genotyping, phenotypic tests, mass spectrometry, and high-performance liquid chromatography). • Controlling for different laboratory factors (eg, laboratory type, technician, testing date, and instrument used) 2. Criteria for the judgement of "No" (high risk): • Application of different methods depending on the comparison group • No adjustment strategy for different laboratory methods 3. Risk of bias will be considered "unclear" if there is not enough information to judge information bias criteria as either "yes" or "no." For example, if methods for analyses are not explained sufficiently to reach a judgement.

Bias domain	Assessment question	Criteria
Confounding	Were adequate methods to control for potential confounding employed?	1. Criteria for the judgement of "Yes" (low risk): • Restriction of the sample population (eg, samples are not collected on a rainy day and instead collected on a dry day) • Samples are collected in different seasons (eg, winter and summer) • Analytical confounding control (eg, stratification, regression adjustment, and test samples are stored correctly) 2. Criteria for the judgement of "No" (high risk): • The sample population is not restricted (eg, samples are collected on a rainy day) • Lack of any confounding control despite being likely (eg, samples are not collected in different seasons [winter and summer] and no consideration of water salinity) • Inappropriate method of confounding control (eg, test samples are not stored correctly) • Controlling for confounding is correctly applied for some potential confounders, but not for all 3. Risk of bias will be considered "unclear" if there is not enough information to judge information bias criteria as either "yes" or "no." For example, if methods to control for confounding are mentioned but the implementation is not explained sufficiently at length to reach a judgement.

[a]WWTP: wastewater treatment plant.

[b]ARB: antibiotic-resistant bacteria.

[c]ARG: antibiotic-resistance gene.

Evidence Synthesis

The reviewers will decide on the aspects of the study for data synthesis by considering accuracy, limitations, and the approach used to assess the effectiveness of the wastewater treatment methods. An acceptable or narrative synthesis method will be followed to synthesize data based on the objectives of the research question, which will be presented in a tabular form. Descriptive characteristics of the study, including study design, location, year, sample type, and quality, as well as variables analyzed in the study, will be provided. Outcomes of the study will be synthesized, which will allow for relevant comparison between treatment methods in WWTPs. Interpretation of the removal rate of the treatment processes for ARB/ARGs and antibiotic residues will be finalized for data synthesis depending on the outcomes in the included studies found after data extraction. We will also present the quality assessment of the included studies and mark the risks as "low," "high," and "unclear" in a tabular form. Heterogeneity in the included studies will be considered, and based on the type of findings an additional meta-analysis may be presented separately if sufficient high-quality homogenous studies are found that would allow findings to be pooled for a fixed- or random-effects meta-analysis.

Ethics Approval

The study was approved by the Ethics Review Board at the International Centre for Diarrhoeal Disease Research, Bangladesh (Protocol Number: PR-20113).

Results

We will start the review on December 1, 2021, and it will be completed by June 30, 2022. Our systematic review results will provide an update to the existing literature by searching on additional databases. Findings from our study will inform the planning of proper treatment methods that can effectively reduce the levels of ARB, ARGs, and residual antibiotics in effluent, thus lowering the risk of environmental spread of AMR and its further transmission to humans and animals.

Discussion

The protocol outlines our methods for a systematic review of the published scientific literature to determine the most effective treatment strategies in WWTPs that do not receive industrial wastewater for the removal of ARB, ARGs, and antibiotic residues from effluent. The provided flow diagram in Figure 1 will be followed as a guide for the review process for searching the literature using the specified keywords, screening phases of the shortlisted literature following the standardized questionnaire, conducting quality assessment of the studies, and finally conducting data extraction after retrieval of full-text articles for evidence synthesis.

A systematic review published in 2018 [50] on the role of WWTPs and agricultural facilities in the dissemination of ARB and ARGs in the natural environment explored outcomes that are closely related to this study. However, we aim to provide an update to the existing literature by searching other databases, such as Ovid MEDLINE, Ovid EMBASE, Web of Science, WHO GIM, and ProQuest Environmental Science Collection. This initiative will enrich the current level of understanding of the impact of ARB and ARGs focusing on effluents from WWTPs that receive municipal, hospital, and domestic wastewater.

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Authors' Contributions

MA, SF, AK, and SKL generated the research questions, and made final decisions on the inclusion and exclusion criteria. MA and SF prepared the first draft of the manuscript together with AK and SKL. AE, AL, MAI, RH, and MR provided their technical inputs that uplifted the draft manuscript. SKL, AK, SF, and FS prepared the data extraction plan together with all authors. RK, ZR, SMP, NA, AL, BTT, NT, MAI, MR, and RH critically reviewed the study design and data extraction plan. All the authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the International Centre for Diarrhoeal Disease Research, Bangladesh.
[PDF File (Adobe PDF File), 81 KB - resprot_v10i11e33365_app1.pdf]

References

1. Gashe F, Mulisa E, Mekonnen M, Zeleke G. Antimicrobial Resistance Profile of Different Clinical Isolates against Third-Generation Cephalosporins. J Pharm (Cairo) 2018 Sep 09;2018:5070742-5070747 [FREE Full text] [doi: 10.1155/2018/5070742] [Medline: 30271652]
2. Koulenti D, Xu E, Song A, Sum Mok IY, Karageorgopoulos DE, Armaganidis A, et al. Emerging Treatment Options for Infections by Multidrug-Resistant Gram-Positive Microorganisms. Microorganisms 2020 Jan 30;8(2):191 [FREE Full text] [doi: 10.3390/microorganisms8020191] [Medline: 32019171]
3. Friedman N, Temkin E, Carmeli Y. The negative impact of antibiotic resistance. Clin Microbiol Infect 2016 May;22(5):416-422 [FREE Full text] [doi: 10.1016/j.cmi.2015.12.002] [Medline: 26706614]
4. Burch TR, Sadowsky MJ, LaPara TM. Fate of antibiotic resistance genes and class 1 integrons in soil microcosms following the application of treated residual municipal wastewater solids. Environ Sci Technol 2014 May 20;48(10):5620-5627. [doi: 10.1021/es501098g] [Medline: 24762092]
5. Manaia CM, Rocha J, Scaccia N, Marano R, Radu E, Biancullo F, et al. Antibiotic resistance in wastewater treatment plants: Tackling the black box. Environ Int 2018 Jun;115:312-324. [doi: 10.1016/j.envint.2018.03.044] [Medline: 29626693]
6. Pal C, Bengtsson-Palme J, Kristiansson E, Larsson DGJ. The structure and diversity of human, animal and environmental resistomes. Microbiome 2016 Oct 07;4(1):54 [FREE Full text] [doi: 10.1186/s40168-016-0199-5] [Medline: 27717408]
7. Almakki A, Jumas-Bilak E, Marchandin H, Licznar-Fajardo P. Antibiotic resistance in urban runoff. Sci Total Environ 2019 Jun 01;667:64-76. [doi: 10.1016/j.scitotenv.2019.02.183] [Medline: 30826682]
8. Primer for Municipal Wastewater Treatment Systems. United States Environmental Protection Agency. URL: https://www3.epa.gov/npdes/pubs/primer.pdf [accessed 2021-06-14]
9. Raven K, Ludden C, Gouliouris T, Blane B, Naydenova P, Brown N, et al. Genomic surveillance of Escherichia coli in municipal wastewater treatment plants as an indicator of clinically relevant pathogens and their resistance genes. Microb Genom 2019 May;5(5) [FREE Full text] [doi: 10.1099/mgen.0.000267] [Medline: 31107200]
10. Nadimpalli M, Delarocque-Astagneau E, Love D, Price L, Huynh B, Collard J, Bacterial Infectionsantibiotic-Resistant Diseases among Young children in low-income countries (BIRDY) Study Group. Combating Global Antibiotic Resistance: Emerging One Health Concerns in Lower- and Middle-Income Countries. Clin Infect Dis 2018 Mar 05;66(6):963-969. [doi: 10.1093/cid/cix879] [Medline: 29346620]
11. Tackling drug-resistant infections globally: final report and recommendations. Review on Antimicrobial Resistance. 2016. URL: https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf [accessed 2021-05-12]
12. Functionality of wastewater treatment plants in low- and middle income countries. WaterAid. URL: https://washmatters.wateraid.org/sites/g/files/jkxoof256/files/functionality-of-wastewater-treatment-plants-in-low--and-middle-income-countries-desk-review_1.pdf [accessed 2021-06-10]
13. Sato T, Qadir M, Yamamoto S, Endo T, Zahoor A. Global, regional, and country level need for data on wastewater generation, treatment, and use. Agricultural Water Management 2013 Dec;130:1-13. [doi: 10.1016/j.agwat.2013.08.007]

14. Pruden A, Larsson DJ, Amézquita A, Collignon P, Brandt KK, Graham DW, et al. Management options for reducing the release of antibiotics and antibiotic resistance genes to the environment. Environ Health Perspect 2013 Aug;121(8):878-885 [FREE Full text] [doi: 10.1289/ehp.1206446] [Medline: 23735422]
15. Xu J, Xu Y, Wang H, Guo C, Qiu H, He Y, et al. Occurrence of antibiotics and antibiotic resistance genes in a sewage treatment plant and its effluent-receiving river. Chemosphere 2015 Jan;119:1379-1385. [doi: 10.1016/j.chemosphere.2014.02.040] [Medline: 24630248]
16. McConnell MM, Truelstrup Hansen L, Jamieson RC, Neudorf KD, Yost CK, Tong A. Removal of antibiotic resistance genes in two tertiary level municipal wastewater treatment plants. Sci Total Environ 2018 Dec 01;643:292-300. [doi: 10.1016/j.scitotenv.2018.06.212] [Medline: 29940441]
17. Berendes D, Kirby A, Brown J, Wester AL. Human faeces-associated extended-spectrum β-lactamase-producing Escherichia coli discharge into sanitation systems in 2015 and 2030: a global and regional analysis. Lancet Planet Health 2020 Jun;4(6):e246-e255 [FREE Full text] [doi: 10.1016/S2542-5196(20)30099-1] [Medline: 32559441]
18. Zhang Y, Zhuang Y, Geng J, Ren H, Zhang Y, Ding L, et al. Inactivation of antibiotic resistance genes in municipal wastewater effluent by chlorination and sequential UV/chlorination disinfection. Sci Total Environ 2015 Apr 15;512-513:125-132. [doi: 10.1016/j.scitotenv.2015.01.028] [Medline: 25616228]
19. Pal P. Treatment and Disposal of Pharmaceutical Wastewater: Toward the Sustainable Strategy. Separation & Purification Reviews 2017 Sep 11;47(3):179-198. [doi: 10.1080/15422119.2017.1354888]
20. Kookana RS, Williams M, Boxall ABA, Larsson DGJ, Gaw S, Choi K, et al. Potential ecological footprints of active pharmaceutical ingredients: an examination of risk factors in low-, middle- and high-income countries. Philos Trans R Soc Lond B Biol Sci 2014 Nov 19;369(1656):20130586 [FREE Full text] [doi: 10.1098/rstb.2013.0586] [Medline: 25405973]
21. Tran NH, Reinhard M, Gin KY. Occurrence and fate of emerging contaminants in municipal wastewater treatment plants from different geographical regions-a review. Water Res 2018 Apr 15;133:182-207. [doi: 10.1016/j.watres.2017.12.029] [Medline: 29407700]
22. Larsson DGJ. Pollution from drug manufacturing: review and perspectives. Philos Trans R Soc Lond B Biol Sci 2014 Nov 19;369(1656):20130571 [FREE Full text] [doi: 10.1098/rstb.2013.0571] [Medline: 25405961]
23. Marano RBM, Cytryn E. The Mobile Resistome in Wastewater Treatment Facilities and Downstream Environments. In: Keen PL, Fugère R, editors. Antimicrobial Resistance in Wastewater Treatment Processes. Hoboken, NJ: John Wiley & Sons, Inc; 2017:129-155.
24. Pescod MB. Wastewater Treatment and Use in Agriculture: No. 47 (FAO Irrigation and Drainage Paper). Rome, Italy: Food & Agriculture Organization of the United Nations; 1992.
25. Samer M. Biological and Chemical Wastewater Treatment Processes. In: Wastewater Treatment Engineering. London, United Kingdom: InTech Europe; 2015.
26. Crini G, Lichtfouse E. Advantages and disadvantages of techniques used for wastewater treatment. Environ Chem Lett 2018 Jul 31;17(1):145-155. [doi: 10.1007/s10311-018-0785-9]
27. Pei M, Zhang B, He Y, Su J, Gin K, Lev O, et al. State of the art of tertiary treatment technologies for controlling antibiotic resistance in wastewater treatment plants. Environ Int 2019 Oct;131:105026 [FREE Full text] [doi: 10.1016/j.envint.2019.105026] [Medline: 31351383]
28. Water Digest. URL: https://thewaterdigest.com/ [accessed 2021-07-02]
29. Sabri N, van Holst S, Schmitt H, van der Zaan B, Gerritsen H, Rijnaarts H, et al. Fate of antibiotics and antibiotic resistance genes during conventional and additional treatment technologies in wastewater treatment plants. Sci Total Environ 2020 Nov 01;741:140199 [FREE Full text] [doi: 10.1016/j.scitotenv.2020.140199] [Medline: 32615424]
30. Hassen A, Mahrouk M, Ouzari H, Cherif M, Boudabous A, Damelincourt JJ. UV disinfection of treated wastewater in a large-scale pilot plant and inactivation of selected bacteria in a laboratory UV device. Bioresource Technology 2000 Sep;74(2):141-150. [doi: 10.1016/s0960-8524(99)00179-0]
31. Destiani R, Templeton MR. Chlorination and ultraviolet disinfection of antibiotic-resistant bacteria and antibiotic resistance genes in drinking water. AIMS Environmental Science 2019;6(3):222-241. [doi: 10.3934/environsci.2019.3.222]
32. Stange C, Sidhu J, Toze S, Tiehm A. Comparative removal of antibiotic resistance genes during chlorination, ozonation, and UV treatment. Int J Hyg Environ Health 2019 Apr;222(3):541-548. [doi: 10.1016/j.ijheh.2019.02.002] [Medline: 30738743]
33. Gadipelly C, Pérez-González A, Yadav GD, Ortiz I, Ibáñez R, Rathod VK, et al. Pharmaceutical Industry Wastewater: Review of the Technologies for Water Treatment and Reuse. Ind. Eng. Chem. Res 2014 Jul 14;53(29):11571-11592. [doi: 10.1021/ie501210j]
34. Barancheshme F, Munir M. Strategies to Combat Antibiotic Resistance in the Wastewater Treatment Plants. Front Microbiol 2017 Jan 17;8:2603 [FREE Full text] [doi: 10.3389/fmicb.2017.02603] [Medline: 29387043]
35. Goic-Barisic I, Hrenovic J, Kovacic A, Musić M. Emergence of Oxacillinases in Environmental Carbapenem-Resistant Acinetobacter baumannii Associated with Clinical Isolates. Microb Drug Resist 2016 Oct;22(7):559-563. [doi: 10.1089/mdr.2015.0275] [Medline: 27705609]
36. Hassen B, Abbassi M, Ruiz-Ripa L, Mama O, Ibrahim C, Benlabidi S, et al. Genetic characterization of extended-spectrum β-lactamase-producing Enterobacteriaceae from a biological industrial wastewater treatment plant in Tunisia with detection

of the colistin-resistance mcr-1 gene. FEMS Microbiol Ecol 2021 Mar 10;97(3):1-9. [doi: 10.1093/femsec/fiaa231] [Medline: 33202005]
37. Topal M, Arslan Topal EI. Occurrence and fate of tetracycline and degradation products in municipal biological wastewater treatment plant and transport of them in surface water. Environ Monit Assess 2015 Dec 13;187(12):750. [doi: 10.1007/s10661-015-4978-4] [Medline: 26566643]
38. Varela AR, André S, Nunes OC, Manaia CM. Insights into the relationship between antimicrobial residues and bacterial populations in a hospital-urban wastewater treatment plant system. Water Res 2014 May 01;54:327-336. [doi: 10.1016/j.watres.2014.02.003] [Medline: 24583524]
39. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane Handbook for Systematic Reviews of Interventions, Second Edition. Hoboken, NJ: John Wiley & Sons; 2019.
40. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015 Jan 01;4(1):1 [FREE Full text] [doi: 10.1186/2046-4053-4-1] [Medline: 25554246]
41. O'Connor AM, Anderson KM, Goodell CK, Sargeant JM. Conducting systematic reviews of intervention questions I: Writing the review protocol, formulating the question and searching the literature. Zoonoses Public Health 2014 Jun 06;61 Suppl 1:28-38. [doi: 10.1111/zph.12125] [Medline: 24905994]
42. Rodríguez-Molina D, Mang P, Schmitt H, Chifiriuc M, Radon K, Wengenroth L. Do wastewater treatment plants increase antibiotic resistant bacteria or genes in the environment? Protocol for a systematic review. Syst Rev 2019 Dec 05;8(1):304-308 [FREE Full text] [doi: 10.1186/s13643-019-1236-9] [Medline: 31806019]
43. Jüni P, Holenstein F, Sterne J, Bartlett C, Egger M. Direction and impact of language bias in meta-analyses of controlled trials: empirical study. Int J Epidemiol 2002 Feb;31(1):115-123. [doi: 10.1093/ije/31.1.115] [Medline: 11914306]
44. Moher D, Pham B, Lawson M, Klassen T. The inclusion of reports of randomised trials published in languages other than English in systematic reviews. Health Technol Assess 2003 Dec;7(41):1-90 [FREE Full text] [doi: 10.3310/hta7410] [Medline: 14670218]
45. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016 Dec 05;5(1):210 [FREE Full text] [doi: 10.1186/s13643-016-0384-4] [Medline: 27919275]
46. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med 2018 Oct 02;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
47. Williams-Nguyen J, Bueno I, Sargeant JM, Nault AJ, Singer RS. What is the evidence that point sources of anthropogenic effluent increase antibiotic resistance in the environment? Protocol for a systematic review. Anim Health Res Rev 2016 Jun;17(1):9-15. [doi: 10.1017/S1466252316000037] [Medline: 27427189]
48. Bueno I, Williams-Nguyen J, Hwang H, Sargeant JM, Nault AJ, Singer RS. Impact of point sources on antibiotic resistance genes in the natural environment: a systematic review of the evidence. Anim Health Res Rev 2017 Dec;18(2):112-127. [doi: 10.1017/S146625231700007X] [Medline: 29231804]
49. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. Cochrane Handbook. 2011. URL: https://training.cochrane.org/handbook/archive/v5.1 [accessed 2021-11-16]
50. Bueno I, Williams-Nguyen J, Hwang H, Sargeant JM, Nault AJ, Singer RS. Systematic Review: Impact of point sources on antibiotic-resistant bacteria in the natural environment. Zoonoses Public Health 2018 Feb 05;65(1):e162-e184. [doi: 10.1111/zph.12426] [Medline: 29205899]

Abbreviations

AMR: antimicrobial resistance
ARB: antibiotic-resistant bacteria
ARG: antibiotic-resistance gene
LMIC: low- and middle-income country
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
WHO GIM: World Health Organization Global Index Medicus
WWTP: wastewater treatment plant

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Protocol

Outcomes of Digital Biomarker–Based Interventions: Protocol for a Systematic Review of Systematic Reviews

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Abstract

Background: Digital biomarkers are defined as objective, quantifiable, physiological, and behavioral data that are collected and measured using digital devices such as portables, wearables, implantables, or digestibles. For their widespread adoption in publicly financed health care systems, it is important to understand how their benefits translate into improved patient outcomes, which is essential for demonstrating their value.

Objective: The paper presents the protocol for a systematic review that aims to assess the quality and strength of the evidence reported in systematic reviews regarding the impact of digital biomarkers on clinical outcomes compared to interventions without digital biomarkers.

Methods: A comprehensive search for reviews from 2019 to 2020 will be conducted in PubMed and the Cochrane Library using keywords related to digital biomarkers and a filter for systematic reviews. Original full-text English publications of systematic reviews comparing clinical outcomes of interventions with and without digital biomarkers via meta-analysis will be included. The AMSTAR-2 tool will be used to assess the methodological quality of these reviews. To assess the quality of evidence, we will evaluate the systematic reviews using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool. To detect the possible presence of reporting bias, we will determine whether a protocol was published prior to the start of the studies. A qualitative summary of the results by digital biomarker technology and outcomes will be provided.

Results: This protocol was submitted before data collection. Search, screening, and data extraction will commence in December 2021 in accordance with the published protocol.

Conclusions: Our study will provide a comprehensive summary of the highest level of evidence available on digital biomarker interventions, providing practical guidance for health care providers. Our results will help identify clinical areas in which the use of digital biomarkers has led to favorable clinical outcomes. In addition, our findings will highlight areas of evidence gaps where the clinical benefits of digital biomarkers have not yet been demonstrated.

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KEYWORDS

digital biomarker; outcome; systematic review; meta-analysis; digital health; mobile health; Grading of Recommendations, Assessment, Development and Evaluation; AMSTAR-2; review; biomarkers; clinical outcome; interventions; wearables; portables; digestables; implants

Introduction

The advent of new medical technologies such as sensors has accelerated the process of collecting patient data for relevant clinical decisions [1], leading to the emergence of a new technology, namely digital biomarkers. By definition, “digital biomarkers are objective, quantifiable, physiological, and behavioral measures collected using digital devices that are portable, wearable, implantable, or digestible” [2].

In addition to their role in routine clinical care, digital biomarkers also play a significant role in clinical trials [3]. Digital biomarkers are considered important enablers of the health care value chain [4], and the global digital biomarker market is projected to grow at a rate of 40.4% between 2019 and 2025, reaching US $5.64 billion in revenue by 2025 [5].

By providing reliable disease-related information [6], digital biomarkers can offer considerable diagnostic and therapeutic value in modern health care systems as monitoring tools and as part of novel therapeutic interventions [7]. Digital biomarkers could reduce clinical errors and improve the accuracy of diagnostic methods for patients and clinicians using measurement-based care [8]. As an alternative to cross-sectional surveillance or prospective follow-ups with a limited number of visits, these technologies can provide more reliable results through continuous and remote home-based observation, and when combined with appropriate interventions, digital biomarkers have the potential to improve therapeutic outcomes [9]. In addition, predicting patients' disease status during continuous monitoring provides opportunities for treatment processes with fewer complications [10].

Given the recent rapid pace of the development of digital health technologies such as software [11], sensors [12], or robotic devices [13,14], their widespread adoption in publicly financed health care systems requires a systematic evaluation and demonstration of their clinical benefits and economic value [15]. The new European Medical Device Regulations effective from May 2021 seek sufficient clinical evidence with the goal of improving clinical security and providing equitable access to appropriate products [16].

Because of rapid technological changes, several potential user groups, and a wide range of functionalities, assessing the value of digital health technologies is a challenging, multidimensional task that often involves broader issues than standard health economic evaluations [17-20]. The National Institute for Clinical Excellence (NICE) has published an evidence framework to guide innovators on what is considered a good level of evidence to support the evaluation of digital health technology. According to the NICE framework, digital biomarkers can fall into several digital health technology risk categories, ranging from simple consumer health monitoring to digital health interventions that potentially impact treatment or diagnosis of care. Although evidence of measurement accuracy and ongoing data collection on use may be sufficient for lower risk categories, for high-risk technologies, demonstration of clinical benefits in high-quality interventional studies is required as a minimum standard of evidence. NICE considers randomized controlled trials (RCTs) conducted in a relevant health care system or meta-analyses of RCTs to be the best practice evidence standard [20].

Numerous studies have conducted systematic reviews of digital biomarkers in recent years with varying results. For instance, a meta-analysis found that implantable cardioverter defibrillators (ICDs) are generally effective in reducing all-cause mortality in patients with nonischemic cardiomyopathy [21], whereas another reported that ICD therapy for the primary prevention of sudden cardiac death in women does not reduce all-cause mortality [16]. In a meta-analysis comparing ICDs with drug treatments, ICDs were found to be more effective than drugs in preventing sudden cardiac death [22]. Some systematic reviews on the use of wearable sensors for monitoring Parkinson disease have reported that wearable sensors are the most effective digital devices to detect differences in standing balance between people with Parkinson disease and control subjects [23] and improve quality of life [24]. In another systematic review, the clinical utility of wearable sensors in patients with Parkinson disease to support clinical decision making was not clear [25]. A 2011 systematic review confirmed no differences between the effectiveness of portable coagulometers and conventional coagulometers in monitoring oral anticoagulation [26].

The inconsistent results from current systematic reviews call for a more systematic assessment of the strength and quality of evidence regarding the health outcomes of interventions based on digital biomarkers. Lack of knowledge about or omission of the quality of evidence of systematic reviews may lead to biased therapeutic guidelines and economic evaluations, and consequently to the widespread adoption of potentially harmful practices and a lag in the adoption of beneficial interventions [27].

Several systems for assessing the quality of evidence have been developed [28], of which the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system has been adopted by organizations such as the World Health Organization, American College of Physicians, and the Cochrane Collaboration due to its simplicity, methodological rigor, and usefulness in systematic reviews, health technology assessments, and therapeutic guidelines [27]. By assessing study limitations, inconsistency of results, indirectness of evidence, imprecision and reporting bias, GRADE classifies the quality of evidence into four levels from high to very low, with high quality indicating that further research is unlikely to alter our confidence in the effect estimate. Furthermore, by assessing the risk and benefit profile of interventions, GRADE offers two grades of recommendation—strong or weak, with strong recommendations indicating a clear positive or negative balance of risks and benefits [27]. However, some systematic reviews do not provide a structured assessment of the quality of synthesized evidence, and the quality of reporting may also limit the quality assessment of their results. Therefore, the AMSTAR-2 tool was developed as a validated tool to assess the methodological quality of systematic reviews [29].

Our goal is to provide innovators and policy makers with practical insights into the state of evidence generation on digital biomarkers, a rapidly evolving area of medicine [2]. This systematic review of systematic reviews will assess the overall

strength of evidence and the reporting quality of systematic reviews that report a quantitative synthesis of the impact of digital biomarkers on health outcomes when compared to interventions without digital biomarkers. Methodological quality of the studies will be assessed using the AMSTAR-2 tool, whereas overall quality of evidence will be evaluated according to GRADE by digital biomarker technologies and reported outcomes.

Methods

This protocol was prepared following the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) statement preferred for describing items for systematic review and meta-analysis protocols [30]. When reporting the results of this study, amendments or deviations from this protocol will be reported.

Eligibility Criteria

Original full-text English publications of systematic reviews that report meta-analyses of clinical outcomes of digital biomarker–based interventions compared with alternative interventions without digital biomarkers will be included. Specifically, we will include studies examining digital biomarkers used for diagnosing humans with any health condition in any age group and across genders. Studies investigating the use of digital biomarkers in animals will be excluded. Furthermore, the definition of digital biomarkers may overlap with sensor applications in the general population such as citizen sensing [31]. In this research, we will only consider systematic reviews focusing on digital devices used by clinicians or patients with the aim of collecting clinical data during treatment.

All interventions that involve the use of digital biomarkers for any purpose related to diagnosing patients, monitoring outcomes, or influencing the delivery of a therapeutic intervention will be considered. There will be no restrictions on comparators as long as the comparator arm does not involve the application of digital biomarkers for the purposes listed above. Only meta-analyses of clinical outcomes that report the intentional or unintentional change in the health status of participants resulting from an intervention will be considered. Systematic reviews that focus on measurement properties or other technical or use-related features of digital biomarkers that are not measures of a change in participants' health status due to an intervention are not eligible for this review.

Systematic reviews published between January 1, 2019, and December 31, 2020, will be included. We will include full-text articles published in English in peer-reviewed journals, conference papers, or systematic review databases, as well as full-text documents of systematic reviews from non–peer-reviewed sources, such as book chapters or health technology assessment reports.

Search Strategy

A comprehensive literature search will be conducted in PubMed and the Cochrane Library. In addition, the reference list of eligible full-text systematic reviews will be searched for other potentially eligible reviews for our study. Keywords related to “digital biomarkers” and filters for “systematic reviews” and publication dates will be combined in the literature search. Automatic expansion of the search terms to include applicable MeSH (Medical Subject Headings) terms will be allowed. For searching the digital biomarker studies, we operationalized the definition of “digital biomarkers” [2]. For identifying systematic reviews, the search filter proposed by the National Library for Medicine will be used [32]. This filter was designed to retrieve systematic reviews from PubMed that have been assigned the publication type “Systematic Review” during MEDLINE indexing, citations that have not yet completed MEDLINE indexing, and non-MEDLINE citations. The full syntax is provided in Table 1. An equivalent syntax will be developed to retrieve Cochrane reviews from the Cochrane Library.

Table 1. Search expressions for PubMed.

Terms	Number	Syntax
Digital biomarkers	#1	“digital biomarker” OR “digital biomarkers” OR portable OR portables OR wearable OR wearables OR implantable OR implantables OR digestible OR digestibles
Systematic reviews	#2	(((systematic review[ti] OR systematic literature review[ti] OR systematic scoping review[ti] OR systematic narrative review[ti] OR systematic qualitative review[ti] OR systematic evidence review[ti] OR systematic quantitative review[ti] OR systematic meta-review[ti] OR systematic critical review[ti] OR systematic mixed studies review[ti] OR systematic mapping review[ti] OR systematic Cochrane review[ti] OR systematic search and review[ti] OR systematic integrative review[ti]) NOT comment[pt] NOT (protocol[ti] OR protocols[ti])) NOT MEDLINE [subset]) OR (Cochrane Database Syst Rev[ta] AND review[pt]) OR systematic review[pt]
Publication date	#3	(“2019/01/01”[Date - Publication]: “2020/12/31”[Date - Publication])
Final search strategy	#4	#1 AND #2 AND #3

Screening and Selection

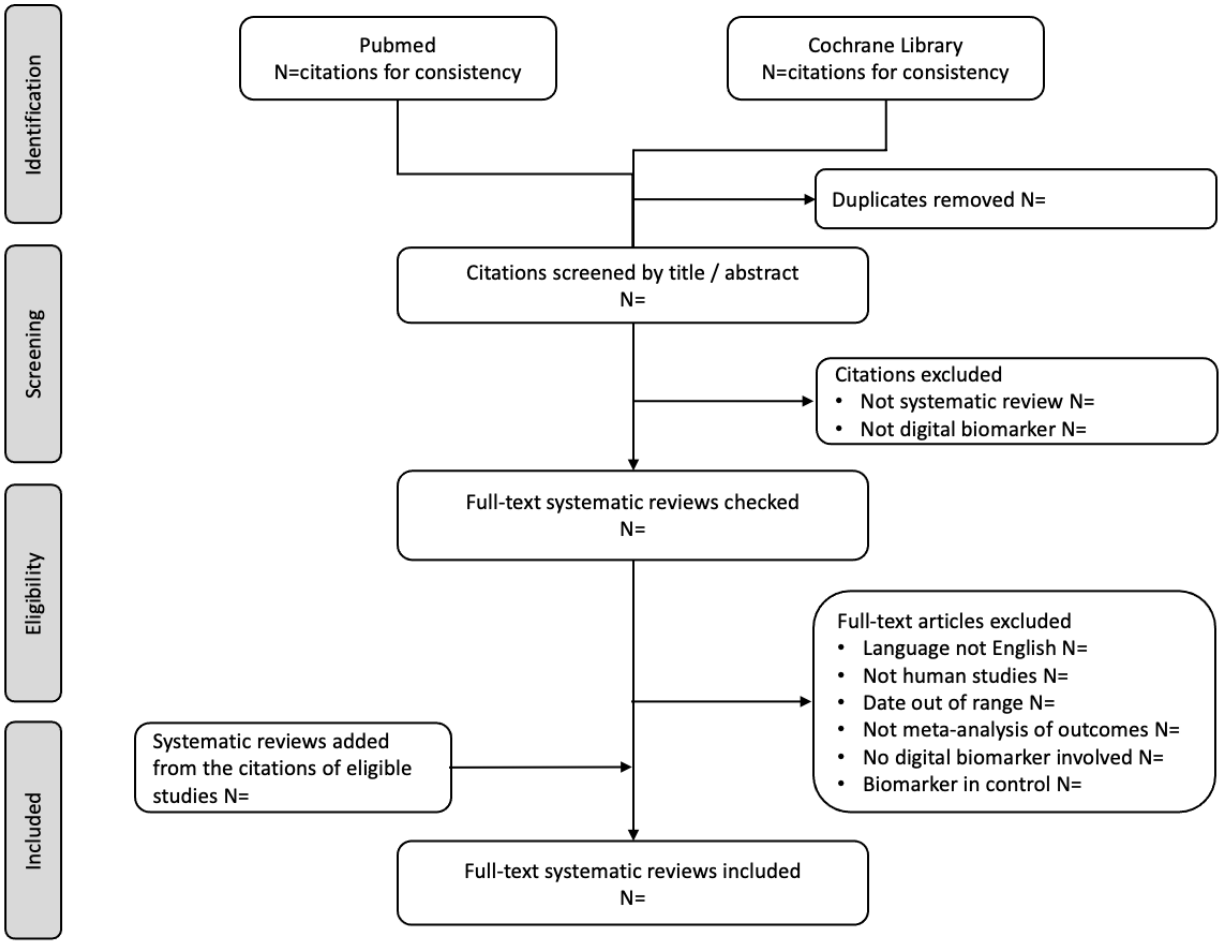
After removing duplicates, 2 reviewers will independently screen the titles and abstracts according to two main eligibility criteria: (1) systematic reviews and (2) interventions including digital biomarkers that meet the definition “objective, quantifiable, physiological, and behavioral measures collected using digital devices that are portable, wearable, implantable, or digestible” [2]. Following this definition, imaging or any other technology that does not measure physiological or behavioral data will be excluded from this study. Portable, wearable, implantable, or digestible medical devices or sensors, which generate physiological or behavioral data, will be considered as digital biomarkers (such as fitness trackers and

defibrillators). We interpret portable as "portable with respect to patients or consumers"; therefore, portable devices that are operated by health care professionals (eg, digital stethoscopes) will be excluded. Studies other than systematic reviews will be excluded in the screening phase. Interreviewer calibration exercises will be performed after title and abstract screening of the first 100 records, using the following method: both screening criteria will be scored as 1 if "criterium not met" and 0 if "criterium met or unsure." Therefore, reviewers can evaluate each record by assigning a score of 1, 2, 3, or 4, denoting response patterns of (0,0), (1,0), (0,1), and (1,1), respectively. Interrater agreement and the κ statistic will be calculated for the score, and reviewers will be retrained if worse than substantial agreement (κ 0.6) is not observed [33]. In case of discordant evaluations, a third reviewer will make decisions.

After screening, full-text articles will be evaluated against all eligibility criteria by 2 independent reviewers: (1) is the language English? (yes/no or unsure), (2) does the review concern human studies? (yes/no or unsure), (3) was the review published between January 1, 2019, and December 31, 2020? (yes/no or unsure), (4) does the review involve a meta-analysis of clinical outcomes? (yes/no or unsure), (5) does the intervention involve a digital biomarker used for diagnosis, patient monitoring, or influencing therapy? (yes/no or unsure), (6) does the comparator arm lack a digital biomarker for the same purposes? (yes/no or unsure). For inclusion, all 6 criteria must have yes as the answer. Discrepancies will have to be resolved by the 2 reviewers. In case of disagreement, a third reviewer will make the decision on including the article. Excluded full-text articles and the reasons for exclusion will be included as an appendix to the publication of results.

The screening results and selection of eligible studies will be visualized using the PRISMA-P 2009 flow diagram shown in Figure 1 [34].

Figure 1. PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) flow diagram of included studies.



Data Extraction

Data extraction will be performed by 2 independent researchers, and a calibration exercise (evaluation of interrater agreement) will be conducted after completing data extraction from 20% of the included studies. Discrepancies between reviewers will be resolved by consensus, and residual differences will be settled by a third reviewer. Any modification needed in the data extraction form will be done at this point.

Study-Level Variables

We will record the following study-level variables: year of publication, the first author's country using code 3166-1 of the International Standards Organization, the total number of

included studies on qualitative and quantitative synthesis as well as separately for every outcome, study designs of the included studies (RCTs and non-RCTs, cohort studies, case-control studies, and cross-sectional studies) [35], population and its age range, disease condition using the International Classification of Diseases 11th Revision coding [36], intervention, type of intervention using the International Classification of Health Interventions coding [37], comparator, type of comparator, digital biomarker, role of digital biomarker (diagnosis, patient monitoring, and influencing intervention), bodily function quantified by the digital biomarker using the International Classification of Functioning, Disability and Health coding [38], and the list of synthesized outcomes. Each eligible study will be summarized in Figure 2.

Figure 2. Summary of the included studies, which will include resources retrieved from non–peer-reviewed sources and reviews retrieved from peer-reviewed sources. Study designs will be listed in abbreviated form as the following: randomized controlled trial (RCT), non–randomized controlled trial (non-RCT), cohort study (C), case-control study (CC), and cross-sectional study (CS).

Digital biomarker	Role of digital biomarker	Author, year, and country	Number of included studies in qualitative and quantitative synthesis	Study designs [35]	Participants: diagnosis (age range)	Intervention	Comparator	Outcome and number of included studies

Assessment of the Methodological Quality of Systematic Reviews

The methodological quality of the eligible systematic reviews will be assessed using the criteria of the AMSTAR-2 tool [29] by 2 independent reviewers. Discrepancies will be resolved by consensus; lingering differences will be resolved by a third reviewer. AMSTAR-2 is a reliable and valid tool used for assessing the methodological quality of systematic reviews of randomized and nonrandomized studies of health care interventions [29,39]. In brief, AMSTAR-2 evaluates methodological quality according to the following 16 criteria: (1) research question according to the PICO (patient, intervention, comparison, outcome) framework, (2) methods established prior to the study, (3) explicit inclusion criteria, (4) comprehensive literature search, (5) study selection in duplicate, (6) data extraction in duplicate, (7) reporting of excluded studies, (8) detailed description of included studies, (9) risk of bias (RoB) assessment, (10) disclosure of funding sources, (11) appropriate statistical methods for evidence synthesis, (12) quantitative assessment of RoB in main results, (13) study-level discussion of RoB, (14) explanation for heterogeneity of results, (15) investigation of publication bias, and (16) reporting conflicts of interest.

For consistent rating [40], we will use the AMSTAR-2 website [41]. The AMSTAR-2 website provides an overall grading of the studies in four categories: critically low, low, medium, and high. It also provides explicit criteria for the answer options (yes, partially yes, and no). For each eligible article, answers for all AMSTAR-2 items and the overall ratings will be presented in Figure 3.The AMSTAR-2 items are presented in Textbox 1.

Figure 3. Assessment of the methodological quality of reviews (AMSTAR-2). Overall quality will be listed as critically low (CL), low (L), medium (M), and high (H).

Study	Items															Overall quality
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	

Textbox 1. AMSTAR-2 items.

1. Did the research questions and inclusion criteria for the review include the components of the PICO (patient, intervention, comparison, outcome) framework?
2. Did the review report contain an explicit statement that the review methods were established prior to conducting the review and did the report justify any significant deviations from the protocol?
3. Did the review authors explain their selection of the study designs for inclusion in the review?
4. Did the review authors use a comprehensive literature search strategy?
5. Did the review authors perform study selection in duplicate?
6. Did the review authors perform data extraction in duplicate?
7. Did the review authors provide a list of excluded studies and justify the exclusions?
8. Did the review authors describe the included studies in adequate detail?
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
10. Did the review authors report on the sources of funding for the studies included in the review?
11. If a meta-analysis was performed, did the review authors use appropriate methods for the statistical combination of results?
12. If a meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
13. Did the review authors account for RoB in individual studies when interpreting and discussing the results of the review?
14. Did the review authors provide a satisfactory explanation for and discussion of any heterogeneity observed in the results of the review?
15. If they performed a quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
16. Did the review authors report any potential sources of conflicts of interest, including any funding they received for conducting the review?

Outcome-Level Variables

In addition to study-level variables, for each outcome synthesized in the meta-analyses, the following information will be extracted by duplicate reviews, using the process described above: the measured outcome, total number of studies per outcome, total number of patients and number of patients in the intervention, effect size and its 95% CI (upper and lower limits), as well as the type of effect size (standardized mean difference, odds ratio, and risk ratio). Quantitative descriptions of outcomes will be grouped by digital biomarker and are provided in Figure 4, along with the assessment of the quality of evidence.

Figure 4. Evidence summary and quality assessment by the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) tool. Measure will be listed as risk ratio (RR), odds ratio (OR), mean difference (MD), and standardized mean difference (SMD). GRADE certainty ratings will be provided as high (H), medium (M), low (L), and very low quality of evidence (VL).

Intervention	Outcome	Author (year)	Total number of patients/ interventions	Effect size (95% CI)/ measure	Limitations	Imprecision	Inconsistency	Indirectness	Publication bias	GRADE overall quality rating	Comments

Assessing the Quality of Evidence

We will evaluate the quality of evidence of the meta-analyses for each outcome using the GRADE system [27,42]. By default, GRADE considers the evidence from RCTs as high quality; however, this assessment may be downgraded for each outcome based on the evaluation of the following quality domains: (1) RoB [43], (2) inconsistency [44], (3) imprecision [45], (4) publication bias [46], and (5) indirectness [47]. Depending on the severity of the quality concerns, for each domain, a downgrade of 0, 1, or 2 can be proposed. We will assign downgrades for RoB according to the following criteria: if 75% or more than 75% of the included studies for a given outcome are reported to have low RoB, no downgrades will be assigned; if less than 75% of the included studies have low RoB, 1 downgrade will be assigned; if the RoB is not reported, 1 downgrade will be allocated [48].

To evaluate inconsistency, the reported heterogeneity (I^2 statistic) of studies for each outcome will be considered. If the heterogeneity of the included studies of an outcome is less than or equal to 75%, no downgrade will be allotted. If the heterogeneity of included studies of the outcome is more than 75%, 1 downgrade will be assigned. If only 1 trial is included in the outcome, no downgrade will be assigned. In cases where the heterogeneity is not reported, we will assign 1 downgrade [48].

To assess imprecision, the sample size and CI will be evaluated [49]. Following the broad recommendations of the GRADE handbook [42], we will apply no downgrade if the pooled sample size is over 2000. We will apply 1 downgrade if the pooled sample size is less than 200. For pooled sample sizes between 200 and 2000, we will assess the optimal information size criterion as follows [42]: by expecting a weak effect size of 0.2 [50], we will calculate the sample size for an RCT using the pooled standard error and pooled sample size assuming a balanced sample, power of 0.8, and significance level of .05. If the calculated sample size is greater than the pooled sample size, 1 downgrade will be applied [42,49].

Publication bias appears when a pooled estimate does not comprise all the studies that could be included in the evidence synthesis [51]. One way to detect publication bias is to visually observe a funnel plot. Owing to the limitations of the funnel plot [46,52], this method may not show publication bias accurately [49,53] and may lead to false conclusions [52,54]. Therefore, we will assess publication bias using the trim and fill method proposed by Duval and Tweedie [55]. Potentially missing studies will be imputed, and the pooled effect size of the complete data set will be recalculated. In case the imputation of potentially missing studies change the conclusions of the analysis (eg, a significant effect size will not be significant anymore), we will apply 1 downgrade attributable to publication bias [55].

When assessing indirectness, any differences between the population, interventions, and comparators in each outcome of the research questions of the reviews will be considered [52]. In this regard, the studies included in each meta-analysis outcome will be evaluated. If the population, interventions, or comparators are consistent with the main aims of the meta-analysis, no downgrading will be considered. If the population, interventions, or comparators of the studies do not match the main objectives of the meta-analysis, depending on the severity of this mismatch, a downgrade of 1 or 2 will be considered based on the consensus of the 2 independent researchers involved in data extraction.

The quality evaluation and assignment of downgrades in each domain will be performed by 2 independent reviewers. Discrepancies will be resolved by consensus, and if required, decisions will be made by a third reviewer. The overall grading of the quality of evidence for each outcome will be performed by consensus. As a starting point for the consensus on overall evaluation, we will use the recommendations by Pollock et al [48]: (1) high quality indicates that further research is very unlikely to change our confidence in the effect estimate (0 downgrades); (2) moderate quality means further research is likely to have an important impact on our confidence in the effect estimate and may change the estimate (1-2 downgrades); (3) low quality implies further research is very likely to have an important impact on our confidence in the effect estimate and is likely to change the estimate (3-4 downgrades); (4) very low quality means any effect estimate is very uncertain (5-6 downgrades) [27,48].

In addition to the quantitative description of outcomes, the number of downgrades (0, 1, or 2) for each domain and the overall quality assessment (high, moderate, low, or very low) of the evidence with reasons for downgrades will be presented in Figure 4 for each outcome by each digital biomarker.

If the required information from the eligible studies is lacking at any stage of the research, or in case of ambiguity, we will contact the corresponding authors of the reviews by email to obtain the required information or to remove the ambiguity. If we do not receive any response, the case will be considered as “missing” or “not reported.”

Evidence Synthesis

Interrater agreement during screening will be evaluated via the percentage of agreement and the Cohen κ statistic. Study characteristics will be summarized using descriptive statistics. Given the heterogeneity of the included populations and interventions, we plan to provide a qualitative synthesis of the results for each digital biomarker by the type of intervention and outcome.

Results

This protocol was submitted before data collection. Search, screening, and data extraction will commence in December 2021 in accordance with the published protocol. The study is funded by the National Research, Development and Innovation Fund of Hungary (reference number: NKFIH-869-10/2019).

Discussion

Our study will provide a comprehensive summary of the breadth and quality of evidence available on the clinical outcomes of interventions involving digital biomarkers.

Strengths

Most of the systematic review studies conducted in the field of digital biomarkers in recent years have been mainly performed with a specific focus on one or more disease areas or technologies such as the effects of wearable fitness trackers on motivation and physical activity [56] or ICD troubleshooting in patients with left ventricular assist devices [57]. To the best of our knowledge, no comprehensive systematic review of systematic reviews has been published on all types of digital biomarkers in all populations and diseases. Therefore, our review aims to assess the quality of methods and evidence of systematic reviews, without being limited to a specific area or technology, using validated tools and standard methodologies. As a result, the strength of evidence can be compared between different types of interventions, providing practical guidance for clinicians and policy makers.

Limitations

One of the potential limitations of this study is the restricted search time period (2019 and 2020). Owing to the breadth of the scope, we chose a shorter timeframe for our review. However, we hypothesized that considering the new European Medical Device Regulations that were published in 2017 [16], this is a highly relevant period for evaluating the available clinical evidence generated prior to the implementation of the regulations. Furthermore, we hypothesized that given the rapid development of the field [3], systematic reviews are published regularly to summarize key developments in the generation of clinical evidence.

We operationalized the definition of digital biomarkers in our search. However, the sensitivity and specificity of our search filter to retrieve articles concerning digital biomarkers has not been tested. In addition to the general keywords applied in our search expressions, digital biomarkers may be identified by specific terms referring to the technology or type of data collected [3]. However, the creation of a comprehensive list of relevant search terms for all existing technologies was beyond the scope of this study and remains a research question to be answered. Furthermore, we will apply the definition of digital biomarkers in a clinical setting. Some sensor applications in the general population may have public health implications (eg, COVID-19 contact tracing apps [58]) , which will be omitted from this review. The challenges of interpreting the digital biomarker definition will be discussed.

Although relevant guidelines for systematic reviews of systematic reviews recommend searching in the Database of Abstracts of Reviews of Effectiveness (DARE) in addition to PubMed and Cochrane [59], we will limit our search to PubMed and Cochrane when retrieving reviews. It should be noted that the DARE was not used in this study as it does not contain new reviews from 2015.

Conclusions

In conclusion, our results will help identify clinical areas where the use of digital biomarkers has led to favorable clinical outcomes. Furthermore, our results will highlight areas with evidence gaps where the clinical usage of digital biomarkers has not yet been studied.

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Authors' Contributions

HM-N, ZZ, LG, and MP developed the concept. HM-N wrote the first manuscript draft. All authors have commented on and approved the final manuscript.

Conflicts of Interest

None declared.

References

1. Califf RM. Biomarker definitions and their applications. Exp Biol Med (Maywood) 2018 Feb;243(3):213-221 [FREE Full text] [doi: 10.1177/1535370217750088] [Medline: 29405771]
2. Babrak L, Menetski J, Rebhan M, Nisato G, Zinggeler M, Brasier N, et al. Traditional and Digital Biomarkers: Two Worlds Apart? Digit Biomark 2019 Aug 16;3(2):92-102 [FREE Full text] [doi: 10.1159/000502000] [Medline: 32095769]

3. Coravos A, Khozin S, Mandl KD. Developing and adopting safe and effective digital biomarkers to improve patient outcomes. NPJ Digit Med 2019;2(1):14 [FREE Full text] [doi: 10.1038/s41746-019-0090-4] [Medline: 30868107]
4. Meister S, Deiters W, Becker S. Digital health and digital biomarkers ? enabling value chains on health data. Curr Dir Biomed Eng 2016 Sep;2(1):577-581. [doi: 10.1515/cdbme-2016-0128]
5. Global Digital Biomarkers Market: Focus on Key Trends, Growth Potential, Competitive Landscape, Components (Data Collection and Integration), End Users, Application (Sleep and Movement, Neuro, Respiratory and Cardiological Disorders) and Region – Analysis and Forecast, 2019-2025. BIS Research. 2020. URL: https://bisresearch.com/industry-report/digital-biomarkers-market.html [accessed 2021-12-27]
6. Lipsmeier F, Taylor KI, Kilchenmann T, Wolf D, Scotland A, Schjodt-Eriksen J, et al. Evaluation of smartphone-based testing to generate exploratory outcome measures in a phase 1 Parkinson's disease clinical trial. Mov Disord 2018 Dec;33(8):1287-1297 [FREE Full text] [doi: 10.1002/mds.27376] [Medline: 29701258]
7. Robb MA, McInnes PM, Califf RM. Biomarkers and Surrogate Endpoints: Developing Common Terminology and Definitions. JAMA 2016 Mar 15;315(11):1107-1108. [doi: 10.1001/jama.2016.2240] [Medline: 26978201]
8. Insel TR. Digital Phenotyping: Technology for a New Science of Behavior. JAMA 2017 Oct 03;318(13):1215-1216. [doi: 10.1001/jama.2017.11295] [Medline: 28973224]
9. Guthrie NL, Carpenter J, Edwards KL, Appelbaum KJ, Dey S, Eisenberg DM, et al. Emergence of digital biomarkers to predict and modify treatment efficacy: machine learning study. BMJ Open 2019 Jul 23;9(7):e030710 [FREE Full text] [doi: 10.1136/bmjopen-2019-030710] [Medline: 31337662]
10. Shin EK, Mahajan R, Akbilgic O, Shaban-Nejad A. Sociomarkers and biomarkers: predictive modeling in identifying pediatric asthma patients at risk of hospital revisits. NPJ Digit Med 2018 Oct 2;1(1):50 [FREE Full text] [doi: 10.1038/s41746-018-0056-y] [Medline: 31304329]
11. Lunde P, Nilsson BB, Bergland A, Kværner KJ, Bye A. The Effectiveness of Smartphone Apps for Lifestyle Improvement in Noncommunicable Diseases: Systematic Review and Meta-Analyses. J Med Internet Res 2018 May 04;20(5):e162 [FREE Full text] [doi: 10.2196/jmir.9751] [Medline: 29728346]
12. Lenouvel E, Novak L, Nef T, Klöppel S. Advances in Sensor Monitoring Effectiveness and Applicability: A Systematic Review and Update. Gerontologist 2020 May 15;60(4):e299-e308. [doi: 10.1093/geront/gnz049] [Medline: 31102436]
13. Nagy, TD. A DVRK-based Framework for Surgical Subtask Automation. Acta Polytechnica Hungarica 2019 Sep 09;16(8):61-78 [FREE Full text] [doi: 10.12700/aph.16.8.2019.8.5]
14. Haidegger, T. Probabilistic Method to Improve the Accuracy of Computer-Integrated Surgical Systems. Acta Polytechnica Hungria 2019 Sep 09;16(8):119-140 [FREE Full text] [doi: 10.12700/aph.16.8.2019.8.8]
15. Drummond MF. The use of health economic information by reimbursement authorities. Rheumatology (Oxford) 2003 Nov;42 Suppl 3:iii60-iii63. [doi: 10.1093/rheumatology/keg499] [Medline: 14585919]
16. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EE. Official Journal of the European Union. 2017 May 5. URL: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745 [accessed 2021-10-15]
17. Biggs JS, Willcocks A, Burger M, Makeham MA. Digital health benefits evaluation frameworks: building the evidence to support Australia's National Digital Health Strategy. Med J Aust 2019 Apr;210 Suppl 6:S9-S11. [doi: 10.5694/mja2.50034] [Medline: 30927475]
18. Enam A, Torres-Bonilla J, Eriksson H. Evidence-Based Evaluation of eHealth Interventions: Systematic Literature Review. J Med Internet Res 2018 Nov 23;20(11):e10971 [FREE Full text] [doi: 10.2196/10971] [Medline: 30470678]
19. Lau F, Kuziemsky C, editors. Handbook of eHealth Evaluation: An Evidence-based Approach. Victoria, BC: University of Victoria; 2017.
20. Evidence Standards Framework for Digital Health Technologies. National Institute for Clinical Excellence. 2019. URL: https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/evidence-standards-framework/digital-evidence-standards-framework.pdf [accessed 2020-12-27]
21. Al-Khatib SM, Fonarow GC, Joglar JA, Inoue LYT, Mark DB, Lee KL, et al. Primary Prevention Implantable Cardioverter Defibrillators in Patients With Nonischemic Cardiomyopathy: A Meta-analysis. JAMA Cardiol 2017 Jun 01;2(6):685-688 [FREE Full text] [doi: 10.1001/jamacardio.2017.0630] [Medline: 28355432]
22. Peck KY, Lim YZ, Hopper I, Krum H. Medical therapy versus implantable cardioverter -defibrillator in preventing sudden cardiac death in patients with left ventricular systolic dysfunction and heart failure: a meta-analysis of > 35,000 patients. Int J Cardiol 2014 May 01;173(2):197-203. [doi: 10.1016/j.ijcard.2014.02.014] [Medline: 24636548]
23. Hubble RP, Naughton GA, Silburn PA, Cole MH. Wearable sensor use for assessing standing balance and walking stability in people with Parkinson's disease: a systematic review. PLoS One 2015;10(4):e0123705 [FREE Full text] [doi: 10.1371/journal.pone.0123705] [Medline: 25894561]
24. Rovini E, Maremmani C, Cavallo F. How Wearable Sensors Can Support Parkinson's Disease Diagnosis and Treatment: A Systematic Review. Front Neurosci 2017 Oct 06;11:555 [FREE Full text] [doi: 10.3389/fnins.2017.00555] [Medline: 29056899]

25. Johansson D, Malmgren K, Alt Murphy M. Wearable sensors for clinical applications in epilepsy, Parkinson's disease, and stroke: a mixed-methods systematic review. J Neurol 2018 Aug 9;265(8):1740-1752 [FREE Full text] [doi: 10.1007/s00415-018-8786-y] [Medline: 29427026]
26. Caballero-Villarraso J, Villegas-Portero R, Rodríguez-Cantalejo F. [Portable coagulometer devices in the monitoring and control of oral anticoagulation therapy: a systematic review]. Aten Primaria 2011 Mar;43(3):148-156 [FREE Full text] [doi: 10.1016/j.aprim.2010.03.017] [Medline: 21036420]
27. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008 Apr 26;336(7650):924-926 [FREE Full text] [doi: 10.1136/bmj.39489.470347.AD] [Medline: 18436948]
28. Atkins D, Eccles M, Flottorp S, Guyatt GH, Henry D, Hill S, GRADE Working Group. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. BMC Health Serv Res 2004 Dec 22;4(1):38 [FREE Full text] [doi: 10.1186/1472-6963-4-38] [Medline: 15615589]
29. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017 Dec 21;358:j4008 [FREE Full text] [doi: 10.1136/bmj.j4008] [Medline: 28935701]
30. Kamioka H. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P） 2015 statement. Jpn Pharmacol Ther 2019;47(8):1177-1185.
31. Pritchard H, Gabrys J. From Citizen Sensing to Collective Monitoring: Working through the Perceptive and Affective Problematics of Environmental Pollution. GeoHumanities 2016 Nov 16;2(2):354-371. [doi: 10.1080/2373566x.2016.1234355]
32. Search Strategy Used to Create the PubMed Systematic Reviews Filter. National Library of Medicine. 2018 Dec. URL: https://www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_strategy.html [accessed 2020-12-27]
33. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med 2012:276-282. [doi: 10.11613/BM.2012.031]
34. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009 Jul 21;6(7):e1000100 [FREE Full text] [doi: 10.1371/journal.pmed.1000100] [Medline: 19621070]
35. Grimes DA, Schulz KF. An overview of clinical research: the lay of the land. Lancet 2002 Jan 05;359(9300):57-61. [doi: 10.1016/S0140-6736(02)07283-5] [Medline: 11809203]
36. ICD-11 International Classification of Diseases 11th Revision: The global standard for diagnostic health information. World Health Organization. 2020. URL: https://icd.who.int/en [accessed 2020-12-27]
37. International Classification of Health Interventions (ICHI). World Health Organization. 2020. URL: https://www.who.int/standards/classifications/international-classification-of-health-interventions [accessed 2020-12-27]
38. ICF Browser. World Health Organization. 2017. URL: https://apps.who.int/classifications/icfbrowser/ [accessed 2021-12-27]
39. Lorenz RC, Matthias K, Pieper D, Wegewitz U, Morche J, Nocon M, et al. A psychometric study found AMSTAR 2 to be a valid and moderately reliable appraisal tool. J Clin Epidemiol 2019 Oct;114:133-140. [doi: 10.1016/j.jclinepi.2019.05.028] [Medline: 31152864]
40. Pieper D, Lorenz RC, Rombey T, Jacobs A, Rissling O, Freitag S, et al. Authors should clearly report how they derived the overall rating when applying AMSTAR 2-a cross-sectional study. J Clin Epidemiol 2021 Jan;129:97-103. [doi: 10.1016/j.jclinepi.2020.09.046] [Medline: 33049325]
41. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017 Sep 21;358:j4008 [FREE Full text] [doi: 10.1136/bmj.j4008] [Medline: 28935701]
42. Schünemann H, Brozek J, Guyatt G, Oxman A. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. 2013. URL: https://gdt.gradepro.org/app/handbook/handbook.html#h.9rdbelsnu4iy [accessed 2020-12-27]
43. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). J Clin Epidemiol 2011 Apr;64(4):407-415. [doi: 10.1016/j.jclinepi.2010.07.017] [Medline: 21247734]
44. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence-inconsistency. J Clin Epidemiol 2011 Dec;64(12):1294-1302. [doi: 10.1016/j.jclinepi.2011.03.017] [Medline: 21803546]
45. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. J Clin Epidemiol 2011 Dec;64(12):1283-1293. [doi: 10.1016/j.jclinepi.2011.01.012] [Medline: 21839614]
46. Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence—publication bias. J Clin Epidemiol 2011 Dec;64(12):1277-1282. [doi: 10.1016/j.jclinepi.2011.01.011] [Medline: 21802904]
47. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence—indirectness. J Clin Epidemiol 2011 Dec;64(12):1303-1310. [doi: 10.1016/j.jclinepi.2011.04.014] [Medline: 21802903]

48. Pollock A, Farmer SE, Brady MC, Langhorne P, Mead GE, Mehrholz J, et al. An algorithm was developed to assign GRADE levels of evidence to comparisons within systematic reviews. J Clin Epidemiol 2016 Feb;70:106-110 [FREE Full text] [doi: 10.1016/j.jclinepi.2015.08.013] [Medline: 26341023]
49. Zhang Y, Coello PA, Guyatt GH, Yepes-Nuñez JJ, Akl EA, Hazlewood G, et al. GRADE guidelines: 20. Assessing the certainty of evidence in the importance of outcomes or values and preferences-inconsistency, imprecision, and other domains. J Clin Epidemiol 2019 Jul;111:83-93. [doi: 10.1016/j.jclinepi.2018.05.011] [Medline: 29800687]
50. Cohen J. Statistical Power Analysis for the Behavioral Sciences. New York, NY: Routledge; 1988.
51. Austin TM, Richter RR, Sebelski CA. Introduction to the GRADE approach for guideline development: considerations for physical therapist practice. Phys Ther 2014 Nov;94(11):1652-1659. [doi: 10.2522/ptj.20130627] [Medline: 25035268]
52. Terrin N, Schmid CH, Lau J. In an empirical evaluation of the funnel plot, researchers could not visually identify publication bias. J Clin Epidemiol 2005 Sep;58(9):894-901. [doi: 10.1016/j.jclinepi.2005.01.006] [Medline: 16085192]
53. Mavridis D, Salanti G. How to assess publication bias: funnel plot, trim-and-fill method and selection models. Evid Based Ment Health 2014 Feb;17(1):30. [doi: 10.1136/eb-2013-101699] [Medline: 24477535]
54. Zwetsloot P, Van Der Naald M, Sena ES, Howells DW, IntHout J, De Groot JA, et al. Standardized mean differences cause funnel plot distortion in publication bias assessments. Elife 2017 Sep 08;6:e24260 [FREE Full text] [doi: 10.7554/eLife.24260] [Medline: 28884685]
55. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000 Jun;56(2):455-463. [doi: 10.1111/j.0006-341x.2000.00455.x] [Medline: 10877304]
56. Nuss K, Moore K, Nelson T, Li K. Effects of Motivational Interviewing and Wearable Fitness Trackers on Motivation and Physical Activity: A Systematic Review. Am J Health Promot 2021 Feb 14;35(2):226-235. [doi: 10.1177/0890117120939030] [Medline: 32662277]
57. Black-Maier E, Lewis RK, Barnett AS, Pokorney SD, Sun AY, Koontz JI, et al. Subcutaneous implantable cardioverter-defibrillator troubleshooting in patients with a left ventricular assist device: A case series and systematic review. Heart Rhythm 2020 Sep;17(9):1536-1544. [doi: 10.1016/j.hrthm.2020.04.019] [Medline: 32304733]
58. Amann J, Sleigh J, Vayena E. Digital contact-tracing during the Covid-19 pandemic: An analysis of newspaper coverage in Germany, Austria, and Switzerland. PLoS One 2021;16(2):e0246524 [FREE Full text] [doi: 10.1371/journal.pone.0246524] [Medline: 33534839]
59. Smith V, Devane D, Begley CM, Clarke M. Methodology in conducting a systematic review of systematic reviews of healthcare interventions. BMC Med Res Methodol 2011;11(1):15 [FREE Full text] [doi: 10.1186/1471-2288-11-15] [Medline: 21291558]

Abbreviations

DARE: Database of Abstracts of Reviews of Effectiveness
GRADE: Grading of Recommendations, Assessment, Development and Evaluation
ICD: implantable cardioverter defibrillator
MeSH: Medical Subject Headings
NICE: National Institute for Clinical Excellence
PICO: patient, intervention, comparison, outcome
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
RCT: randomized clinical trial
RoB: risk of bias

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Protocol

Objective Measurements of Physical Activity and Sedentary Behavior Using Wearable Devices in Patients With Axial Spondyloarthritis: Protocol for a Systematic Review

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Abstract

Background: Axial spondyloarthritis (axSpA) is a subgroup of inflammatory rheumatic diseases. Practicing regular exercise is critical to manage pain and stiffness, reduce disease activity, and improve physical functioning, spinal mobility, and cardiorespiratory function. Accordingly, monitoring physical activity and sedentary behavior in patients with axSpA is relevant for clinical outcomes and disease management.

Objective: This review aims to determine which wearable devices, assessment methods, and associated metrics are commonly used to quantify physical activity or sedentary behavior in patients with axSpA.

Methods: The PubMed, Physiotherapy Evidence Database (PEDro), and Cochrane electronic databases will be searched, with no limit on publication date, to identify all the studies matching the inclusion criteria. Only original English-language articles published in a peer-reviewed journal will be included. The search strategy will include a combination of keywords related to the study population, wearable devices, physical activity, and sedentary behavior. We will use the Boolean operators “AND” and “OR” to combine keywords as well as Medical Subject Headings terms.

Results: Search strategy was completed in June 2020 with 23 records obtained. Data extraction and synthesis are currently ongoing. Dissemination of study results in peer-reviewed journals is expected at the end of 2021.

Conclusions: This review will provide a comprehensive and detailed synthesis of published studies that examine the use of wearable devices for objective assessment of physical activity and sedentary behavior in patients with axSpA.

Trial Registration: PROSPERO CRD42020182398; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=182398

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KEYWORDS

axial spondyloarthritis; rheumatology; physical activity; sedentary behavior; objective measures; wearable; systematic review

Introduction

Axial spondyloarthritis (axSpA) is a subgroup of inflammatory rheumatic diseases that predominantly affect the axial skeleton and the sacroiliac joints [1-3]. Some clinical manifestations of axSpA are inflammatory back pain and spinal stiffness [4-7]. It is now well established that practicing regular exercise results in health benefits in patients with axSpA by managing correctly inflammatory joint diseases [8-10], pain [11], and stiffness [11]; by decreasing disease activity [12]; and by improving physical functioning [13,14], spinal mobility [14,15], and cardiorespiratory function [16]. Interestingly, lack of exercise has been identified as a risk factor for the appearance of depressive symptoms [17], suggesting the benefits of practicing physical activity to manage mental comorbidities of axSpA [17].

Accordingly, monitoring physical activity and sedentary behavior in patients with axSpA is relevant for clinical outcomes and disease management. Traditionally, physical activity and sedentary behavior are assessed using either subjective measures (eg, self-reported questionnaires) [18-27] or objective measures (eg, accelerometers) [23-26,28-31]. At this point, however, recent studies have demonstrated that self-reported physical activity is a less valid and less reliable method for measuring physical activity in patients with axSpA than device-measured physical activity [32,33]. These results support the use of wearable devices for objective assessment of physical activity or sedentary behavior in patients with axSpA [14,32,34-38] as well as in patients with rheumatoid arthritis (eg, [34]). At this point, however, to the best of our knowledge, no systematic review has identified and synthesized the available evidence on the use of wearable devices for this specific population. This review is hence specifically designed to address this issue and, more specifically, to answer the following question: which wearable devices, assessment methods, and associated metrics have been used to quantify physical activity or sedentary behavior in patients with axSpA?

Methods

Design

This systematic review will be conducted under the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines provided by Moher et al [39].

The present review protocol has been registered in PROSPERO (CRD42020182398). This research is exempt from ethics approval because the data are available through published and publicly available resources.

Inclusion Criteria

All published studies assessing physical activity or sedentary behavior patterns of adults with a diagnosis of axSpA will be included. Only original articles published in English in a peer-reviewed scientific journal will be covered by this review.

The following inclusion criteria will be used:

- Type of participants: All articles including participants aged over 18 years with a diagnosis of axSpA will be included.
- Type of intervention or exposure: Participants are not required to undergo any type of intervention. This review is designed to identify and synthesize current practices of wearable-based monitoring of physical activity or sedentary behavior in patients with axSpA. The effects of the interventions will not be analyzed. Only baseline data on physical activity and sedentary will be extracted.
- Type of outcome measurements: Studies will discuss the use of wearable devices to measure physical activity or sedentary behavior in patients with axSpA.

Exclusion Criteria

Case reports, abstracts, editorials, conference abstracts, letters to the editor, reviews, and meta-analyses will be excluded from this review. Furthermore, published studies without an objective assessment of physical activity or sedentary behavior of patients with axSpA extracted from wearable devices will be ineligible.

Data Sources and Search Strategy

The following electronic databases will be systematically searched to identify studies satisfying the search criteria: PubMed, Physiotherapy Evidence Database (PEDro), and Cochrane, with no limit on publication date.

The search strategy includes a combination of the following keywords, using the Boolean operators “AND” and “OR” and Medical Subject Headings terms:

(“ankylosing spondylitis” OR spondyloarthritis) AND (“wearable technology” OR “wearable sensor” OR “wearable device” OR “ambulatory monitoring” OR “fitness tracker” OR “activity tracker” OR “activity monitor” OR “step counter” OR Actigraphy OR Pedometer OR “inertial sensor” OR “inertial measurement unit” OR “pendant sensor” OR accelerometer OR inclinometer OR gyroscope) AND (“physical activity” OR “physical activities” OR “physical inactivity” or “physical exertion” OR fitness OR exercise OR sports OR lifetime OR training OR “leisure time” OR “aerobic activity” OR “aerobic activities” OR “activity level” OR Sedentary OR Sedentariness OR “sedentary behaviour” OR “sedentary behaviours” OR “sedentary behavior” OR “sedentary behaviors” OR “sedentary time” OR “sedentary lifestyle” OR “sedentary activity” OR “sedentary activities” OR “prolonged sitting” OR “sitting time” OR seated OR Standing OR walking OR running OR sleep OR Step OR steps OR “covered distance” OR Vo2 or “Maximal oxygen uptake” OR “energy expenditure” OR “moderate- to vigorous-intensity physical activity” OR MVPA).

Study Selection

Two reviewers (A and B) will independently screen each search match and decide on their potential inclusion based on data extracted from titles, abstracts, and keywords. Subsequently, the full-length text of the potentially included studies will be reviewed in detail to determine whether they satisfy the inclusion criteria mentioned above. Finally, based on inclusion and exclusion criteria, each reviewer (A and B) will decide independently on the eligibility of each search match. Any discrepancies between the two reviewers (A and B) will be resolved at a consensus meeting. If disagreement persists, a third reviewer (C) will be consulted to reach a final decision.

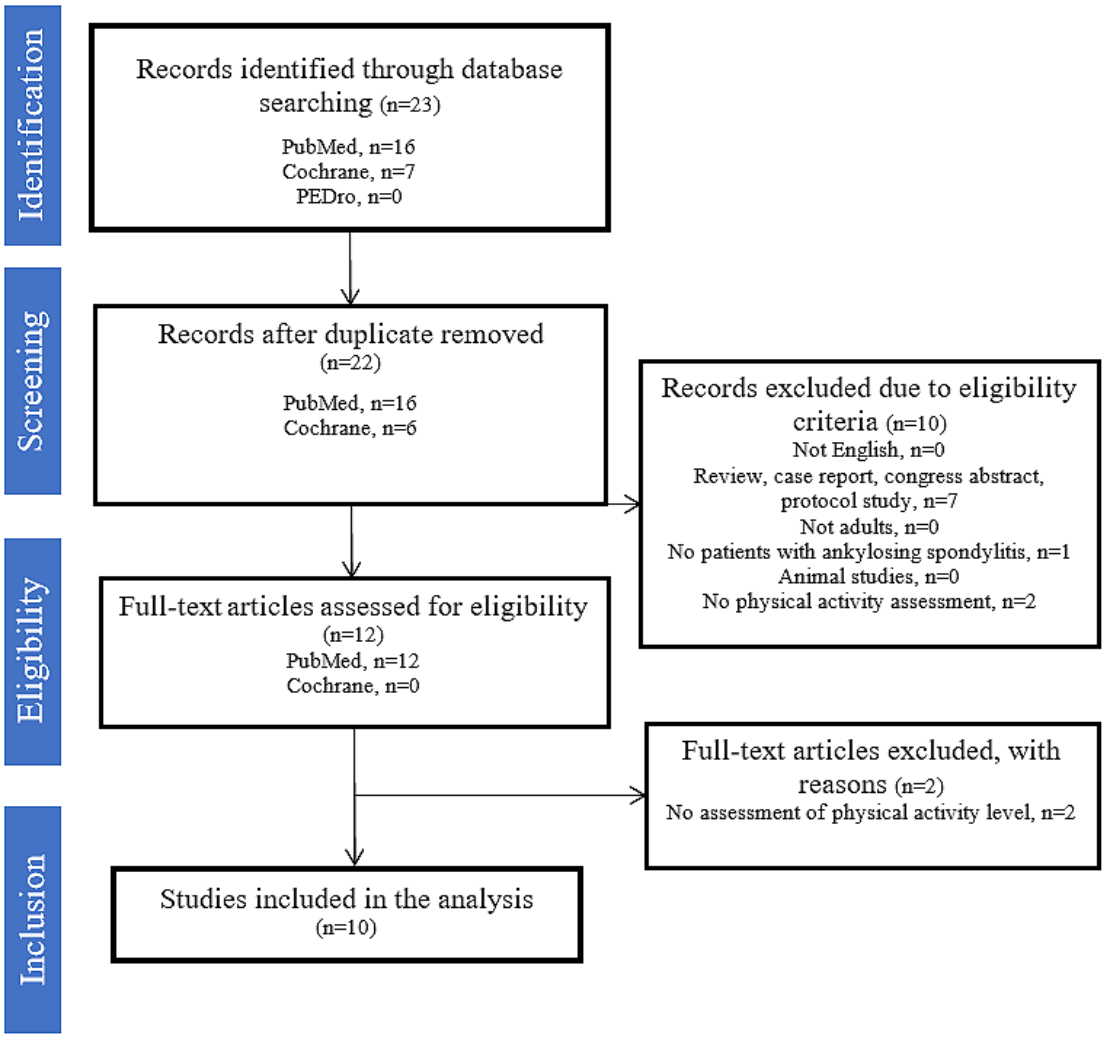
Risk of Bias in Individual Studies

As our aim is not to evaluate the effect of an intervention, we will not perform a risk of bias assessment. We will conduct a systematic review of published studies that used wearable sensors for objective assessment of physical activity or sedentary behavior in patients with axSpA.

Data Extraction

In line with PRISMA guidelines [39], a flow chart summarizes each stage of the review with the corresponding number of citations (Figure 1).

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart of the selection process. PEDro: Physiotherapy Evidence Database.



Furthermore, the following 4 data sets will be extracted from the retrieved articles by two independent reviewers:

1. Study characteristics: first author, title, year of publication, journal's name, country, study design, study duration, mention of any adverse events that occurred during the study, and funding.
2. Sample description: sample size, age, gender, weight, height, body mass index, health status, disease duration, functional status measurements, level of pain, description of radiographic damage, biologic medications, Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Activity Index (BASDAI), Bath Ankylosing Spondylitis Metrology Index (BASMI), and fall status.
3. Physical activity and/or sedentary behavior measurement method: measurement tool, protocol, outcome measures.
4. Main results obtained from physical activity and/or sedentary behavior assessment.

Results

The search using this strategy was completed in June 2020. We obtained a total of 23 records and 22 records after 1 duplicate was removed. A total of 12 full texts were included after screening of the abstracts and titles. Of these, 2 were then excluded after full-text screening, for a total of 10 studies included in the final review (Figure 1). Data extraction and synthesis are ongoing. Naturally, this first preliminary structured search will be repeated before the completion of the final review

process. Dissemination of the study results in peer-reviewed journals is expected at the end of 2021.

Discussion

This systematic review is designed to provide a first comprehensive and detailed synthesis of published studies that examine the use of wearable sensors for objective assessment of physical activity or sedentary behavior in patients with axSpA. The strengths of this study are its ability to directly influence future research and clinical care and the fact that this is the first time that a detailed synthesis of published studies in which wearable sensors were used for objective assessment of physical activity or sedentary behavior in patients with axSpA will be conducted. We do believe that our results could help clinicians to choose the most appropriate method to accurately monitor physical activity or sedentary behavior in this population. These results could have a major impact on diagnosis and monitoring in patients with axSpA. Furthermore, this work can guide future studies identifying preferable positions, durations, and environments. This could ultimately enable wearable device–based monitoring systems to find their way into routine clinical assessment and monitoring of patients. A major limitation of this review is the relatively small number of included studies.

The main advantage of a wearable-based monitoring approach is the passive and objective nature of the wearable data. The passive nature creates less burden for patients compared to timely manual completion of patient-reported outcomes. For clinicians, the potential benefit of wearables is related to the continuous, remote, and objective nature of the data. On the other hand, patients may be uncomfortable with continuous surveillance, and this could result in low acceptance of wearable technology despite its benefits. Furthermore, device placement errors could falsify data and lead patients and clinicians to make wrong decisions.

Acknowledgments

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Authors' Contributions

NV designed the systematic review protocol. TC prepared the first draft. All authors reviewed and revised the first draft. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

References

1. Raychaudhuri SP, Deodhar A. The classification and diagnostic criteria of ankylosing spondylitis. J Autoimmun 2014 Feb;48-49:128-133. [doi: 10.1016/j.jaut.2014.01.015] [Medline: 24534717]
2. Rudwaleit M, van der Heijde D, Landewé R, Akkoc N, Brandt J, Chou CT, et al. The assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis 2011 Jan;70(1):25-31. [doi: 10.1136/ard.2010.133645] [Medline: 21109520]
3. Sieper J, Braun J, Rudwaleit M, Boonen A, Zink A. Ankylosing spondylitis: an overview. Ann Rheum Dis 2002 Dec;61 Suppl 3:iii8-ii18 [FREE Full text] [doi: 10.1136/ard.61.suppl_3.iii8] [Medline: 12381506]
4. Sieper J, Poddubnyy D. Axial spondyloarthritis. Lancet 2017 Jul 01;390(10089):73-84. [doi: 10.1016/S0140-6736(16)31591-4] [Medline: 28110981]
5. Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis 2009 Jun;68 Suppl 2:ii1-ii44. [doi: 10.1136/ard.2008.104018] [Medline: 19433414]
6. Sağ S, Nas K, Sağ MS, Tekeoğlu, Kamanlı A. Relationship of work disability between the disease activity, depression and quality of life in patients with ankylosing spondylitis. J Back Musculoskelet Rehabil 2018;31(3):499-505. [doi: 10.3233/BMR-169657] [Medline: 29504521]
7. Imkamp M, Lima Passos V, Boonen A, Arends S, Dougados M, Landewé R, et al. Uncovering the heterogeneity of disease impact in axial spondyloarthritis: bivariate trajectories of disease activity and quality of life. RMD Open 2018;4(2):e000755 [FREE Full text] [doi: 10.1136/rmdopen-2018-000755] [Medline: 30487997]
8. van der Heijde D, Ramiro S, Landewé R, Baraliakos X, Van den Bosch F, Sepriano A, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis 2017 Jan 13;76(6):978-991. [doi: 10.1136/annrheumdis-2016-210770] [Medline: 28087505]
9. Braun J, van den Berg R, Baraliakos X, Boehm H, Burgos-Vargas R, Collantes-Estevez E, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis 2011 May 02;70(6):896-904. [doi: 10.1136/ard.2011.151027] [Medline: 21540199]

10. Dagfinrund H, Hagen K, Kvien T. Physiotherapy interventions for ankylosing spondylitis. Cochrane Database of Systematic Reviews 2004(4):CD002822. [doi: 10.1002/14651858.cd002822.pub2]
11. Reveille JD, Weisman MH. The epidemiology of back pain, axial spondyloarthritis and HLA-B27 in the United States. Am J Med Sci 2013 Jun;345(6):431-436 [FREE Full text] [doi: 10.1097/maj.0b013e318294457f] [Medline: 23841117]
12. Brophy S, Cooksey R, Davies H, Dennis MS, Zhou S, Siebert S. The effect of physical activity and motivation on function in ankylosing spondylitis: a cohort study. Semin Arthritis Rheum 2013 Jun;42(6):619-626 [FREE Full text] [doi: 10.1016/j.semarthrit.2012.09.007] [Medline: 23351615]
13. O'Dwyer T, O'Shea F, Wilson F. Physical activity in spondyloarthritis: a systematic review. Rheumatol Int 2015 Mar;35(3):393-404. [doi: 10.1007/s00296-014-3141-9] [Medline: 25300728]
14. Coulter EH, McDonald MT, Cameron S, Siebert S, Paul L. Physical activity and sedentary behaviour and their associations with clinical measures in axial spondyloarthritis. Rheumatol Int 2020 Mar;40(3):375-381 [FREE Full text] [doi: 10.1007/s00296-019-04494-3] [Medline: 31848736]
15. Levitova A, Hulejova H, Spiritovic M, Pavelka K, Senolt L, Husakova M. Clinical improvement and reduction in serum calprotectin levels after an intensive exercise programme for patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis. Arthritis Res Ther 2016 Nov 25;18(1):275 [FREE Full text] [doi: 10.1186/s13075-016-1180-1] [Medline: 27887637]
16. Zão A, Cantista P. The role of land and aquatic exercise in ankylosing spondylitis: a systematic review. Rheumatol Int 2017 Dec;37(12):1979-1990. [doi: 10.1007/s00296-017-3829-8] [Medline: 28983663]
17. Redeker I, Hoffmann F, Callhoff J, Haibel H, Sieper J, Zink A, et al. Determinants of psychological well-being in axial spondyloarthritis: an analysis based on linked claims and patient-reported survey data. Ann Rheum Dis 2018 Jul;77(7):1017-1024 [FREE Full text] [doi: 10.1136/annrheumdis-2017-212629] [Medline: 29525776]
18. Kayes NM, McPherson KM. Measuring what matters: does 'objectivity' mean good science? Disabil Rehabil 2010;32(12):1011-1019. [doi: 10.3109/09638281003775501] [Medline: 20384538]
19. van Boxtel MP, Langerak K, Houx PJ, Jolles J. Self-reported physical activity, subjective health, and cognitive performance in older adults. Exp Aging Res 1996 Sep 27;22(4):363-379. [doi: 10.1080/03610739608254017] [Medline: 8968708]
20. Baecke J, Burema J, Frijters J. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr 1982 Nov 01;36(5):936-942. [doi: 10.1093/ajcn/36.5.936] [Medline: 7137077]
21. InterAct Consortium, Peters T, Brage S, Westgate K, Franks PW, Gradmark A, et al. Validity of a short questionnaire to assess physical activity in 10 European countries. Eur J Epidemiol 2012 Jan;27(1):15-25 [FREE Full text] [doi: 10.1007/s10654-011-9625-y] [Medline: 22089423]
22. Sallis JF, Saelens BE. Assessment of physical activity by self-report: status, limitations, and future directions. Res Q Exerc Sport 2000 Jun;71(2 Suppl):S1-14. [Medline: 10925819]
23. Welk G, editor. Physical activity assessments for health-related research. Champaign, IL: Human Kinetics; 2002:1-280.
24. Kang M, Rowe DA. Issues and challenges in sedentary behavior measurement. Meas Phys Educ Exerc Sci 2015 Aug 19;19(3):105-115. [doi: 10.1080/1091367x.2015.1055566]
25. Bond DS, Thomas JG, Unick JL, Raynor HA, Vithiananthan S, Wing RR. Self-reported and objectively measured sedentary behavior in bariatric surgery candidates. Surg Obes Relat Dis 2013;9(1):123-128 [FREE Full text] [doi: 10.1016/j.soard.2012.09.008] [Medline: 23265767]
26. Hart TL, Ainsworth BE, Tudor-Locke C. Objective and subjective measures of sedentary behavior and physical activity. Med Sci Sports Exerc 2011 Mar;43(3):449-456. [doi: 10.1249/MSS.0b013e3181ef5a93] [Medline: 20631642]
27. Sternfeld B, Goldman-Rosas L. A systematic approach to selecting an appropriate measure of self-reported physical activity or sedentary behavior. J Phys Act Health 2012 Jan;9 Suppl 1:S19-S28. [doi: 10.1123/jpah.9.s1.s19] [Medline: 22287444]
28. Blair SN, Haskell WL. Objectively measured physical activity and mortality in older adults. JAMA 2006 Jul 12;296(2):216-218. [doi: 10.1001/jama.296.2.216] [Medline: 16835428]
29. LaPorte RE, Kuller L, Kupfer D, McPartland RJ, Matthews G, Caspersen C. An objective measure of physical activity for epidemiologic research. Am J Epidemiol 1979 Feb;109(2):158-168. [doi: 10.1093/oxfordjournals.aje.a112671] [Medline: 425955]
30. Vanhees L, Lefevre J, Philippaerts R, Martens M, Huygens W, Troosters T, et al. How to assess physical activity? How to assess physical fitness? Eur J Cardiovasc Prev Rehabil 2005 Apr;12(2):102-114. [doi: 10.1097/01.hjr.0000161551.73095.9c] [Medline: 15785295]
31. Harris TJ, Owen CG, Victor CR, Adams R, Cook DG. What factors are associated with physical activity in older people, assessed objectively by accelerometry? Br J Sports Med 2009 Jun;43(6):442-450. [doi: 10.1136/bjsm.2008.048033] [Medline: 18487253]
32. Arends S, Hofman M, Kamsma YP, van der Veer E, Houtman PM, Kallenberg CG, et al. Daily physical activity in ankylosing spondylitis: validity and reliability of the IPAQ and SQUASH and the relation with clinical assessments. Arthritis Res Ther 2013 Aug 23;15(4):R99 [FREE Full text] [doi: 10.1186/ar4279] [Medline: 23971767]
33. Prince SA, Adamo KB, Hamel ME, Hardt J, Connor Gorber S, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. Int J Behav Nutr Phys Act 2008 Nov 06;5:56 [FREE Full text] [doi: 10.1186/1479-5868-5-56] [Medline: 18990237]

34. Jacquemin C, Servy H, Molto A, Sellam J, Foltz V, Gandjbakhch F, et al. Physical activity assessment using an activity tracker in patients with rheumatoid arthritis and axial spondyloarthritis: prospective observational study. JMIR mHealth uHealth 2018 Jan 02;6(1):e1 [FREE Full text] [doi: 10.2196/mhealth.7948] [Medline: 29295810]
35. Plasqui G, Boonen A, Geusens P, Kroot EJ, Starmans M, van der Linden S. Physical activity and body composition in patients with ankylosing spondylitis. Arthritis Care Res (Hoboken) 2012 Jan;64(1):101-107 [FREE Full text] [doi: 10.1002/acr.20566] [Medline: 22213726]
36. Niedermann K, Sidelnikov E, Muggli C, Dagfinrud H, Hermann M, Tamborrini G, et al. Effect of cardiovascular training on fitness and perceived disease activity in people with ankylosing spondylitis. Arthritis Care Res (Hoboken) 2013 Nov;65(11):1844-1852 [FREE Full text] [doi: 10.1002/acr.22062] [Medline: 23836515]
37. Swinnen TW, Scheers T, Lefevre J, Dankaerts W, Westhovens R, de Vlam K. Physical activity assessment in patients with axial spondyloarthritis compared to healthy controls: a technology-based approach. PLoS One 2014;9(2):e85309 [FREE Full text] [doi: 10.1371/journal.pone.0085309] [Medline: 24586239]
38. Fongen C, Halvorsen S, Dagfinrud H. High disease activity is related to low levels of physical activity in patients with ankylosing spondylitis. Clin Rheumatol 2013 Dec;32(12):1719-1725. [doi: 10.1007/s10067-013-2320-5] [Medline: 23900575]
39. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009 Jul 21;6(7):e1000097 [FREE Full text] [doi: 10.1371/journal.pmed.1000097] [Medline: 19621072]

Abbreviations

axSpA: axial spondyloarthritis
BASDAI: Bath Ankylosing Spondylitis Functional Index
BASFI: Bath Ankylosing Spondylitis Functional Index
BASMI: Bath Ankylosing Spondylitis Metrology Index
PEDro: Physiotherapy Evidence Database
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Outcomes After Receipt of Neuraxial or Regional Anesthesia Instead of General Anesthesia for Lower Limb Revascularization Surgery: Protocol for a Systematic Review and Meta-analysis

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Abstract

Background: Patients undergoing lower limb revascularization surgery for peripheral artery disease (PAD) have a high risk of perioperative morbidity and mortality and often have long hospital stays. Use of neuraxial or regional anesthesia instead of general anesthesia may represent one approach to improving outcomes and reducing resource use among these patients.

Objective: The aim is to conduct a systematic review and meta-analysis to determine whether receipt of neuraxial or regional anesthesia instead of general anesthesia in adults undergoing lower limb revascularization surgery for PAD results in improved health outcomes and costs and a shorter length of hospitalization.

Methods: We will search electronic bibliographic databases (MEDLINE, EMBASE, the seven databases in Evidence-Based Medicine Reviews, medRxiv, bioRxiv, and Google Scholar), review papers identified during the search, and included article bibliographies. We will include randomized and nonrandomized studies comparing the use of neuraxial or regional anesthesia instead of general anesthesia in adults undergoing lower limb revascularization surgery for PAD. Two investigators will independently evaluate the risk of bias. The primary outcome will be short-term (in-hospital or 30-day) mortality. Secondary outcomes will include longer-term mortality; major adverse cardiovascular, pulmonary, renal, and limb events; delirium; deep vein thrombosis or pulmonary embolism; neuraxial or regional anesthesia–related complications; graft-related outcomes; length of operation and hospital stay; costs; and patient-reported or functional outcomes. We will calculate summary odds ratios (ORs) and standardized mean differences (SMDs) using random-effects models. Heterogeneity will be explored using stratified meta-analyses and meta-regression. We will assess for publication bias using the Begg and Egger tests and use the trim-and-fill method to estimate the potential influence of this bias on summary estimates. Finally, we will use Grading of Recommendations,

Assessment, Development, and Evaluation (GRADE) methodology to make an overall rating of the quality of evidence in our effect estimates.

Results: The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO). We executed the peer-reviewed search strategy on March 2, 2021. We completed the review of titles and abstracts on July 30, 2021, and plan to complete the review of full-text papers by September 30, 2021. We will complete full-text study data extraction and the risk-of-bias assessment by November 15, 2021, and conduct qualitative and then quantitative data synthesis and GRADE assessment of results by January 1, 2022, before drafting the manuscript. We anticipate that we will be able to submit the manuscript for peer review by the end of February 2022.

Conclusions: This study will synthesize existing evidence regarding whether receipt of neuraxial or regional anesthesia instead of general anesthesia in adults undergoing lower limb revascularization surgery for PAD results in improved health outcomes, graft patency, and costs and a shorter length of hospital stay. Study results will be used to inform practice and future research, including creation of a pilot and then multicenter randomized controlled trial.

Trial Registration: Prospero CRD42021237060; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=237060

International Registered Report Identifier (IRRID): PRR1-10.2196/32170

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KEYWORDS

epidural anesthesia; lower limb revascularization surgery; neuraxial anesthesia; peripheral artery disease; spinal anesthesia; vascular surgery; anesthesia; surgery; limb; nerves; spine; outcome; protocol; review; artery; cardiovascular; hospital

Introduction

Background

Lower limb revascularization surgeries (ie, endarterectomy, patch angioplasty, and arterial bypass) are commonly performed across North America [1-4]. In the United States, at least 15,000 to 20,000 lower limb arterial bypass surgeries are performed annually, while an average of 1650 lower limb revascularization surgeries are performed per annum in Ontario (Canada's most populous province) [1,5,6]. Although endovascular therapy is increasingly used for treatment of chronic limb-threatening ischemia (CLTI), defined as peripheral artery disease (PAD) manifested by rest pain or tissue loss, and some patients with lifestyle-limiting vasculogenic intermittent claudication, it is less durable than surgical revascularization and not suitable for some patients' anatomical pattern of disease [1,7]. There is also equipoise among many clinicians as to whether endovascular or surgical revascularization should be offered to patients with PAD who are candidates for both [1,7].

Patients undergoing lower limb revascularization surgery for PAD are typically older (average age of approximately 70 years), are current or past cigarette smokers, and have several comorbidities that place them at high risk for perioperative morbidity and mortality [2,3]. These include diabetes and coronary artery disease, chronic obstructive pulmonary disease, and chronic kidney disease [2,3]. Compared to adults with coronary artery or cerebrovascular disease, those with PAD have a higher risk of cardiovascular events, hospitalization, and hospitalization for coronary, carotid, or lower limb revascularization [8]. Those patients undergoing lower limb revascularization surgery for PAD also often require long postoperative (and sometimes preoperative) hospital stays and consume substantial health care system resources [9,10]. Hospitalization costs for those with PAD exceed those for patients with coronary artery or cerebrovascular disease, with lower limb revascularization procedures accounting for a substantial amount of these costs [8].

Use of neuraxial (spinal or epidural) or regional (peripheral nerve block) anesthesia instead of general anesthesia may represent one approach to improving postoperative health outcomes and reducing resource use among patients undergoing lower limb revascularization surgery for PAD [1,2,11,12]. Both neuraxial and regional anesthesia improve peripheral circulation and avoid mechanical ventilation, while neuraxial anesthesia improves coagulation and blunts surgical stress responses [1,13-17]. A 2013 Cochrane systematic review of four small randomized controlled trials (RCTs) reported that patients who received neuraxial instead of general anesthesia for lower limb revascularization surgery had a lower pooled risk of pneumonia [18]. An increasing number of large nonrandomized comparative studies have also recently reported that use of neuraxial or regional anesthesia (instead of general anesthesia) is associated with variable reductions in adjusted perioperative cardiopulmonary and renal complications, lengths of hospital stay, in-hospital or short-term mortality, and health care system costs [1,3,11,12,19]. However, reported findings of these studies are inconsistent and some remain limited by a risk of residual confounding by indication [1]. This type of confounding occurs because anesthetic techniques may be chosen based on patient, provider, and hospital characteristics, and these characteristics predict subsequent health and health care system outcomes [1,20].

Objectives

We propose to conduct a systematic review and meta-analysis of randomized and nonrandomized comparative studies to determine whether receipt of neuraxial or regional anesthesia instead of general anesthesia in adults undergoing lower limb revascularization surgery for PAD results in improved health outcomes, graft patency, and costs and a shorter length of hospital stay. We will also determine whether results of these

studies vary by differences in study design, included patient populations, or risk of bias.

Methods

Protocol and Role of the Sponsor

This systematic review protocol was developed and reported according to the Preferred Reporting Items in Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [21] and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) proposal [22]. It is reported according to the PRIMSA protocols (PRISMA-P) statement (see Multimedia Appendix 1 for the completed PRISMA-P checklist) [23,24]. The protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration no. CRD42021237060). The University of Ottawa had no role in the development of the protocol.

Focused Clinical Question

We formulated the focused clinical question for the study according to the patient, intervention (or exposure, for nonrandomized studies), comparison, outcome, and design (PI[E]COD) method of designing clinical questions for systematic reviews. Our focused clinical question was:

- P: for adults (≥18 years of age) undergoing lower limb revascularization surgery for PAD
- I(E): does receipt of neuraxial (spinal or epidural) or regional (peripheral nerve block) anesthesia (as the primary anesthetic technique)
- C: compared with general anesthesia (as the primary anesthetic technique), including general anesthesia combined with other anesthesia techniques
- O: Result in improved outcomes, including (1) primary outcome (short-term [in-hospital or 30-day] mortality) and (2) secondary outcomes (longer-term mortality; major adverse cardiovascular, pulmonary, renal, and limb events; delirium; deep vein thrombosis or pulmonary embolism; neuraxial or regional anesthesia–related complications; graft-related outcomes; length of operation and hospital stay; costs; and patient-reported or functional outcomes [see below for definitions of these outcomes])
- D: in randomized and nonrandomized comparative studies?

Information Sources

We will search MEDLINE; MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations; EMBASE; the seven databases contained within Evidence-Based Medicine Reviews (American College of Physicians [ACP] Journal Club®; the Cochrane Central Register of Controlled Trials, the Database of Systematic Reviews, and the Methodology Register Database; the Database of Abstracts of Reviews of Effects; the Health Technology Assessment Database; and the National Health Service Economic Evaluation Database); and medRxiv, bioRxiv, and Google Scholar from their first available date until study initiation without language, publication date, or other restrictions. To identify additional citations, we will also use the PubMed "related articles" feature and search bibliographies of included studies and relevant review papers identified during the search.

Search Strategy

A vascular surgeon and epidemiologist with graduate training in information science and evidence synthesis methods (author DJR) created the initial MEDLINE search strategy. Using a combination of Medical Subject Heading (MeSH) terms and keywords, search filters were constructed covering the themes *anesthetic type* and *lower limb revascularization surgery*. With assistance from a medical librarian, this strategy was then piloted and refined by adding additional MeSH terms when new and relevant citations were located in iterative pilot searches. We then adapted the search for EMBASE by searching for Emtree terms covering subjects similar to the MeSH terms (see Tables 1 and 2 for our final electronic bibliographic database search strategies).

Table 1. Ovid MEDLINE database search strategies.

Search theme	MeSH[a] search terms	Search term text words
Lower limb revascularization surgery	arterial occlusive disease/surgery OR blood vessel prosthesis OR blood vessel prosthesis implantation OR endarterectomy OR ischemia/surgery OR lower extremity/surgery OR peripheral arterial disease/surgery OR peripheral vascular diseases/surgery OR vascular surgical procedures	((iliofemoral OR femoral OR femoral artery*) adj3 (endarterectom* OR patch* OR repair*)) OR ((femoral-distal OR femoral distal OR femoral-popliteal OR femoral popliteal OR femoral-tibial OR femoral tibial OR infrageniculate OR supragageniculate OR infrainguinal OR lower extremity OR lower limb OR peripheral vascular) adj3 (arterial surg* OR arterial bypass* OR bypass* OR bypass graft* OR bypass surg* OR graft* OR intervention* OR revascularization* OR revascularization procedure* OR vascular bypass* OR vascular bypass surg* OR vascular graft* OR vein graft* OR prosthetic graft*))
Anesthetic type	Anesthesia OR anesthesia, endotracheal OR anesthesia, epidural* OR anesthesia, spinal* OR anesthesia, local* OR anesthesia, general* OR nerve block	((general OR regional OR neuraxial OR epidural OR spinal) adj3 (anesthe*)) OR epidural* OR nerve block* OR peripheral nerve block* OR spinal*

[a]MeSH: Medical Subject Heading.

Table 2. Ovid EMBASE database search strategies.

Search theme	Emtree search terms	Search term text words
Lower limb revascularization surgery	artery bypass OR blood vessel graft OR bypass surgery OR critical limb ischemia/surgery OR endarterectomy OR limb ischemia/surgery OR peripheral artery occlusive disease/surgery OR prosthetic vascular graft OR vascular surgery OR vein bypass	((iliofemoral OR femoral OR femoral artery*) adj3 (endarterectom* OR patch* OR repair*)) OR ((femoral-distal OR femoral distal OR femoral-popliteal OR femoral popliteal OR femoral-tibial OR femoral tibial OR infrageniculate OR suprageniculate OR infrainguinal OR lower extremity OR lower limb OR peripheral vascular) adj3 (arterial surg* OR arterial bypass* OR bypass* OR bypass graft* OR bypass surg* OR graft* OR intervention* OR revascularization* OR revascularization procedure* OR vascular bypass* OR vascular bypass surg* OR vascular graft* OR vein graft* OR prosthetic graft*))
Anesthetic type	Anesthesia OR general anesthesia OR epidural anesthesia OR nerve block OR regional anesthesia OR spinal anesthesia	((general OR regional OR neuraxial OR epidural OR spinal) adj3 (anesthe*)) OR epidural* OR nerve block* OR peripheral nerve block* OR spinal*

Data Management and Selection Process

The titles and abstracts of citations identified during the search will be exported into EndNote X9 reference management software (Clarivate, Thomson Reuters Corporation, Fairfax, VA, USA). This software will then be used to remove identical duplicates from the citation list. Two investigators will subsequently independently review the titles and abstracts of all identified citations and select any paper deemed potentially relevant by either investigator for full-text review using Covidence (Covidence, Melbourne, Australia). Finally, these two investigators will review the full text of all potentially relevant citations and select studies for inclusion in the systematic review. Disagreements regarding study inclusion will be resolved via consensus or arbitration by a third investigator (DJR).

Eligibility Criteria

Population

We will include studies where participants were adults (≥18 years of age) undergoing lower limb revascularization surgery for PAD. Lower limb revascularization surgery will be considered to include iliofemoral or femoral endarterectomy or patch angioplasty and iliofemoral or infrainguinal bypass (eg, femoral-popliteal or femoral-tibial bypass) [1]. We will exclude studies that (1) included patients who underwent lower limb revascularization surgery that utilized a suprainguinal source of inflow aside from the external iliac arteries (eg, aortofemoral or axillofemoral bypass) because these procedures require general anesthesia [25] or (2) included >20% of patients reported to undergo surgery for indications other than PAD (eg, aneurysms or trauma).

Intervention/Exposure and Comparison

The intervention (for randomized studies) or exposure (for nonrandomized comparative studies) of interest will include neuraxial or regional anesthesia as the primary anesthesia technique. Neuraxial anesthesia will be defined as spinal, epidural, or combined spinal-epidural anesthesia without general anesthesia, while regional anesthesia will be defined as use of a peripheral nerve block without general anesthesia. The comparison of interest will be general anesthesia (including general anesthesia in combination with neuraxial or regional anesthesia).

Outcomes

The primary outcome will be short-term (in-hospital or 30-day) mortality. Secondary outcomes will include (1) longer-term mortality (mortality beyond 30 days); (2) major adverse cardiovascular events (cardiovascular death, stroke, or myocardial infarction) [26]; (3) delirium; (4) postoperative pulmonary complications (pneumonia, unplanned or prolonged mechanical ventilation, or acute respiratory distress syndrome); (5) deep vein thrombosis or pulmonary embolism; (6) acute kidney injury or initiation of new dialysis; (7) major adverse limb events (acute limb ischemia or amputation) [27]; (8) arterial bypass graft-related outcomes (primary, primary assisted, and secondary patency) [28]; (9) neuraxial or regional anesthesia–related adverse events (epidural hematoma, spinal cord injury, intracranial hemorrhage, or peripheral nerve injury); (10) costs; (11) length of operation and hospital stay; and (12) patient-reported or functional outcomes. Primary, primary-assisted, and secondary arterial bypass graft patency will be defined according to the reporting standards of the Society for Vascular Surgery [28]. According to these standards, primary patency refers to patency obtained without a need for additional or secondary surgical or endovascular procedures (or the interval of time from the original intervention until any intervention performed to maintain or re-establish patency) [28]. Primary-assisted patency represents patency achieved with the use of additional or secondary surgical or endovascular procedures, as long as occlusion of the primary treated site has not occurred [28]. Finally, secondary patency is patency obtained with the use of an additional or secondary surgical or endovascular procedure after occlusion occurs [28].

Design

The included studies must be randomized or nonrandomized (ie, cohort, case–control, or comparative effectiveness) comparative (ie, with a comparator group) studies of the above interventions [29,30]. We will include abstracts of studies not published in full, if they reported sufficient detail to determine

eligibility. We will exclude nonrandomized studies that did not control for confounding in their effect estimates using matching, regression, propensity scores, instrumental variables, or another method [31]. For the primary analysis, we will limit inclusion of nonrandomized comparative studies to those controlling for a minimum set of confounders, including age, sex, type of lower limb revascularization surgery, surgical urgency, cardiovascular and pulmonary comorbidities, diabetes, and cognitive status/dementia [2,19], as has been recommended by guidance documents on meta-analyses of nonrandomized studies [31].

Setting and Language

There will be no restrictions regarding the setting or language of the study.

Data Items and Collection Process

The same two investigators will independently extract data using an electronic data extraction spreadsheet and tables piloted on a representative sample of three randomized and three nonrandomized studies. We will extract the following data from included studies (where applicable or reported): (1) year of publication, design, data source, and study country or setting; (2) patient recruitment period; (3) inclusion and exclusion criteria; (4) patient and procedural characteristics, including the types of lower limb revascularization surgeries performed and the urgency of and indication(s) for these procedures; (5) characteristics of the anesthetics provided to the intervention and comparison groups (ie, percentage of spinal and epidural anesthesia, types of medications administered into the spinal or epidural space, and types of peripheral nerve blocks and medications used for these blocks); (6) follow-up duration; and (7) study outcomes and their definitions (as reported by study authors). For reported study outcomes, we will extract event rates or odds ratios (ORs), with 95% confidence intervals (CIs); group means (with SDs), for continuous differences; and other relative or absolute effect measures describing one or more outcomes of interest between the groups (or we will calculate them from the data provided). For nonrandomized comparative studies, we will extract the most thoroughly adjusted effect estimates (and which confounding factors were adjusted for) when variably adjusted outcomes were reported [32]. Where necessary, authors of studies will be contacted for additional clarifying or outcome information. In randomized studies, we will extract outcomes analyzed according to an intent-to-treat principle.

Risk-of-Bias Assessment

Two investigators will independently judge the risk of bias among the included RCTs using the Cochrane Collaboration tool [29,33]. This tool includes questions regarding random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases [29]. Using this tool, we will judge each RCT to be at low, unclear, or high risk of bias in each of the above domains.

The same two investigators will also judge the risk of bias among the included nonrandomized studies using the Risk of Bias in Non-randomised Studies – of Interventions (ROBINS-I) tool [30]. This tool includes questions regarding bias due to confounding, in selection of participants into the study, in classification of interventions, due to deviations from intended interventions or missing data, in measurement of outcomes, and in selection of the reported result [30]. We will answer each question using the response options yes, probably yes, probably no, no, and no information [30]. We will then use these judgments within each domain to make an overall domain-level judgment about the risk of bias, as is recommended by the ROBINS-I authors [30].

Discrepancies between investigators in study-level risk-of-bias assessments will be resolved by discussion and consensus between the investigators or arbitration by a third investigator (DJR).

Data Synthesis

Qualitative Data Synthesis

Characteristics of the included studies (including year of publication, country of origin, patient recruitment periods, inclusion and exclusion criteria, interventions and comparisons, and follow-up durations) and their included patient populations (mean/median ages and types of lower limb revascularization surgeries performed) will be tabulated by study design (randomized or nonrandomized comparative) and types of comparisons (ie, neuraxial or regional anesthesia compared with general anesthesia). This will allow us to compare recruitment periods and determine whether potentially overlapping data may have been reported before performing randomized and nonrandomized comparative study meta-analyses. We will also tabulate results of risk-of-bias assessments by study design (randomized or nonrandomized).

Quantitative Data Synthesis and Statistical Analyses

We will use the OR (for dichotomous outcomes) and the standardized mean difference (SMD) (for continuous outcomes) as the summary measures of association when combining results of randomized and nonrandomized studies, respectively. When risk ratios (RRs) or hazard ratios (HRs) were reported instead of ORs by study authors, we will pool these measures of association separately by estimate type, as has been suggested [31].

Results of randomized and nonrandomized studies will be pooled separately by comparison type (ie, by whether neuraxial or regional anesthesia was compared to general anesthesia) in primary analyses using the method of restricted maximum likelihood (REML) [34]. This method will be chosen to estimate between-study variance in meta-analyses, as has been recommended over other methods based on results of simulation studies [34]. If overlapping or duplicate data were used in nonrandomized studies, we will include the study with the largest sample size that reported an adjusted measure of association in meta-analyses. To assess for interstudy heterogeneity in our pooled estimates, we will inspect forest plots, calculate Cochran Q homogeneity and I^2 inconsistency statistics, and conduct tests of homogeneity (P value<.10 considered significant, given the low power of these tests) [35-37]. As suggested by Higgins et al, we will consider I^2

statistics of >25%, >50%, and >75% to represent low, moderate, and high degrees of heterogeneity, respectively [36].

In the presence of low or greater interstudy heterogeneity, we will conduct prespecified subgroup analyses using random-effects models and meta-regression, with the summary OR for in-hospital mortality as the dependent variable. We will use the following predictor variables in an attempt to explain heterogeneity in these stratified analyses or meta-regressions: (1) study design (randomized vs nonrandomized comparative), (2) publication status (abstract vs full-text publication), (3) whether there was a low versus higher risk of bias related to random sequence generation or allocation concealment in randomized studies, (4) whether nonrandomized studies reported an OR or other measure of association that was adjusted using the minimum confounder set (to determine whether better-adjusted estimates more closely agree with those obtained from randomized studies) [31], and (5) the proportion of patients included in the study who had a combined general and neuraxial or regional anesthetic in combination with a general anesthetic or who underwent an emergent operation, underwent a groin-only lower limb revascularization surgery, or were diagnosed with coronary artery disease, diabetes, chronic kidney disease, or critical limb ischemia.

We will evaluate for the presence of small study effects potentially due to publication bias for each outcome by visually inspecting produced funnel plots and using Begg and Egger tests (P value<.05 considered significant) [38]. When evidence of small study effects exists, we will use the Duval and Tweedie "trim and fill" method to estimate the potential influence of this type of bias on our pooled estimates [39-41]. In this method, small outlying studies are first "trimmed" (removed until the funnel plot is symmetrical) and then the remaining symmetrical studies are used to re-estimate the "true" center of the plot [39-41]. The plot is then "filled" (the missing, outlying study results and their theoretical balancing counterparts are replaced around the new center), and a small study effect–adjusted center is recalculated.

Statistical analyses will be performed using Stata MP version 13.1 (Stata Corporation, College Station, TX, USA) by a trained meta-analyst [39-41].

Confidence in Cumulative Evidence

We will use the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology to make an overall rating of the quality of evidence in our effect estimates for the primary and secondary outcomes (ie, confidence that our effect estimates are correct) [42,43]. To do this, we will first assess the risk of bias, consistency, directness, precision, and risk of publication bias associated with the evidence for the primary and each secondary outcome [44-48]. The overall confidence in these effect estimates will then be adjudicated as high ("further research is very unlikely to change our confidence in the estimate of effects"), moderate ("further research is likely to have an important impact on our confidence in the estimate of effects and may change the estimate"), low ("further research is very likely to have an important impact on our confidence in the estimate of effects and is likely to change the estimate"), or very low ("uncertain about the estimate of effects") [24].

Data Sharing

We will provide the raw data included in meta-analyses at the point of publication.

Results

We executed the peer-reviewed search strategy on March 2, 2021. We completed the review of titles and abstracts on July 30, 2021, and plan to complete the review of full-text papers by September 30, 2021. We will complete full-text study data extraction and the risk-of-bias assessment by November 15, 2021. Subsequently, we will conduct qualitative and then quantitative data synthesis and the GRADE assessment of the results by January 1, 2022, before drafting the manuscript. We anticipate that we will be able to submit the manuscript for peer review by the end of February 2022.

Discussion

Summary

Patients undergoing lower limb revascularization surgery for PAD are at high risk of serious postoperative adverse events and consume substantial health care resources. We hypothesize that avoidance of general anesthesia may represent an efficacious approach to improving their health outcomes and reducing resource use [1,2,11,12]. Use of neuraxial or regional anesthesia instead of general anesthesia could improve outcomes after lower limb revascularization surgery in several biologically plausible ways. Clinical and translational research suggest that neuraxial and regional anesthesia improve peripheral circulation and avoid mechanical ventilation, while neuraxial anesthesia improves coagulation and blunts surgical stress responses [1,13-17]. Avoidance of general anesthesia may also help to reduce pulmonary complications by avoiding airway manipulation and invasive or positive-pressure ventilation [18].

By evaluating a variety of relevant primary and secondary outcomes, our systematic review will help to identify which outcomes (if any) are likely to be improved after receipt of neuraxial or regional anesthesia instead of general anesthesia in patients undergoing lower limb revascularization surgery. After synthesizing the available evidence, we will use the GRADE methodology to assess the risk of bias, consistency, directness, precision, and publication bias associated with the evidence for each outcome. We will then use these assessments to rate the overall confidence in the cumulative evidence for each of these outcomes to inform current lower limb revascularization surgery practice. We will also identify important knowledge gaps not addressed by the current literature on this topic. These may include a lack of patient-reported, functional, and longer-term outcomes after use of different types of anesthesia in patients undergoing lower limb revascularization surgery.

To the best of our knowledge, no multicenter RCTs comparing neuraxial or regional anesthesia and general anesthesia in adults undergoing lower limb revascularization surgery have been reported. If none are identified and future RCTs comparing neuraxial or regional anesthesia and general anesthesia are required, the findings of our systematic review will inform their

design. For example, patients undergoing these surgeries often have multiple and sometimes life-threatening comorbidities and take a number of different medications, including antiplatelets and anticoagulants, some of which contraindicate the use of neuraxial anesthesia [1]. Our systematic review will identify common and relevant inclusion and exclusion criteria from existing RCTs, while helping to determine which lower limb revascularization surgeries may be appropriate to serve as inclusion criteria for an RCT. As different lower limb revascularization surgeries have different anticipated operative durations (eg, femoral endarterectomy vs femoral-tibial bypass), different approaches to using neuraxial anesthesia may be required for different surgeries (eg, a spinal anesthetic may be used for shorter duration surgeries while a combined spinal-epidural anesthetic may be needed for longer surgeries).

Conclusion

In summary, we propose to synthesize existing evidence regarding whether receipt of neuraxial or regional anesthesia instead of general anesthesia in adults undergoing lower limb revascularization surgery results in improved health outcomes, graft patency, and costs and a shorter length of hospital stay. Study results will be used to inform practice and future research, including creation of a pilot and then multicenter RCTs comparing neuraxial and general anesthesia in this patient population.

Authors' Contributions

DJR is the guarantor. DJR conceived and DJR, HD, SKN, AL, JPL, TB, PJ, LD, HTS, and DIM designed the study. DJR and DIM designed the quantitative and statistical analysis plan. DJR designed the search strategy, which was refined by HD, SKN, AL, JPL, TB, PJ, LD, HTS, and DIM. DJR wrote the first draft of the protocol, which was critically revised by HD, SKN, AL, JPL, TB, PJ, LD, HTS, and DIM. DJR submitted the protocol to PROSPERO. DJR, HD, SKN, AL, JPL, TB, PJ, LD, HTS, and DIM read and approved the final protocol.

Conflicts of Interest

The authors declare that they have no competing interests.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items in Systematic Reviews and Meta-Analyses Protocols) checklist.
[DOCX File , 39 KB - resprot_v10i11e32170_app1.docx]

References

1. Roberts DJ, Nagpal SK, Kubelik D, Brandys T, Stelfox HT, Lalu MM, et al. Association between neuraxial anaesthesia or general anaesthesia for lower limb revascularisation surgery in adults and clinical outcomes: population based comparative effectiveness study. BMJ 2020 Nov 25;371:m4104 [FREE Full text] [doi: 10.1136/bmj.m4104] [Medline: 33239330]
2. Singh N, Sidawy AN, Dezee K, Neville RF, Weiswasser J, Arora S, et al. The effects of the type of anesthesia on outcomes of lower extremity infrainguinal bypass. J Vasc Surg 2006 Nov;44(5):964-968 [FREE Full text] [doi: 10.1016/j.jvs.2006.06.035] [Medline: 17000075]
3. Ghanami RJ, Hurie J, Andrews JS, Harrington RN, Corriere MA, Goodney PP, et al. Anesthesia-based evaluation of outcomes of lower-extremity vascular bypass procedures. Ann Vasc Surg 2013 Feb;27(2):199-207 [FREE Full text] [doi: 10.1016/j.avsg.2012.04.006] [Medline: 22944010]
4. LaMuraglia GM, Conrad MF, Chung T, Hutter M, Watkins MT, Cambria RP. Significant perioperative morbidity accompanies contemporary infrainguinal bypass surgery: an NSQIP report. J Vasc Surg 2009 Aug;50(2):299-304, 304.e1 [FREE Full text] [doi: 10.1016/j.jvs.2009.01.043] [Medline: 19631864]
5. Mustapha JA, Katzen BT, Neville RF, Lookstein RA, Zeller T, Miller LE, et al. Determinants of long-term outcomes and costs in the management of critical limb ischemia: a population-based cohort study. J Am Heart Assoc 2018 Aug 21;7(16):e009724 [FREE Full text] [doi: 10.1161/JAHA.118.009724] [Medline: 30369325]
6. Nejim BJ, Wang S, Arhuidese I, Obeid T, Alshaikh HN, Dakour Aridi H, et al. Regional variation in the cost of infrainguinal lower extremity bypass surgery in the United States. J Vasc Surg 2018 Apr;67(4):1170-1180.e4 [FREE Full text] [doi: 10.1016/j.jvs.2017.08.055] [Medline: 29074114]
7. Adam DJ, Beard JD, Cleveland T, Bell J, Bradbury AW, Forbes JF, BASIL trial participants. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. Lancet 2005 Dec 03;366(9501):1925-1934. [doi: 10.1016/S0140-6736(05)67704-5] [Medline: 16325694]
8. Smolderen KG, Bell A, Lei Y, Cohen EA, Gabriel Steg P, Bhatt DL, et al. One-year costs associated with cardiovascular disease in Canada: insights from the REduction of Atherothrombosis for Continued Health (REACH) registry. Can J Cardiol 2010 Oct;26(8):e297-e305 [FREE Full text] [doi: 10.1016/s0828-282x(10)70437-2] [Medline: 20931098]
9. Bonaca M, Bauersachs R, Anand S, Debus E, Nehler M, Patel M. Rivaroxaban in peripheral artery disease after revascularization. J Vasc Surg 2020 Jul;72(1):368. [doi: 10.1016/j.jvs.2020.04.470]

10. Moriarty JP, Murad MH, Shah ND, Prasad C, Montori VM, Erwin PJ, Society for Vascular Surgery Committee on Comparative Effectiveness. A systematic review of lower extremity arterial revascularization economic analyses. J Vasc Surg 2011 Oct;54(4):1131-1144.e1 [FREE Full text] [doi: 10.1016/j.jvs.2011.04.058] [Medline: 21971093]
11. Fereydooni A, O'Meara T, Popescu WM, Dardik A, Ochoa Chaar CI. Use of neuraxial anesthesia for hybrid lower extremity revascularization is associated with reduced perioperative morbidity. J Vasc Surg 2020 Apr;71(4):1296-1304.e7. [doi: 10.1016/j.jvs.2019.07.072] [Medline: 31708304]
12. Kikuchi S, Yamaguchi T, Miyake K, Uchida D, Koya A, Iida T, et al. Effectiveness and safety of ultrasound guided lower extremity nerve blockade in infragenicular bypass grafting for high risk patients with chronic limb threatening ischaemia. Eur J Vasc Endovasc Surg 2019 Aug;58(2):206-213 [FREE Full text] [doi: 10.1016/j.ejvs.2019.03.023] [Medline: 31272780]
13. Rosenfeld BA, Beattie C, Christopherson R, Norris EJ, Frank SM, Breslow MJ, et al. The effects of different anesthetic regimens on fibrinolysis and the development of postoperative arterial thrombosis. Perioperative Ischemia Randomized Anesthesia Trial Study Group. Anesthesiology 1993 Sep;79(3):435-443 [FREE Full text] [doi: 10.1097/00000542-199309000-00005] [Medline: 8363067]
14. Tuman KJ, McCarthy RJ, March RJ, DeLaria GA, Patel RV, Ivankovich AD. Effects of epidural anesthesia and analgesia on coagulation and outcome after major vascular surgery. Anesth Analg 1991 Dec;73(6):696-704. [doi: 10.1213/00000539-199112000-00005] [Medline: 1952169]
15. Breslow MJ, Parker SD, Frank SM, Norris EJ, Yates H, Raff H, et al. Determinants of catecholamine and cortisol responses to lower extremity revascularization. The PIRAT Study Group. Anesthesiology 1993 Dec;79(6):1202-1209 [FREE Full text] [doi: 10.1097/00000542-199312000-00010] [Medline: 8267195]
16. Parker SD, Breslow MJ, Frank SM, Rosenfeld BA, Norris EJ, Christopherson R, et al. Catecholamine and cortisol responses to lower extremity revascularization: correlation with outcome variables. Perioperative Ischemia Randomized Anesthesia Trial Study Group. Crit Care Med 1995 Dec;23(12):1954-1961. [doi: 10.1097/00003246-199512000-00003] [Medline: 7497717]
17. Aitken E, Jackson A, Kearns R, Steven M, Kinsella J, Clancy M, et al. Effect of regional versus local anaesthesia on outcome after arteriovenous fistula creation: a randomised controlled trial. Lancet 2016 Sep 10;388(10049):1067-1074. [doi: 10.1016/S0140-6736(16)30948-5] [Medline: 27492881]
18. Guay J, Choi PT, Suresh S, Albert N, Kopp S, Pace NL. Neuraxial anesthesia for the prevention of postoperative mortality and major morbidity. Anesth Analg 2014;119(3):716-725. [doi: 10.1213/ane.0000000000000339]
19. Sgroi MD, McFarland G, Mell MW. Utilization of regional versus general anesthesia and its impact on lower extremity bypass outcomes. J Vasc Surg 2019 Jun;69(6):1874-1879 [FREE Full text] [doi: 10.1016/j.jvs.2018.08.190] [Medline: 30792062]
20. Sox HC, Goodman SN. The methods of comparative effectiveness research. Annu Rev Public Health 2012 Apr;33:425-445. [doi: 10.1146/annurev-publhealth-031811-124610] [Medline: 22224891]
21. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021 Mar 29;372:n71 [FREE Full text] [doi: 10.1136/bmj.n71] [Medline: 33782057]
22. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000 Apr 19;283(15):2008-2012. [doi: 10.1001/jama.283.15.2008] [Medline: 10789670]
23. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015 Jan 01;4:1 [FREE Full text] [doi: 10.1186/2046-4053-4-1] [Medline: 25554246]
24. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015 Jan 02;350:g7647 [FREE Full text] [doi: 10.1136/bmj.g7647] [Medline: 25555855]
25. Gropper M, Eriksson L, Fleisher L, Wiener-Kronish J, Cohen N, Leslie K, editors. Miller's Anesthesia. PA: Elsevier; 2019.
26. Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, COMPASS Investigators. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet 2018;391(10117):219-229. [doi: 10.1016/S0140-6736(17)32409-1]
27. Anand SS, Caron F, Eikelboom JW, Bosch J, Dyal L, Aboyans V, et al. Major adverse limb events and mortality in patients with peripheral artery disease: the COMPASS trial. J Am Coll Cardiol 2018 May 22;71(20):2306-2315 [FREE Full text] [doi: 10.1016/j.jacc.2018.03.008] [Medline: 29540326]
28. Stoner MC, Calligaro KD, Chaer RA, Dietzek AM, Farber A, Guzman RJ, Society for Vascular Surgery. Reporting standards of the Society for Vascular Surgery for endovascular treatment of chronic lower extremity peripheral artery disease. J Vasc Surg 2016 Jul;64(1):e1-e21 [FREE Full text] [doi: 10.1016/j.jvs.2016.03.420] [Medline: 27345516]
29. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Cochrane Bias Methods Group, Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011 Oct 18;343:d5928 [FREE Full text] [doi: 10.1136/bmj.d5928] [Medline: 22008217]

30. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016 Oct 12;355:i4919 [FREE Full text] [doi: 10.1136/bmj.i4919] [Medline: 27733354]
31. Riley RD, Moons KGM, Snell KIE, Ensor J, Hooft L, Altman DG, et al. A guide to systematic review and meta-analysis of prognostic factor studies. BMJ 2019 Jan 30;364:k4597. [doi: 10.1136/bmj.k4597] [Medline: 30700442]
32. Altman DG. Systematic reviews of evaluations of prognostic variables. BMJ 2001 Jul 28;323(7306):224-228 [FREE Full text] [doi: 10.1136/bmj.323.7306.224] [Medline: 11473921]
33. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019 Aug 28;366:l4898. [doi: 10.1136/bmj.l4898] [Medline: 31462531]
34. Langan D, Higgins JPT, Jackson D, Bowden J, Veroniki AA, Kontopantelis E, et al. A comparison of heterogeneity variance estimators in simulated random-effects meta-analyses. Res Synth Methods 2019 Mar;10(1):83-98. [doi: 10.1002/jrsm.1316] [Medline: 30067315]
35. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002 Jun 15;21(11):1539-1558. [doi: 10.1002/sim.1186] [Medline: 12111919]
36. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003 Sep 06;327(7414):557-560 [FREE Full text] [doi: 10.1136/bmj.327.7414.557] [Medline: 12958120]
37. Egger M, Davey Smith G, Altman DG, editors. Systematic Reviews in Health Care: Meta‐Analysis in Context. London, UK: BMJ Publishing Group; 2001.
38. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994 Dec;50(4):1088-1101. [Medline: 7786990]
39. Duval S, Tweedie R. A nonparametric "trim and fill" method of accounting for publication bias in meta-analysis. J Am Stat Assoc 2000 Mar;95(449):89-98. [doi: 10.1080/01621459.2000.10473905]
40. Cosic N, Roberts DJ, Stelfox HT. Efficacy and safety of damage control in experimental animal models of injury: protocol for a systematic review and meta-analysis. Syst Rev 2014 Nov 22;3(1):136-136 [FREE Full text] [doi: 10.1186/2046-4053-3-136] [Medline: 25416175]
41. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000 Jun;56(2):455-463. [doi: 10.1111/j.0006-341x.2000.00455.x] [Medline: 10877304]
42. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011 Apr;64(4):401-406. [doi: 10.1016/j.jclinepi.2010.07.015] [Medline: 21208779]
43. Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. J Clin Epidemiol 2013 Feb;66(2):151-157. [doi: 10.1016/j.jclinepi.2012.01.006] [Medline: 22542023]
44. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol 2011 Apr;64(4):407-415. [doi: 10.1016/j.jclinepi.2010.07.017] [Medline: 21247734]
45. Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. J Clin Epidemiol 2011 Dec;64(12):1277-1282. [doi: 10.1016/j.jclinepi.2011.01.011] [Medline: 21802904]
46. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol 2011 Dec;64(12):1283-1293. [doi: 10.1016/j.jclinepi.2011.01.012] [Medline: 21839614]
47. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, GRADE Working Group. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. J Clin Epidemiol 2011 Dec;64(12):1294-1302. [doi: 10.1016/j.jclinepi.2011.03.017] [Medline: 21803546]
48. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence--indirectness. J Clin Epidemiol 2011 Dec;64(12):1303-1310. [doi: 10.1016/j.jclinepi.2011.04.014] [Medline: 21802903]

Abbreviations

CLTI: chronic limb-threatening ischemia
GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
HR: hazard ratio
MeSH: Medical Subject Heading
OR: odds ratio
PAD: peripheral artery disease
PI(E)COD: patient, intervention (or exposure), comparison, outcome, and design
PRISMA: Preferred Reporting Items in Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items in Systematic Reviews and Meta-Analyses Protocols

RCT: randomized controlled trial
REML: restricted maximum likelihood
ROBINS-I: Risk of Bias in Non-randomised Studies – of Interventions
RR: risk ratio

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Protocol

A Novel Risk and Crisis Communication Platform to Bridge the Gap Between Policy Makers and the Public in the Context of the COVID-19 Crisis (PubliCo): Protocol for a Mixed Methods Study

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Abstract

Background: Since the end of 2019, COVID-19 has had a significant impact on people around the globe. As governments institute more restrictive measures, public adherence could decrease and discontent may grow. Providing high-quality information and countering fake news are important. However, we also need feedback loops so that government officials can refine preventive measures and communication strategies. Policy makers need information—preferably based on real-time data—on people's cognitive, emotional, and behavioral reactions to public health messages and restrictive measures. PubliCo aims to foster effective and tailored risk and crisis communication as well as provide an assessment of the risks and benefits of prevention and control measures, since their effectiveness depends on public trust and cooperation.

Objective: Our project aims to develop a tool that helps tackle the COVID-19 infodemic, with a focus on enabling a nuanced and in-depth understanding of public perception. The project adopts a transdisciplinary multistakeholder approach, including participatory citizen science.

Methods: We aim to combine a literature and media review and analysis as well as empirical research using mixed methods, including an online survey and diary-based research, both of which are ongoing and continuously updated. Building on real-time data and continuous data collection, our research results will be highly adaptable to the evolving situation.

Results: As of September 2021, two-thirds of the proposed tool is operational. The current development cycles are focusing on analytics, user experience, and interface refinement. We have collected a total of 473 responses through PubliCo Survey and 22 diaries through PubliCo Diaries.

Conclusions: Pilot data show that PubliCo is a promising and efficient concept for bidirectional risk and crisis communication in the context of public health crises. Further data are needed to assess its function at a larger scale or in the context of an issue other than COVID-19.

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KEYWORDS

disease outbreaks; coronavirus; COVID-19 surveys; COVID-19 questionnaires; qualitative methods; health literacy; policy making; risk and crisis communication; COVID-19

Introduction

Background

Since the end of 2019, COVID-19 has significantly impacted the lives of people around the globe. In addition to infection, disease, and death, the global public has been exposed to increasingly restrictive policy measures. Within weeks or even days, measures evolved from recommendations, such as frequent handwashing, to more disruptive interventions, including social distancing, cancelations of social events, closure of schools, and closed borders. Public life and ways of socializing that were once taken for granted have come to an abrupt halt.

Exceptional circumstances, like this pandemic, generally have significant short-, mid-, and long-term consequences in social, economic, and perhaps cultural and political terms. Some issues have already emerged, including social isolation of vulnerable groups, panic buying and stolen supplies, or instances of reprimanding people for their "irresponsible" behavior. While the gradual easing of containment measures alleviated frustration in parts of the population following the first wave, the reinstallment of restrictive measures may lead to mounting discontent and decreasing public adherence to containment measures.

Measures in Switzerland have been less restrictive than in many other countries. However, more drastic dispositions could be implemented and are legally covered by the Swiss Epidemics Law should the situation require them, including a general curfew, mandatory testing, or the use of mobile phone data for surveillance purposes. During the first wave (March to June 2020), the Swiss population generally supported the measures that were implemented. As subsequent waves unfold, however, debate on public health measures like contact tracing, limits on visiting nursing home residents, working from home, etc, has intensified.

"Anticorona" demonstrations in several cities, gatherings of hundreds of people celebrating the end of the lockdown, and organized "illegal" soccer games were among the first signs of resistance to public health measures in Switzerland [1]. In order to effectively manage the current pandemic crisis, we must better understand how the Swiss public perceives the public health measures implemented and concerns they have about the pandemic and the government's response to it.

Information Gaps

While governments are trying to steer through this crisis as cautiously as possible, the public is struggling to understand the situation. Communication is therefore key. Existing literature suggests that effective health communication can help enhance positive outcomes of public policy [2,3]. Importantly, exposure to focused health campaigns in the context of epidemics has proven to be an efficient tool not only to increase epidemic-related knowledge, but also to foster the adoption of recommended health behaviors [4,5].

While international organizations, national governments, public health authorities, scientific institutions, and high-quality media are trying to inform the public as responsibly as possible, many other information sources of questionable credibility exist across media platforms throughout Europe. Formal and informal opinion groups share content from these sources and influence public opinions in problematic ways, for example, by blaming specific social and ethnic groups for the pandemic or by encouraging defiance of public health recommendations. Some media draw on dystopic imagery and morally loaded language, using metaphors of war and reproaching those who voice doubts and criticism, which leads to polarization and affectively charged debates producing strong counterreactions rather than factual and nuanced public deliberation [6]. This situation has led the World Health Organization (WHO) to warn of an "infodemic," wherein too much information of mixed quality make it difficult for people to find reliable information [7]. The WHO and other public health agencies are working on refuting myths regarding, for example, false preventive measures and false cures, through fact checks of social media and writing of responses [8].

However, providing high-quality information and countering fake news are not enough. Policy makers also need feedback loops to give them real-time data on people's cognitive, emotional, and behavioral reactions to public health measures, allowing them to continuously refine and adjust preventive, control, and containment measures and communication strategies.

A better understanding of the population's reaction to mitigation measures would allow for a better estimation of their potential effectiveness, influencing both communication strategies and policy choices [9,10]. It would also help to understand to what extent policy decisions match with citizens' moral values and preferences regarding, for example, the allocation of scarce medical resources, contact tracing, or obligatory mask wearing [11]. Finally, understanding how different segments of the population perceive both the pandemic and public health measures is vital, as both disproportionately affected social groups that were already vulnerable before the pandemic, such as migrants and low-income workers [12]. How do, for example, frontline health care workers, older people, those who are chronically ill, or those who are economically vulnerable cope with the pandemic and mitigation measures? Given the limitations of "one-size-fits-all" approaches to mitigation measures, local and subgroup data are critically needed to develop more efficient strategies [13].

So far, there has been mainly "one-way communication." We know little about different subgroups' understanding of the situation and readiness to comply with policies, and how this is affected by their preferred sources of information. Cross-sectional opinion polls [14-16] encounter important limits in rapidly evolving situations—they are resource-intensive and limited in scope, their items are typically designed in a top-down way, and they struggle with high nonresponse rates and provide snapshots rather than continuous monitoring [11]. Consequently, policy makers might rely on a suboptimal picture of reality in order to make their choices, and some citizens may feel that large demonstrations are the only way to make themselves heard. Even if the majority of the public supports public policies and cooperates with them, this consensus may become fragile in the future if authorities disregard misunderstandings, concerns, or unrest in certain segments of the population. Better monitoring of public perceptions would enable better communication and

more effective containment measures that reduce collateral damage to society.

However, such monitoring must be done in a way that citizens do not perceive as unwanted surveillance but rather as an initiative that invites their active input and values their views and opinions.

Aims

PubliCo seeks to address these gaps. It is an experimental online platform built with a strong participatory citizen science component that will serve three purposes:

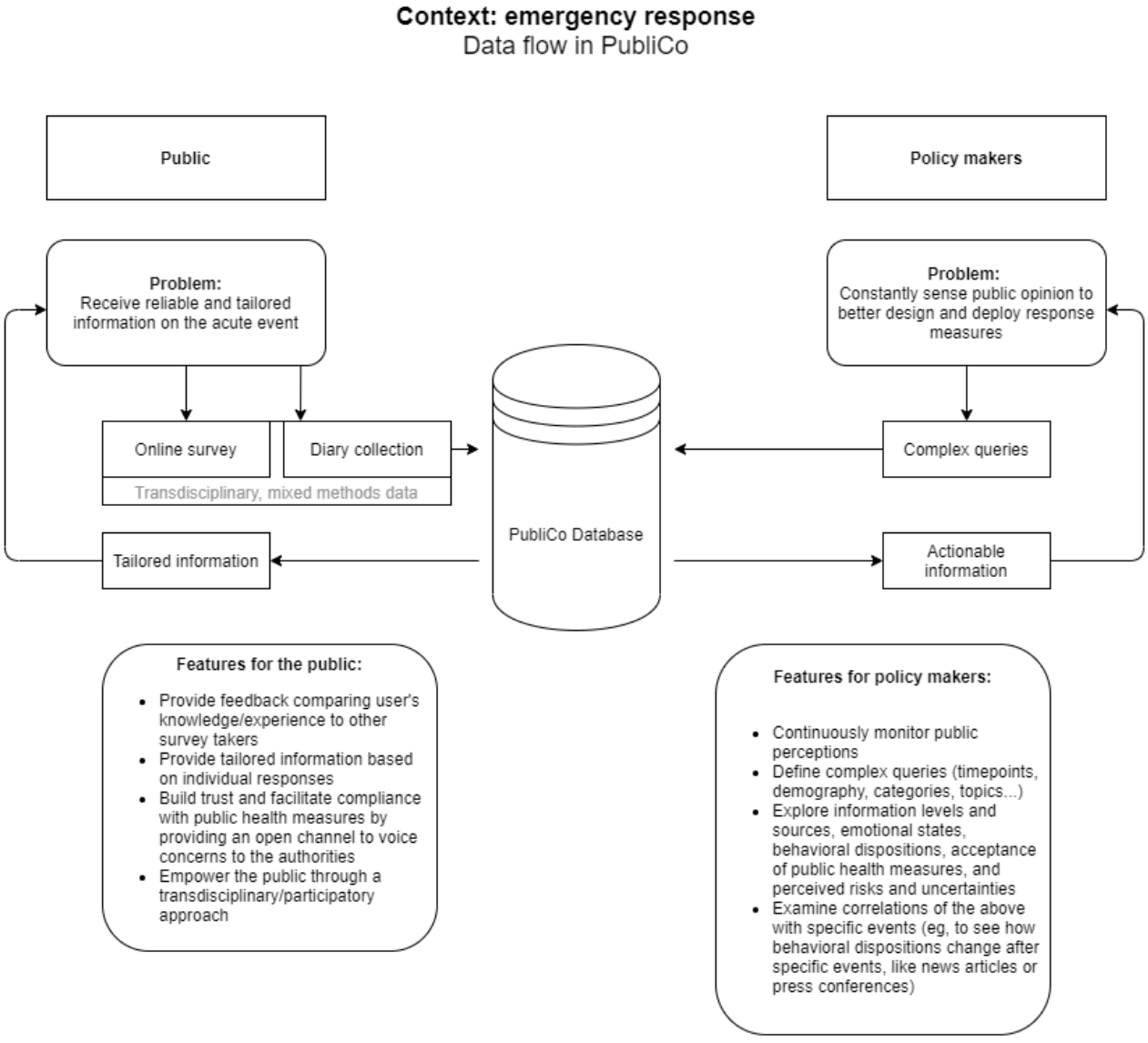
1. Collect real-time data on COVID-19–related public perception;
2. Provide tailored, timely, and reliable information to the public;
3. Facilitate well-targeted health policy making based on the theory that successful communication, public understanding, and consent reinforce the effectiveness of public health measures [2,3,5].

Methods

Concept

The project combines analytical work and empirical studies using mixed methods and strong citizen science components in order to deliver a functional platform composed of three main elements: PubliCo Survey, PubliCo Diaries, and PubliCo Analytics (Figure 1).

Figure 1. The PubliCo conceptual structure. After completing a short survey (PubliCo Survey), citizens can receive information tailored to their needs. Users can also register as citizen scientists and contribute diaries (PubliCo Diaries). Policy makers can study the information provided by citizens in order to conceive, deploy, and evaluate more efficient mitigation and containment measures (PubliCo Analytics).



PubliCo Survey will be the main source of quantitative information. Based on demographic characteristics and scores on selected subscales, citizens will obtain information specific to their needs. For example, people living in border regions will receive information about neighboring countries, and people with children will receive information about safety measures

in schools. The survey will be ongoing, providing real-time data on public perception and readiness to cooperate with public health strategies.

PubliCo Diaries will be the main source of qualitative information. Qualitative solicited diaries can provide "unique insights into the life-worlds inhabited by individuals; their experiences, actions, behaviors, and emotions and how these are played out across time and space" [17]. The diary approach empowers citizens to integrate their personal experiences and perceptions [18] while remaining in control not only of the content described but also of the pace and time of data collection [17]. In this way, this participatory method allows for the involvement of citizens in the research process and the visualization of everyday negotiation processes in real time due to the immediacy of documentation [17,19].

Users will register as citizen scientists and keep a weekly diary to record their reflections on how COVID-19 and related policy measures affect their daily routine, social practices, values, and priorities. Citizen scientists may also keep their diaries offline or record audio files and have the text entered by project staff afterward so that segments of the population that do not have time to keep a written diary or are less tech-savvy can participate. In this way, PubliCo Diaries attempts to reach diverse groups of citizens currently encountering different personal situations and possibilities (eg, pregnant women, older people, people on short-time work, youth, or people with a migration background). These texts will provide information about meaning, as well as new insights on emerging, unforeseen impacts of the pandemic that diary authors discuss in their entries. Finally, qualitative analysis of the diary data will inform the revision or generation of new survey items.

PubliCo Analytics will be the "access door" to the data collected through the survey and the diaries. It will provide information to be used for analyses directed to policy makers regarding information levels, behavioral dispositions, emotional states, and moral preferences related to pandemic response measures. It also allows for analysis of correlations (eg, vaccine prioritization preference vs demographic subgroups; support of preventive measures vs COVID-19 experience). Finally, PubliCo Analytics will contain thematically focused policy briefs, in which we contextualize the data, interpret core findings, and make recommendations.

Ethics Approval

As assessed by the Cantonal Ethics Committee of Canton Zurich, PubliCo does not fall under the scope of the Swiss Human Research Act (BASEC #2020-02917; December 15, 2020). Our risk assessment and data protection plan were also reviewed and approved by Ethics Review (CEBES), the institutional review board of the Institute of Biomedical Ethics and History of Medicine at the University of Zurich (CEBES #2020-13, December 15, 2020).

Development

Developing the PubliCo platform involved work on three components:

- Development of PubliCo Survey and user feedback;
- Realization and testing of the platform;
- Definition of the analytic capabilities of PubliCo Analytics.

PubliCo Survey and User Feedback

In order to define the content of the survey and user feedback, we adopted a 3-fold strategy: identify the type of information people look for by analyzing Google Trends data, map the information available on media platforms through natural language processing (NLP) of news from major media outlets, and determine the focus of COVID-19–related behavioral and social science research (BSSR) assessing the content of the data collection instruments for COVID-19 compiled by the National Institutes of Health (NIH) Office of Behavioural and Social Sciences.

The analysis of Google Trends data on searches related to COVID-19 performed in Switzerland between January and July 2020 displayed great diversity in information consumption patterns; this varied greatly depending on the canton of residency. Swiss residents may therefore welcome a system like PubliCo, which delivers personalized information [20].

We identified the following categories of queries regarding the pandemic and its effects: georeferenced information, information from official sources (eg, WHO, federal authorities), quantitative information, news and updates, medical information, and tips.

In order to understand how the media discuss and frame COVID-19 in Switzerland, we used Factiva, a news-monitoring and search engine tool developed and owned by Dow Jones & Company that has access to full-text articles published by major media outlets worldwide. We gathered and downloaded all the news articles published between January and July 2020 on COVID-19 and Switzerland.

NLP and analysis of the frequencies of lemmas [21] revealed some differences across languages. The analysis of German lemmas indicates that public discourse was focused on the quantitative aspects of the pandemic. The French subcorpus focused on describing the pandemic and its effects on people. The Italian subcorpus focused more on cases and fatalities. The English subcorpus seemed to be dominated by information reported from other sources, which is expected since English is not an official language of the Confederation. It also contained many lemmas like "company," "group," and "market," suggesting greater attention to the economic and financial impact of the pandemic [20].

All the subcorpora provided the following macrocategories of information: georeferenced information (information specific to countries, cantons, or cities); general information about the pandemic and the virus; reports from authorities and official bodies; and quantitative information.

The NIH Office of Behavioural and Social Sciences released a document listing "data collection instruments, including surveys, for assessing COVID-19-relevant BSSR domains for clinical or population research" [22]. Reviewing the surveys listed in the document, we identified 6 main topics of interest: financial impact, social practices, behavioral dispositions, moral preferences, emotional state, and cognitive understanding [20].

A comparison between information consumption patterns, information available in the media, and BSSR research interests identified 5 categories of information to collect and to provide through PubliCo: demographics, cognitive understanding, behavioral dispositions, emotional state, and moral orientations.

Citizen scientists will be involved in the validation of the survey and of the information we intend to provide. This will be accomplished through the web-based project builder of the Citizen Science Center Zurich [23].

Realization and Testing of the Platform

The PubliCo platform is being developed in cooperation with Belka, a software company based in Trento, Italy, and Munich, Germany, with extensive expertise in user experience design and development. The platform is web-based, mobile first, and built on a stack of open-source software: React (Facebook Open Source), SurveyJS (Devsoft Baltic), Typescript (Microsoft Corp), Diango (Django Software Foundation), MariaDB (MariaDB Foundation), Docker (Docker), CircleCI (Circle Internet Services), and NGINX (F5 Networks).

Particular attention is being devoted to the development of PubliCo Diaries, the interface through which registered citizen scientists can contribute their diaries. Early users have been involved in providing bottom-up feedback to refine and improve the interface. User experience testing will help ensure the platform is accessible to a large part of the Swiss population.

Another critical activity on the platform is the development of a backend for researchers, allowing nontechnical staff to view, add, and modify surveys, information for users, translations, and analytics components in an intuitive and collaborative way. The content management system fully supports a multilingual interface. Therefore, the final aim is to develop a tool that can be easily deployed and maintained everywhere, with little or no knowledge of the code running behind the interfaces.

Defining the Analytic Capabilities of PubliCo Analytics

Results from the online survey will be analyzed in multiple ways. Users will have direct feedback for certain variables (eg, information level, behavioral dispositions), including scores and official information based on responses to knowledge questions as well as basic descriptive statistics (means and frequencies) for all users and specific subgroups or respondents from specific cantons.

In addition, through PubliCo Analytics, researchers and policy makers will be able to answer complex questions like “Are people who know someone who got infected with COVID-19 more likely to get vaccinated?” and “How would people who have personal experience with COVID-19 prefer the vaccine to be distributed?” Queries can be restricted to specific subgroups (eg, age, residency, level of education).

Project researchers will also analyze results for periodic policy briefs. Questions to be examined will vary over time and will include basic descriptive statistics for the different domains included in the survey (knowledge, emotional state, behavioral dispositions, and moral preferences), subgroup analyses by geographical area and target group, and correlation analyses. Questions to be examined through the correlation analysis include:

- What is the relationship between participants’ knowledge and willingness to comply with public health restrictions?
- What is the relationship between participants’ knowledge and emotional state?
- What is the relationship between participants’ emotional state and their willingness to comply with public health restrictions?
- What factors influence participants’ moral preferences?

These and other questions will be analyzed using regression analysis with a significance level of α=.05.

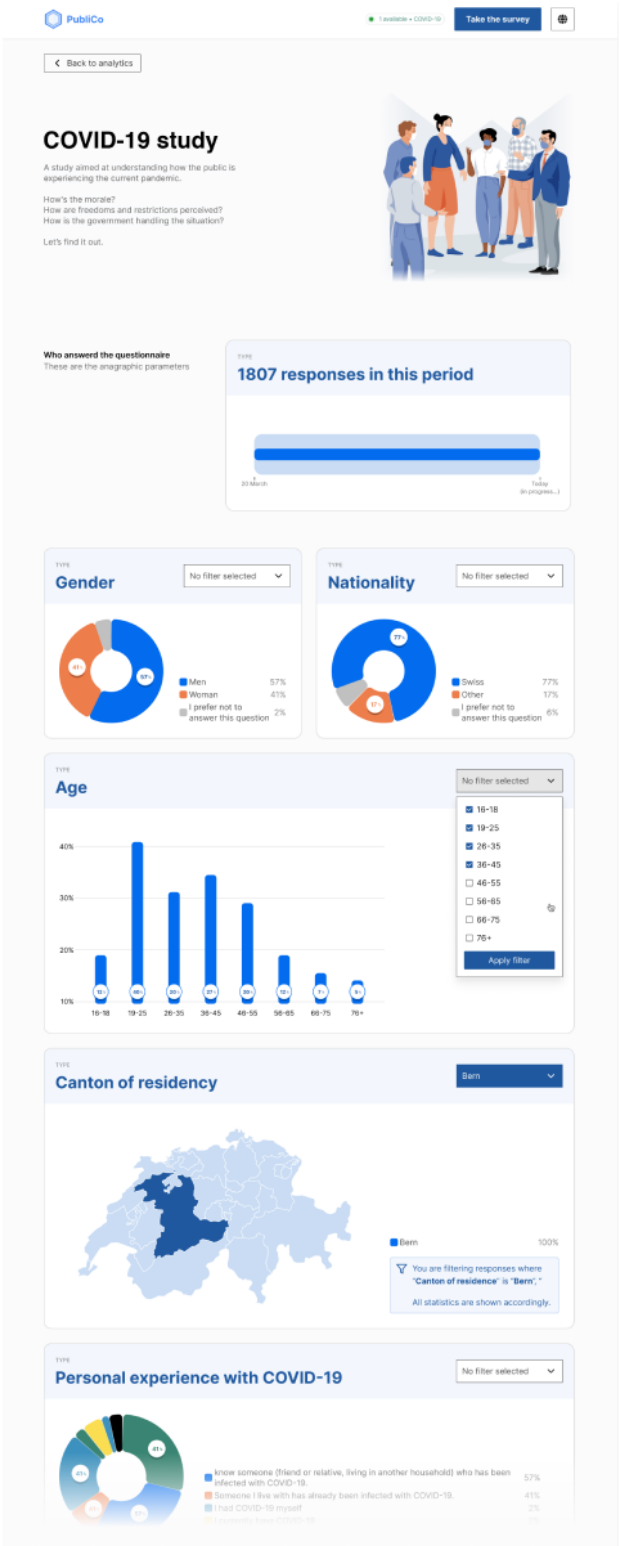
The diary narratives will be anonymized and analyzed in conjunction with the ongoing data collection by means of thematic analysis [19] using the software MAXQDA (VERBI GmbH) [24].

Selected data will be displayed in PubliCo Analytics in a visually appealing way (eg, infographics, live maps), as shown in Figure 2 (for a higher-resolution version, see Multimedia Appendix 1).

Advanced analytics will be employed whenever possible (NLP for text elements; predictive modeling of, for example, public behavior in case of new measures implemented). Many passages, from the analysis of diaries to the automated analysis of selected subscales, will be automatized by means of NLP and other related artificial intelligence applications. These techniques will ensure that the platform is more cost-effective and that the results of the analysis and actionable information are available faster.

Data collection will be adapted to how the situation evolves, taking up emerging themes (eg, vaccine distribution, balancing work requirements, and protection of at-risk persons). Core findings and recommendations will be published in thematically focused policy briefs.

Figure 2. A high-level mock-up of PubliCo Analytics. Different kinds of survey data can be presented with an appropriate visualization. Visualizations can also be used to dynamically select a subset of the data frame (eg, selecting only specific demographic variables). The interface is meant to be informative, clear, and comprehensive to the general public. Every visualization is accompanied by an explanatory note.



Results

Data Collection

Data collection for PubliCo Survey started with a pilot phase (December 2020 to April 2021), during which we collected analytics on how the platform and its different tools are used. For this purpose, we used a shorter version of the PubliCo survey, evaluated by citizen scientists through Citizen Science Center Zurich. This yielded more bottom-up input before deploying the full survey.

Data collection for PubliCo Diaries started during the pilot phase as well. Participants were given a brief guide to the diary method, which informed them about the openness of the method (eg, without concerns about spelling and grammar). The guide

asked them to jot down their experiences and thoughts from the beginning of the pandemic to the current day and their everyday worries, emotions, risks, experiences, decisions, and actions during and/or after the pandemic on at least a weekly basis for a duration of at least 4 weeks. This will allow us to monitor changes in participants' values, attitudes, level of knowledge, and behaviors [25].

Following the pilot phase, in order to increase the user base, PubliCo is in the process of being disseminated through:

- General media through featured articles in order to reach the general population;
- Mailing lists of the University of Zurich and the University of Basel in order to reach undergraduate and graduate students;
- Facebook groups in order to reach selected target groups, including migrants and parents;
- Teachers' associations in order to reach high school students;
- Participants of the Swiss branch of the DIPEx International Study on COVID-19 in order to reach people who had direct experience of COVID-19;
- A demoscopic company that will solicit a representative sample for comparative purposes.

The outboarding section also invites the users to share the tool further via social media, email, or similar systems, and to register as citizen scientists for the PubliCo Diaries component. We will also investigate possibilities of disseminating through official channels, like the automatic SMS sender of the Federal Office of Public Health.

As of September 2021, we collected a total of 473 responses through PubliCo Survey, and 22 diaries through PubliCo Diaries. Data collection will be iterative and will proceed for at least 2 years. We expect the tool to be refined and enhanced as data collection and analysis moves forward. Because of the design of the tool, data saturation will be determined a posteriori by analyzing the demographic data of surveys and diary users. The current version of the tool is available at online [26].

Availability of Data

Preliminary and Intermediate Data

The Google Trends data set used to define the survey component is available through our Zenodo repository [27]. The software used for the analysis of the Factiva corpus is also available through our Zenodo repository [28], as are the raw results of the analysis of the Factiva corpus [21]. Due to copyright restrictions, the Factiva corpus is available through Factiva.

Research Data

Data generated from PubliCo will be available through the PubliCo Analytics interface. Diary data are available upon request.

Discussion

Ethics and Dissemination

One aim of PubliCo is to deliver personalized information in the context of public health emergencies. However, providing personalized information can be potentially problematic. Feedback on knowledge-based questions simply involves notifying users of wrong answers and providing access to reliable sources, like the WHO or official information outlets [29]. Some uneasiness remains around making assumptions about citizens' informational needs and possibly contributing to knowledge "bubbles." Providing personalized information from subscales regarding emotional response, moral preferences, or mental well-being is more challenging. For these topics, we will provide a comparison between individual scores and sample means. In this sense, it is fundamental to clarify the descriptive nature of the scores without any claims as to what the norm should be (the is-ought problem). The final strategy needs to be defined with expert advisors and citizen scientists after evaluating potential outcomes.

The Swiss cantons have been affected in different ways by the COVID-19 pandemic. Our approach, comparing geolocated data, might reveal differences in behaviors and attitudes that could correlate with the course and the severity of the pandemic. Because of this, we will collect some demographic information (personal data; potentially also sensitive data as defined in the Law on Information and Data Protection (IDG) paragraph 3 of the Canton of Zurich) and some information about personal philosophical or religious beliefs (sensitive data as defined in IDG paragraph 3).

The potential harms generated by the project, assessed in Table 1, fall into two categories: reidentification (and thus attribution of specific opinions to specific persons) and morally problematic questions.

The most prominent category of risk is connected to the reidentification of participants. To minimize the chances of this, the survey component is completely anonymous by design (not even the IP [Internet Protocol] address is collected), and the diary component is pseudonymous (we can attribute diaries to users, but we cannot attribute users to persons). The only remaining concrete risk for reidentification is posed by what users could write in the diaries. Because of this, we are taking extra care in planning the access, use, and management of this category of data: no personal identifiers are collected upon registration, diary text is accessible upon request to trusted third parties (eg, research institutions), and the content is manually checked for full anonymity beforehand. We are confident that the instrument is safe from a data protection point of view.

All the data will be stored in a virtual machine hosted in the data center of the University of Zurich with access restricted to the project members. The chances of identification, in the eventuality of a data leak, are very low.

In order to mitigate the second category of risk, we are discussing the whole survey tool with expert advisors and citizen scientists in order to get additional feedback on the issues involved. However, the impact would still be low, and, more importantly, an unsatisfied user can pause or end participation at any time.

The very nature of this project implies another general risk: in a less democratic context, the tool we are developing could be used for social control. This is a potential risk we cannot

mitigate for other countries. For Switzerland, the whole infrastructure of the project was built keeping in mind a transparent and democratic approach, important in general in the scientific enterprise, but fundamental in a context in which the data yielded from the system are used in order to make decisions impacting the public.

Overall, participants do not have an immediate personal benefit beyond the insights gained through the survey experience and feedback, but they do have a long-term community benefit resulting from the tool being used to deploy public health measures that consider and take into account their preferences. Therefore, we consider the risk-benefit balance justifiable.

Table 1. Risk assessment of PubliCo.

Potential event and consequences	Type of harm	Severity (1-5)	Likelihood (1-5)
Reidentification of a participant			
Participants can feel betrayed by the data controller and lose trust in the research or society	Psychological	2	1
Participants with controversial opinions could lose their jobs if these views are considered particularly dangerous by their employers	Economical	3	1
Participants with controversial opinions could be rejected and isolated from the societies they belong to	Social	3	1
Participants with controversial opinions could be physically assaulted because of their opinions	Physical	5	1
Morally problematic questions			
Participants can be upset when asked about morally problematic topics (eg, allocation of scarce resources), especially if directly impacted by the issue at stake	Psychological	2	3

Open Science by Design

We believe that adopting a democratic, bottom-up approach to design and develop PubliCo would greatly improve public perception of the project, while allowing us to tackle urgent and unforeseen issues [30]. As such, every component of PubliCo will be publicly available: the research project, the intermediate data sets and the software used to compile them, the source code, the raw data, and the interpretative briefs. The only data that will be subject to manual checks before release is the raw text of the diaries, as stated above.

This setup will increase trust in the project, encourage secondary use of PubliCo data, and facilitate the implementation of the tool in other countries.

Limitations

This design has two main limitations. Our approach focuses on public perception rather than on observational data of real practices. There may be discrepancies between opinions, attitudes, and behavioral dispositions and what people do in reality. On the other hand, we think much insight is to be gained already from what people are, in principle, agreeable to or what they will consider unacceptable.

The second limitation concerns the information that is provided at the end of the survey. For some topics (eg, the concrete risk posed by COVID-19), it remains difficult to find solid metrics, and the way they are communicated can generate problems and misunderstandings. In this sense, we have opted to use a different approach: users will be pointed first to the official information provided by the Federal Office of Public Health, and secondly (depending on their scores in cognitive understanding) to PubMed queries designed to yield systematic reviews or meta-analyses. This way, following once again an open-science spirit, citizens will be able to access the relevant literature.

Conclusions

Pilot data show that PubliCo is a promising and efficient concept for bidirectional risk and crisis communication in the context of public health crises, as it can reach and engage different segments of the Swiss population, collecting and providing information at the same time. Further data are needed to assess its function at a larger scale or in the context of an issue other than COVID-19.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Higher-resolution version of the high-level mock-up of PubliCo Analytics.
[PNG File , 985 KB - resprot_v10i11e33653_app1.png]

Multimedia Appendix 2
Peer-review report 1 by the Swiss National Science Foundation.
[PDF File (Adobe PDF File), 90 KB - resprot_v10i11e33653_app2.pdf]

Multimedia Appendix 3
Peer-review report 2 by the Swiss National Science Foundation.
[PDF File (Adobe PDF File), 85 KB - resprot_v10i11e33653_app3.pdf]

Multimedia Appendix 4
Peer-review report 3 by the Swiss National Science Foundation.
[PDF File (Adobe PDF File), 96 KB - resprot_v10i11e33653_app4.pdf]

Multimedia Appendix 5
Peer-review report 4 by the Swiss National Science Foundation.
[PDF File (Adobe PDF File), 92 KB - resprot_v10i11e33653_app5.pdf]

Multimedia Appendix 6
Peer-review report 5 by the Swiss National Science Foundation.
[PDF File (Adobe PDF File), 92 KB - resprot_v10i11e33653_app6.pdf]

References

1. 1,000 people gather for unofficial football match. Swissinfo.ch. 2020 May 22. URL: https://www.swissinfo.ch/eng/corona-restrictions-broken-_1-000-people-gather-for-unofficial-football-match-/45778644 [accessed 2020-11-27]
2. Lee ST, Basnyat I. From press release to news: mapping the framing of the 2009 H1N1 A influenza pandemic. Health Commun 2012 Mar 22;28(2):119-132. [doi: 10.1080/10410236.2012.658550] [Medline: 22439616]
3. Sandell T, Sebar B, Harris N. Framing risk: communication messages in the Australian and Swedish print media surrounding the 2009 H1N1 pandemic. Scand J Public Health 2013 Dec 19;41(8):860-865. [doi: 10.1177/1403494813498158] [Medline: 23873631]
4. Ning L, Niu J, Bi X, Yang C, Liu Z, Wu Q, et al. The impacts of knowledge, risk perception, emotion and information on citizens' protective behaviors during the outbreak of COVID-19: a cross-sectional study in China. BMC Public Health 2020 Nov 23;20(1):1751 [FREE Full text] [doi: 10.1186/s12889-020-09892-y] [Medline: 33225934]
5. Lin L, Savoia E, Agboola F, Viswanath K. What have we learned about communication inequalities during the H1N1 pandemic: a systematic review of the literature. BMC Public Health 2014 May 21;14(1):484 [FREE Full text] [doi: 10.1186/1471-2458-14-484] [Medline: 24884634]
6. Semino E. "Not Soldiers but Fire-fighters" - Metaphors and Covid-19. Health Commun 2021 Jan 10;36(1):50-58. [doi: 10.1080/10410236.2020.1844989] [Medline: 33167731]
7. Novel Coronavirus (2019-nCoV) Situation Report - 13. World Health Organization. 2020 Feb 2. URL: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200202-sitrep-13-ncov-v3.pdf [accessed 2020-05-04]
8. Coronavirus disease (COVID-19) advice for the public: Mythbusters. World Health Organization. 2020. URL: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public/myth-busters [accessed 2020-05-04]
9. Plough A, Bristow B, Fielding J, Caldwell S, Khan S. Pandemics and health equity: lessons learned from the H1N1 response in Los Angeles County. J Public Health Manag Pract 2011;17(1):20-27. [doi: 10.1097/PHH.0b013e3181ff2ad7] [Medline: 21135657]
10. van der Weerd W, Timmermans DR, Beaujean DJ, Oudhoff J, van Steenbergen JE. Monitoring the level of government trust, risk perception and intention of the general public to adopt protective measures during the influenza A (H1N1) pandemic in The Netherlands. BMC Public Health 2011 Jul 19;11(1):575 [FREE Full text] [doi: 10.1186/1471-2458-11-575] [Medline: 21771296]
11. Kaplan G, Baron-Epel O. Personal needs versus national needs: public attitudes regarding health care priorities at the personal and national levels. Isr J Health Policy Res 2015 May 15;4(1):15 [FREE Full text] [doi: 10.1186/s13584-015-0010-2] [Medline: 25984294]

12. Adams-Prassl A, Boneva T, Golin M, Rauh C. Inequality in the impact of the coronavirus shock: Evidence from real time surveys. Journal of Public Economics 2020 Sep;189:104245. [doi: 10.1016/j.jpubeco.2020.104245]
13. SteelFisher G, Blendon R, Ward J, Rapoport R, Kahn E, Kohl K. Public response to the 2009 influenza A H1N1 pandemic: a polling study in five countries. The Lancet Infectious Diseases 2012 Nov;12(11):845-850. [doi: 10.1016/s1473-3099(12)70206-2]
14. Hostettler B, Rehberg M. Umfrage der SRG - So denkt die Schweiz über die Corona-Krise. SRF. 2020 Mar 24. URL: https://www.srf.ch/news/schweiz/umfrage-der-srg-so-denkt-die-schweiz-ueber-die-corona-krise [accessed 2020-06-07]
15. Deutsche finden Versammlungsverbot richtig. Tagesschau. 2020 Mar 23. URL: https://www.tagesschau.de/inland/deutschlandtrend-extra-blitzumfrage-103.html [accessed 2020-06-07]
16. Betsch C, Wieler L, Bosnjak M, Ramharter M, Stollorz V, Omer S, et al. Germany COVID-19 Snapshot MOnitoring (COSMO Germany): Monitoring knowledge, risk perceptions, preventive behaviours, and public trust in the current coronavirus outbreak in Germany. PsychArchives 2020:1-6 [FREE Full text] [doi: 10.23668/psycharchives.2776]
17. Milligan C, Bartlett R. Solicited Diary Methods. In: Liamputtong P, editor. Handbook of Research Methods in Health Social Sciences. Singapore: Springer; 2019:1447-1464.
18. Harvey L. Intimate reflections: private diaries in qualitative research. Qualitative Research 2011 Dec 02;11(6):664-682. [doi: 10.1177/1468794111415959]
19. Hyers L. Diary Methods: Understanding Qualitative Research. Oxford, UK: Oxford Scholarship Online; 2018.
20. Jafflin K, Merten S, Spitale G, Schwind B, Kaiser-Grolimund A, Biller-Andorno N. PubliCo: Improving risk and crisis communication in the context of the COVID-19 crisis. Zenodo. 2021 Oct 21. URL: https://zenodo.org/record/5587997#.YXESdBpByUk [accessed 2021-10-21]
21. Spitale G, Merten S, Biller-Andorno N. Lemmas and Named Entities analysis in major media outlets regarding Switzerland and Covid-19 [Data set]. Zenodo. 2020 Sep 18. URL: https://doi.org/10.5281/zenodo.4036071 [accessed 2021-10-20]
22. COVID-19 OBSSR Research Tools. NIH National Institute of Environmental Health Sciences, US National Library of Medicine. 2020 May 14. URL: https://www.nlm.nih.gov/dr2/COVID-19_BSSR_Research_Tools.pdf [accessed 2020-06-10]
23. PubliCo. Beta | Citizen Science Center Zurich. 2020. URL: https://lab.citizenscience.ch/en/project/231 [accessed 2020-11-27]
24. Morse J, Woolf N, Silver C. Qualitative Analysis Using MAXQDA: The Five-Level QDATM Method. New York: Routledge; 2017.
25. Constant N, Roberts L. Narratives as a mode of research evaluation in citizen science: understanding broader science communication impacts. JCOM 2017;16(04):A03. [doi: 10.22323/2.16040203]
26. Spitale G, Merten S, Jafflin K, Schwind B, Kaiser-Grolimund A, Biller-Andorno N. PubliCo. 2020. URL: https://www.publico.community/ [accessed 2021-10-20]
27. Spitale G, Biller-Andorno N, Jafflin K, Merten S. Google Trends normalized hits for COVID-19 generated in Switzerland (Version 2) [Data set]. Zenodo. 2020. URL: https://doi.org/10.5281/zenodo.5012680 [accessed 2021-10-20]
28. Spitale G, Merten S, Biller-Andorno N. Factiva parser and NLP pipeline for news articles related to COVID-19 (1.1.0). Zenodo. 2020. URL: https://doi.org/10.5281/zenodo.3991821 [accessed 2021-10-20]
29. EU vs Disinfo. 2020. URL: https://euvsdisinfo.eu/ [accessed 2020-06-10]
30. Smart P, Holmes S, Lettice F, Pitts FH, Zwiegelaar JB, Schwartz G, et al. Open Science and Open Innovation in a socio-political context: knowledge production for societal impact in an age of post-truth populism. R&D Management 2019 May 29;49(3):279-297. [doi: 10.1111/radm.12377]

Abbreviations

BSSR: behavioral and social science research
CEBES: Checkliste für den Ethik-Begutachtungsprozess von nichtbewilligungspflichtigen empirischen Studien (Ethics Review)
IDG: Law on Information and Data Protection
IP: Internet Protocol
NIH: National Institutes of Health
NLP: natural language processing
WHO: World Health Organization

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Protocol

Smartband-Based Automatic Smoking Detection and Real-time Mindfulness Intervention: Protocol for a Feasibility Trial

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Abstract

Background: Smoking is the leading cause of preventable death in the United States. Smoking cessation interventions delivered by smartphone apps are a promising tool for helping smokers quit. However, currently available smartphone apps for smoking cessation have not exploited their unique potential advantages to aid quitting. Notably, few to no available apps use wearable technologies, most apps require users to self-report their smoking, and few to no apps deliver treatment automatically contingent upon smoking.

Objective: This pilot trial tests the feasibility of using a smartband and smartphone to monitor and detect smoking and deliver brief mindfulness interventions in real time to reduce smoking.

Methods: Daily smokers (N=100, ≥5 cigarettes per day) wear a smartband for 60 days to monitor and detect smoking, notify them about their smoking events in real time, and deliver real-time brief mindfulness exercises triggered by detected smoking events or targeted at predicted smoking events. Smokers set a quit date at 30 days. A three-step intervention to reduce smoking is tested. First, participants wear a smartband to monitor and detect smoking, and notify them of smoking events in real time to bring awareness to smoking and triggers for 21 days. Next, a "mindful smoking" exercise is triggered by detected smoking events to bring a clear recognition of the actual effects of smoking for 7 days. Finally, after their quit date, a "RAIN" (recognize, allow, investigate, nonidentification) exercise is delivered to predicted smoking events (based on the initial 3 weeks of tracking smoking data) to help smokers learn to work mindfully with cravings rather than smoke for 30 days. The primary outcomes are feasibility measures of treatment fidelity, adherence, and acceptability. The secondary outcomes are smoking rates at end of treatment.

Results: Recruitment for this trial started in May 2021 and will continue until November 2021 or until enrollment is completed. Data monitoring and management are ongoing for enrolled participants. The final 60-day end of treatment data is anticipated in January 2022. We expect that all trial results will be available in April 2022.

Conclusions: Findings will provide data and information on the feasibility of using a smartband and smartphone to monitor and detect smoking and deliver real-time brief mindfulness interventions, and whether the intervention warrants additional testing for smoking cessation.

Trial Registration: ClinicalTrials.gov NCT03995225; https://clinicaltrials.gov/ct2/show/NCT03995225

International Registered Report Identifier (IRRID): DERR1-10.2196/32521

(JMIR Res Protoc 2021;10(11):e32521) doi:10.2196/32521

KEYWORDS

smartband; smartphone; smoking; mindfulness; craving; mHealth

Introduction

Smoking is the leading cause of preventable disease, disability, and death in the United States [1]. Despite large-scale efforts to reduce smoking, the efficacy of clinical interventions for smoking cessation remains low [2]. Although 68% of smokers want to quit, only 7.4% achieve this annually [3], demonstrating an urgent need for more effective treatments [2]. A potentially impactful way to aid smoking cessation is by delivering interventions via mobile health (mHealth) technology such as smartphone apps, which may deliver scalable and effective treatments more efficiently [4-9]. Smartphone apps have numerous advantages for delivering evidence-based treatment for smoking; however, reviews of existing apps report that they have not yet used key potential features to aid smoking cessation [6,7]. In particular, few smoking cessation apps use wearable technologies, most apps require users to self-report smoking, and few apps deliver real-time interventions contingent upon smoking events.

One feature of mHealth technology not yet well-integrated into available smoking cessation apps is data from wearables. Many behavioral treatments for smoking teach smokers to self-monitor their smoking habits, including when, where, and how often they smoke, to learn to identify their smoking patterns and triggers. Wearable technologies such as smartbands are being developed to advance current tracking methods by automatically monitoring and detecting smoking and notifying smokers of smoking events in real time. This feature alone has been found to reduce smoking as compared to a control in a pilot trial [10], a finding consistent with early studies indicating that self-monitoring of smoking behavior alone could reduce smoking [11] particularly among smokers motivated to quit [12]. The ability to accurately track smoking is a critical issue as smokers may underestimate or deny smoking [13], and discordance between detected and self-reported smoking rates can negatively impact clinical trials and population studies that are used to allocate resources and set health priorities [14]. Automatic monitoring and detection of smoking also enables triggering real-time interventions contingent upon detected smoking events. Furthermore, data from wearables can be used to identify individualized profiles of smoking behavior to deliver real-time interventions targeted to *predicted* smoking events. Individual differences in smoking behavior in daily smokers can be characterized by regular patterns of smoking frequency [15], driven by nicotine dependence and other affective and situational factors [16,17]. Therefore, this study tests the feasibility of using a smartband [10] to automatically monitor and detect smoking, deliver real-time interventions triggered by smoking events, and deliver real-time interventions targeted to predicted smoking events according to individualized smoking profiles.

This study uses smartband and smartphone technology to deliver brief mindfulness interventions for smoking cessation. Mindfulness has been defined as the awareness that arises when paying attention in the present moment, on purpose and nonjudgmentally [18]. Mindfulness has been operationalized in research to include maintaining attention on one's immediate experience and cultivating an attitude of acceptance or nonjudgement toward one's experience [19]. Mindfulness training typically involves the practice of attention regulation, body awareness, and emotion regulation [20]. For smoking cessation, mindfulness training may help smokers learn to work mindfully with cues, cravings, and affective states that trigger smoking. Smokers may learn to become aware of cues and triggers, pay attention to cravings as they arise, and accept their experience and learn to ride out the cravings rather than to react by smoking [21]. Previous studies indicate that mindfulness training may reduce cigarette craving and withdrawal [22,23], aid in smoking cessation [24,25], and support recovery from lapses following a quit attempt [26]. Furthermore, mindfulness training for smoking cessation delivered by a smartphone app has been demonstrated to be feasible and found to lessen the association between craving and smoking across treatment versus a comparator app [27] and to reduce the neural response to smoking cues and related cigarette consumption [28]. The ability to deliver mindfulness interventions for smoking in context, at the critical moment when smoking or craving occurs, may boost efficacy. Furthermore, brief mindfulness practices may be efficient, accessible, and feasible to learn [29]. Brief mindfulness interventions for smoking have been associated with significant reductions in negative affect, cravings, withdrawal symptoms, and smoking behavior [22,30,31], and with significant increases in mindfulness [29] and have been correlated with outcomes as a component of larger mindfulness training programs for smoking cessation [30,32].

Building upon the extant literature, this study tests the feasibility of using a smartphone and smartband to deliver brief mindfulness exercises to intervene with craving and smoking in real time. This trial tests a three-step intervention among daily smokers making a quit attempt. First, a smartband is used to monitor and detect smoking and notify smokers of smoking events in real time to bring awareness to their smoking behavior and triggers. Next, a "mindful smoking" exercise is triggered by detected smoking events to bring awareness to the present moment effects of smoking—the physical sensations, emotions, and thoughts that result from smoking [21,33]—to begin a process of disenchantment with smoking [21,34]. Last, a "RAIN" (recognize, allow, investigate, nonidentification [21]) mindfulness exercise is targeted to predicted smoking events according to individualized smoking profiles to help smokers work mindfully with cravings rather than to react by smoking [27,32]. The goals of this feasibility trial are to establish that treatment can be delivered per protocol, participants will adhere to treatment, and treatment will be acceptable, prior to a larger clinical efficacy trial. This study will evaluate treatment fidelity, adherence, and acceptability, using outcomes consistent with guidelines and prior studies [35,36].

Methods

Overview

A feasibility clinical trial funded by the National Center for Complementary and Integrative Health will be conducted. Ethical approval for the procedures of this trial was obtained from the Yale University Institutional Review Board. All participants will provide online informed consent.

Setting

The study will be conducted by smartband and smartphone, and be online and optimized for mobile phones. Treatment delivery will be smartphone- and smartband-based.

Participants

Participants (N=100) will be eligible if they are 18 years or older, smoke at least 5 cigarettes per day (CPD) for at least 2 years, own an iPhone or Android, are fluent in English as intervention content was only available in English at study onset, and are motivated to quit as indicated by a score of at least 4 of 5 on one item of the Action subscale of the Readiness to Change Questionnaire, "I am trying to smoke less than I used to" from 1 (strongly disagree) to 5 (strongly agree) [37].

Recruitment

Participants will be recruited using online advertising (eg, Facebook ads) and directed to a study website and online screening survey. This recruitment method has been used previously to enroll 505 participants and randomize 56 participants per month in a similar smartband-based clinical trial [27]. This approach should have broad reach. The study website will link to a short screening survey on Yale Qualtrics Survey Tool. The survey will notify an individual if they are eligible or not eligible. If eligible, they will be asked for their contact information and directed to an online informed consent form. Those who provide contact information and online informed consent will receive an email with a copy of the consent form. Participants will then be asked to respond by text to confirm their interest in enrolling in the study and to schedule a short video call with a researcher for onboarding to the study technology. To finalize enrollment, participants must complete the onboarding session.

Smartband Technology

The smartband used in this study is developed by Somatix, Inc [10] and uses a machine learning algorithm to identify the hand-to-mouth gestures that characterize smoking a cigarette and differentiate these from other similar hand gestures for a given individual. Briefly, raw data are collected from the accelerometer and gyroscope sensors, and following data stabilization and noise filtering, the algorithm determines which movements being performed by the individual signify smoking. Upon smoking detection (3-4 puffs) the user is asked to confirm or deny smoking on the associated smartphone app.

Onboarding

Upon SMS text message confirmation of interest in enrollment, participants will be shipped the study equipment (smartband, charger, brief instructions, prepaid return envelope). Upon receipt of study equipment, a researcher will conduct an onboarding session with the participant by video call. The onboarding session will walk the participant through using the smartband and smartphone app, including charging and setting up the smartband, pairing and using the smartband and app, and reviewing study instructions. At the end of the onboarding session, participants will be sent a reminder of the study instructions by email. That email will also include troubleshooting tips to use as needed during the trial. Additionally, the email will include a recommendation for quit smoking medications [6]. After onboarding, participants will be SMS text messaged a link to the baseline survey to begin the study. Treatment starters will be defined as completing onboarding and wearing the smartband for 1 day.

Retention Strategies

Treatment retention will be defined as wearing the smartband on 75% (45/60) of treatment days. Retention rates will be ensured by emphasizing the importance of follow-up at study initiation, onboarding, and at each study survey; paying US $10 for onboarding, US $20 for the survey at 21 days, US $10 each for surveys at 28 and 60 days, and US $1 per day for wearing the smartband for 12 waking hours; paying for surveys immediately upon survey completion; and paying a US $50 completion bonus at the end of the study for completing all parts of the study.

Intervention

All participants will receive a smartband and smartphone app for the smartband (Figure 1) and take part in a 60-day intervention (Figure 2). For the first 21 days, the smartband will automatically monitor and detect smoking and notify the participant of smoking events in real time to bring awareness to smoking behavior and triggers. When smoking is detected, the smartband will vibrate and the participant will receive a notification on their smartphone app asking them to confirm or deny smoking. The notification will remain until they reply. Alternatively, if a participant smokes and it is not detected by the smartband, participants will be asked to manually report the smoking event on the smartphone app. They will be instructed to smoke as much or as little as they like [31] but will be asked to set a quit date in 30 days. Participants will be instructed to wear the smartband for 12 waking hours per day. They will be automatically sent a reminder notification from the app if they wear the smartband for <12 hours each day. Additional SMS text message reminders will be sent by the study team if they wear the smartband for <12 hours per day for 48 and 72 hours. If they do not wear the smartband at all, they will receive an additional SMS text message, email, or phone call at 48 and 72 hours. Data from this initial 21 days of smoking monitoring and detection will be used to predict individual patterns of smoking for RAIN mindfulness exercise delivery later in the intervention.

Figure 1. Smartband app smoking notification and tracking. Panel 1: Smoking is detected in real time and a notification is pushed to the user to confirm or deny smoking. Panel 2: Cigarettes smoked per day are displayed on the home page of the app. Panel 2-3: The user can report a smoking event manually if smoking is not detected by the smartband by pressing "+" on the home page and confirming smoking.

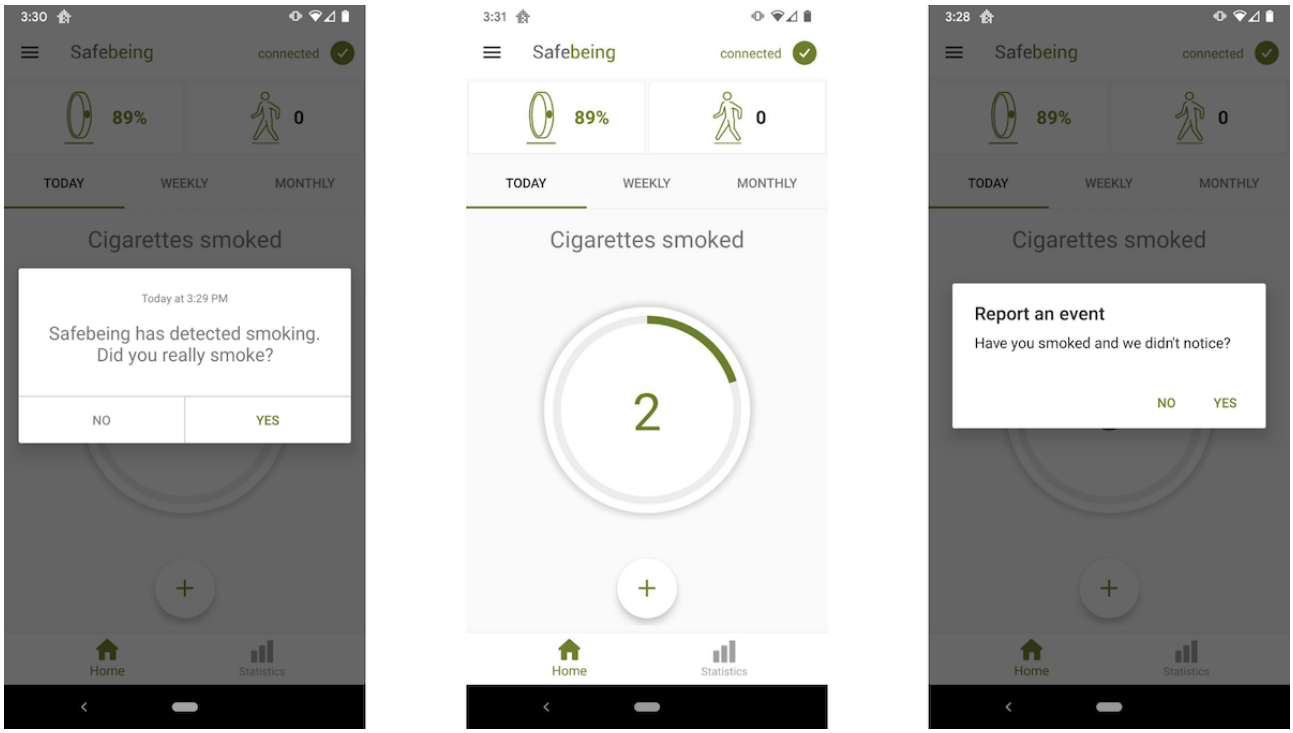
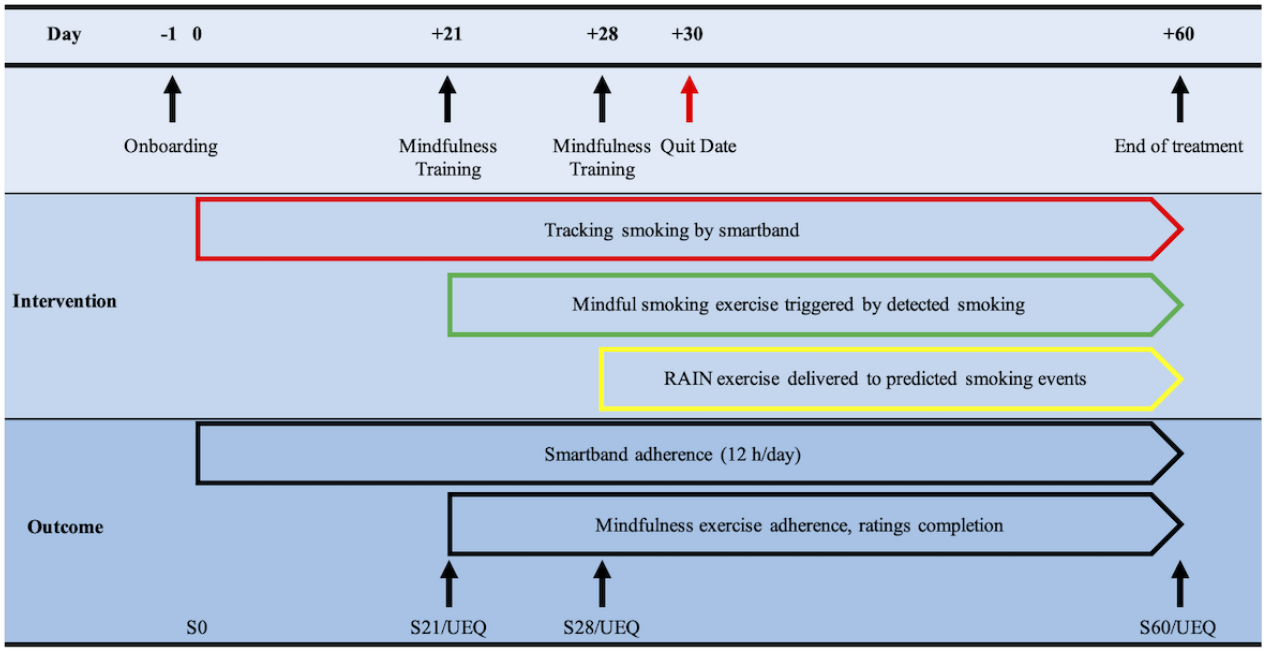


Figure 2. Study timeline. RAIN: recognize, allow, investigate, nonidentification; S: survey; UEQ: User Experiences Questionnaire.



At 21 days, participants will be SMS text messaged a link to the 21-day survey. At the end of the survey, they will take part in a brief mindfulness training adapted from Craving to Quit, a smartphone app for mindfulness training for smoking cessation [27,38]. The mindfulness training uses videos and animation to introduce mindfulness, introduces habit formation using an animation, and provides a guided mindful smoking exercise, which helps participants bring awareness to the present moment effects of smoking to gain a clear recognition of the effects of smoking. After the mindfulness training, participants will be instructed that, for the next week, the smartband will continue to automatically monitor and detect smoking, notify them of smoking events in real time, and ask them to confirm or deny smoking. They should continue to manually report any smoking events that are not detected by the smartband. In addition, anytime smoking is detected by the smartband or manually reported, they will automatically receive an SMS text message with a link to the mindful smoking exercise. They can also access mindful smoking anytime by clicking the link in their text messages. They will be instructed to try to use the mindful smoking exercise any time they smoke. After the mindful smoking exercise, they will be asked to rate how helpful they

found it. The link will direct the participant to a 2-minute audio-guided mindful smoking exercise with subtitles, followed by an ecological momentary assessment (EMA) rating, "How helpful did you find this exercise?" (visual analog scale [VAS]: "Not at all helpful" to "Very helpful").

At 28 days, participants will be SMS text messaged a link to the 28-day survey. At the end of the survey, they will take part in another brief mindfulness training adapted from Craving to Quit. The mindfulness training uses videos and animation to introduce the concept of craving, including using an animation with the metaphor of craving as a tantrum toddler (ie, let the toddler cry it out, introduces the concept of urge surfing, and provides a guided mindfulness exercise, RAIN) [21]. This exercise teaches smokers how to work mindfully with triggers to smoke using RAIN. Smokers learn to recognize cues, cravings, or affective states that trigger smoking; allow and accept their experience, however pleasant or unpleasant, without trying to change it; investigate what the experience feels like in the body, emotions, and thoughts; and nonidentification with what is happening from moment-to-moment (RAIN). By openly investigating one's present moment experiences of craving in a nonjudgmental way, one may learn that cravings are physical sensations, thoughts, and emotions that will subside. After the mindfulness training, participants will be reminded of their quit date, and instructed that, for 30 days after their quit date, the RAIN exercise will be sent to them by SMS text message at the times they typically smoke. They can also access the RAIN exercise anytime by clicking the link in their SMS text messages. They will be instructed to try to use the RAIN exercise any time they have a craving to smoke. RAIN will be delivered according to individualized smoking profiles generated from smoking data from the first 21 days of the intervention. Briefly, a prediction algorithm is run every 5 minutes and if >1 smoking event is detected within 15 minutes of the current time on any day in the 21 days, the answer is true. A text cooldown period is set at 45 minutes such that RAIN will not be sent twice within 45 minutes. These parameters were determined by an initial pilot study (n=8 completers) to provide support but minimize text burden. Before and after the RAIN exercise, they will be asked to rate their craving and affect [39]. After the RAIN exercise, they will also be asked to rate how helpful and timely they found it. The link will direct participants to a 2-minute audio-guided RAIN exercise with subtitles, preceded by rating, "How much are you craving a cigarette right now?" (VAS: "Not at all" to "Very much") and "How are you feeling right now?" (VAS: "Very bad" to "Very good"), and followed by the same ratings plus "How helpful did you find this exercise?" (VAS: "Not at all helpful" to "Very helpful") and "How was the timing of this exercise?" (VAS: "Too early" to "Too late"). Additionally, participants will be instructed that the smartband will continue to automatically monitor and detect smoking, notify them of smoking events in real time, and ask them to confirm or deny smoking. They should continue to manually report any smoking events that are not detected by the smartband. Anytime smoking is detected by the smartband or manually reported, they will continue to automatically receive an SMS text message with a link to the mindful smoking exercise.

Throughout the intervention, participants can delay or skip mindfulness exercises by ignoring the SMS text message. They can also access the mindfulness exercises at any time by clicking the link in their SMS text messages. Completion of mindfulness exercises will be time-stamped including onset and offset times for the 2-minute guided audio. To encourage completion of mindfulness exercises, participants will be sent encouraging SMS text messages indicating the number of exercises they completed on the previous day with congratulations or a reminder to use the mindfulness exercises if none were completed. These texts will be sent daily for mindful smoking (week 4) and for the first week of RAIN (week 5), and weekly thereafter for RAIN (weeks 6-8).

At 60 days, participants will be SMS text messaged a link to the 60-day (end of treatment) survey. At the end of the survey, individuals who report 1-week point prevalence abstinence from smoking (up to n=30) will take part in carbon monoxide (CO) monitoring. CO levels will be measured using piCO+ Smokerlyzer breath CO monitors (Bedfont Scientific Ltd). Participants will be shipped the CO monitor, brief instructions, and a prepaid return envelope. They will set up a video call with a researcher (recorded), during which they will use the CO monitor and display the output [27,40,41]. Once a participant has completed the 60-day survey and returned any study equipment, they will be paid their final study payment.

Measurements

Primary Outcome Measures

The primary outcome measures for this feasibility clinical trial are treatment fidelity, adherence, and acceptability across the 60-day intervention.

Treatment Fidelity

Treatment fidelity measures will include the following: *whether we can accurately detect smoking events* will be measured as the percent of smoking events detected and the rate of false alarms in the first 21 days of the study during which smokers are wearing the smartband to monitor and detect smoking, are notified of smoking events in real time, and are asked to confirm or deny smoking and to self-report any undetected smoking events. We expect to replicate previous findings of >80% detection and negligible rate of false alarms [10]. *Whether we can deliver mindful smoking triggered by smoking events* will be determined by the percent of mindful smoking exercises correctly triggered by smoking events and the rate of false alarms in the next 7 days (days 21-28) of the study during which any detected or reported smoking event triggers delivery of the mindful smoking exercise by SMS text message. Again, we expect to replicate previous findings of >80% detection and a negligible rate of false alarms [10]. *Whether we can deliver RAIN to predicted smoking events* will be measured as average timeliness ratings in the final 30 days (days 30-60) of the study during which RAIN is delivered to predicted smoking events, and the participant is asked to rate timeliness. Additionally, craving ratings obtained before participants complete RAIN will be used as a proxy for whether we have targeted moments of high craving. We expect on average high timeliness and craving ratings. Ratings will be evaluated as percent of

participants and score range (very low, low, moderate, high, very high), with feasibility determined by 75% of participants rating an item as moderate or higher.

Adherence

Adherence will be measured as percent of days participants wear the smartband for 12 waking hours during the 60-day study, percent of smoking notifications answered (confirmed or denied) of those sent during the 60-day study, percent of mindful smoking exercises completed of those sent during the mindful smoking period (days 21-28) of the study, and percent of RAIN exercises completed of those sent during the RAIN period (days 30-60) of the study. Based on our pilot data, adherence cut-offs will be 80% of mindfulness exercises completed relative to the participant's baseline CPD.

Acceptability

Acceptability will be measured as mean helpfulness ratings, separately for mindful smoking and RAIN exercises. Again, ratings will be evaluated as percent of participants and score range (very low, low, moderate, high, very high), with feasibility determined by 75% of participants rating an item as moderate or higher. Acceptability will additionally be evaluated from feedback on User Experiences Questionnaires administered as part of the surveys at each time point (21, 28, and 60 days), which ask about the acceptability of the technology (eg, was it easy/difficult to complete onboarding, get technical support, keep the smartband charged, or keep the smartband paired with the smartphone) and intervention (eg, helpfulness of mindfulness exercises; liking of mindfulness exercises; or effect of mindfulness exercises on awareness, craving, and smoking). Average responses for a given rating will be evaluated as percent of participants and score range (very low, low, moderate, high, very high), with feasibility determined by 75% of participants rating an item as moderate or higher. The User Experiences Questionnaire at 60 days also includes items adapted from standardized measures including the User Burden Scale [42], System Usability Scale [43], Mobile Application Rating Scale [44], and the 4-item Acceptability of Intervention Measure [45].

Secondary Outcome Measures

The secondary outcome measures will be smoking and abstinence rates. CPD will be measured by self-report at each study survey (baseline, 21, 28, and 60 days) and detected by the smartband. Each study survey will also include the Timeline Followback [46] for the previous study period (between surveys). Additionally, 1-week point prevalence abstinence rates at 60 days will be measured by self-report (60-day survey), detected by smartband (no smoking events for the past 7 days), and based on biochemical verification (<6 parts per million CO; n=30). Continuous abstinence (<5 cigarettes since quit date [47]) will also be measured by self-report.

Exploratory Outcomes

Exploratory measures will include survey data collected at baseline, 21, 28, and 60 days (Table 1): demographics, smoking characteristics including the Fagerström Test for Nicotine Dependence [48] and Minnesota Tobacco Withdrawal Scale [49], and the Five Facet Mindfulness Questionnaire short form [50,51] as well as EMA ratings (craving, affect) collected throughout the intervention.

Table 1. Study measures.

Domain and measures	Screen	Day 0	Day 21	Day 28	Day 60
Demographics					
Demographics	✓[a]	—[b]	—	—	—
Socioeconomic status	—	✓	—	—	—
Language preference	—	✓	—	—	—
PhenX Gender Identity [52]	✓	—	—	—	—
PhenX Educational Attainment [52]	—	✓	—	—	—
Smoking					
Smoking Status [47]	✓	✓	✓	✓	✓
Timeline Followback [53]	—	✓	✓	✓	✓
Biochemical verification of abstinence	—	—	—	—	✓
Nicotine dependence					
Fagerström Test for Nicotine Dependence [48]	—	✓	—	—	✓
Minnesota Nicotine Withdrawal Scale [49]	—	✓	✓	✓	✓
Other treatments					
Medication Use Questionnaire	—	✓	✓	✓	✓
Current e-cigarette use	✓	✓	✓	✓	✓
Smoking self-efficacy					
Self-efficacy Questionnaire [54]	—	✓	✓	✓	✓
Readiness to change [37]	✓	—	—	—	—
Mindfulness					
Five Facet Mindfulness Questionnaire [51]	—	✓	✓	✓	✓
User Experiences Questionnaire					
User Experiences Questionnaire	—	—	✓	✓	✓
User Burden Scale [42]	—	—	—	—	✓
System Usability Scale [43]	—	—	—	—	✓
Mobile Application Rating Scale [44]	—	—	—	—	✓
Acceptability of Intervention Measure [45]	—	—	—	—	✓
Feasibility of Intervention Measure [45]	—	—	—	—	✓
Other					
eHealth literacy [55]	—	✓	—	—	—

[a]Indicates this item is included.

[b]Indicates this item is not included.

Statistical Analysis

Descriptive statistics of primary and secondary outcome measures will be reported prior to statistical analysis. For treatment fidelity, adherence, and acceptability, we will estimate proportions with 95% CIs. Change in smoking will be assessed using mixed regression models to compare self-reported and smartband-detected CPD, using all available data with focused contrasts on changes from baseline to 60 days. Random effects or structured variance-covariance matrix of the errors will be used to take into account correlations of repeated measures within an individual, and the best-fitting model will be selected based on Bayesian information criterion. We will perform exploratory mediation analysis of the exploratory outcomes to test mechanistic hypotheses related to smoking, craving, affect and mindfulness, and other psychological variables.

Results

The study was approved by the Yale University Institutional Review Board in March 2019 and funded in May 2019. The development and programming of the study intervention has been completed. All study methods and materials have been developed and manualized. An initial pilot study (n=30) was conducted between November 2020 and January 2021 to test and finalize the study intervention and procedures. Recruitment

for the full feasibility trial began in May 2021 and will continue until November 2021 or until enrollment is complete. Data monitoring and management are ongoing for enrolled participants. The final 60-day end of treatment data is anticipated to be collected in January 2022. We expect that all trial results will be available in April 2022.

Discussion

Principal Results

This trial is designed to test the feasibility of using a smartband and smartphone to automatically monitor and detect smoking, notify smokers of smoking events in real time, and deliver brief mindfulness interventions to help daily smokers in a smoking quit attempt. We anticipate collecting important data and information regarding innovative features of the intervention including using wearable technology (smartband) to monitor and detect (track) smoking, automatically detecting smoking rather than relying on self-report, using data from wearables to identify patterns of individual smoking behavior over time, delivering interventions contingent on smoking events and targeted to predicted smoking events, and combining novel mHealth technology with an evidence-based mindfulness intervention for smoking cessation.

Limitations

There are several potential limitations of this study. First, it is possible that data from the initial 21 days of tracking smoking by smartband may not be sufficient to obtain predictable individualized smoking profiles. This is an empirical question—the trial will provide useful data and information on our ability to predict smoking based on 21 days of smartband data. Second, smoking patterns may change over time in response to being monitored for smoking and other factors. Averaging smoking patterns for an individual across 21 days allows us to account for these changes but stay in line with clinical guidelines for setting a quit date at 30 days [56]. Third, additional psychological mechanisms other than craving and affect may impact smoking. Once the feasibility of the approach is established, future studies can include additional EMA ratings to evaluate other key psychosocial factors (eg, anxiety, stress, or activity). Fourth, an alternative design would be to combine the smartband technology with another full-scale treatment for smoking such as the Craving to Quit app [27]. However, it is a challenge in clinical trials of smartphone apps to determine efficacious components of multifeatured apps. This study takes a component approach by testing mindful smoking and RAIN exercises, which also builds upon prior work including our own demonstrating that brief mindfulness interventions can reduce craving and smoking. Last, individuals may use the technology inappropriately, such as wearing the smartband on the hand not used for smoking or not wearing the smartband upon waking up. Although we cannot completely control for missed cigarettes due to these or other factors, tracking smoking by smartband vastly improves smoking estimates beyond self-report, and this study will be one of the first to test how smartband-based smoking detection relates to self-reported CPD. These activities and other factors will also be queried on user experience questionnaires at each time point.

Conclusions

This study will provide data and information on whether smartphone- and smartband-based smoking monitoring and detection, notification, and delivery of brief mindfulness interventions aid daily smokers in a quit attempt. Feasibility outcomes will be used to inform future randomized clinical trials of the tested technology and intervention.

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Authors' Contributions

KAG conceived the study. JAB, SSO, and RG contributed to the study design. JAB designed the mindfulness training and exercises as part of the Craving to Quit app. MH, AG, and NK contributed to the study start up activities under the supervision of KG. MH and KG are conducting the study. KAG, MH, and AG wrote the paper. All authors reviewed and edited the paper.

Conflicts of Interest

JAB owns stock in and serves as a paid consultant for Sharecare Inc, the company that owns the mindfulness app used in this study. This financial interest has been disclosed to and is being managed by Brown University, in accordance with its Conflict of Interest and Conflict of Commitment policies. Unrelated to the study, SSO is a member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, supported by Alkermes, Amygdala, Arbor Pharma, Dicerna, Ethypharm, Indivior, Lundbeck, Mitsubishi Tanabe, and Otsuka; consultant/advisory board member Alkermes, Amygdala, Dicerna, and Opiant; medication supplies Astra Zeneca and Novartis; Data Safety and Monitoring Board member for National Institute on Drug Abuse Clinical Trials Network and Emmes Corporation; and has been involved in a provisional patent application with Yale University and Novartis. RG discloses the following interests unrelated to this work: royalties from book "Statistical Methods in Psychiatry and Related Fields" published by CRC Press, and a United States patent application 20200143922 by Yale University. All other authors report no biomedical financial interests or potential conflicts of interest.

Multimedia Appendix 1
External peer-review report.
[PDF File (Adobe PDF File), 178 KB - resprot_v10i11e32521_app1.pdf]

References

1. WHO global report: mortality attributable to tobacco. World Health Organization. Geneva, Switzerland; 2012 Jun 16. URL: https://www.who.int/publications/i/item/9789241564434 [accessed 2021-09-25]
2. Centers for Disease Control and Prevention (CDC). Quitting smoking among adults— United States, 2001-2010. MMWR Morb Mortal Wkly Rep 2011 Nov 11;60(44):1513-1519 [FREE Full text] [Medline: 22071589]
3. Babb S, Malarcher A, Schauer G, Asman K, Jamal A. Quitting smoking among adults - United States, 2000-2015. MMWR Morb Mortal Wkly Rep 2017 Jan 06;65(52):1457-1464. [doi: 10.15585/mmwr.mm6552a1] [Medline: 28056007]
4. Garrison KA, O'Malley SS, Brewer JA, Potenza MN. Mobile applications for mindfulness training in the treatment of substance-use disorders. In: Potenza MN, Faust K, Faust D, editors. The Oxford Handbook of Digital Technologies and Mental Health. New York, NY: Oxford University Press; 2020.
5. Haskins BL, Lesperance D, Gibbons P, Boudreaux ED. A systematic review of smartphone applications for smoking cessation. Transl Behav Med 2017 Jun;7(2):292-299 [FREE Full text] [doi: 10.1007/s13142-017-0492-2] [Medline: 28527027]
6. Abroms LC, Lee Westmaas J, Bontemps-Jones J, Ramani R, Mellerson J. A content analysis of popular smartphone apps for smoking cessation. Am J Prev Med 2013 Dec;45(6):732-736 [FREE Full text] [doi: 10.1016/j.amepre.2013.07.008] [Medline: 24237915]
7. Hoeppner BB, Hoeppner SS, Seaboyer L, Schick MR, Wu GWY, Bergman BG, et al. How smart are smartphone apps for smoking cessation? A content analysis. Nicotine Tob Res 2016 May;18(5):1025-1031 [FREE Full text] [doi: 10.1093/ntr/ntv117] [Medline: 26045249]
8. Bhattacharya A, Vilardaga R, Kientz JA, Munson SA. Lessons from practice: designing tools to facilitate individualized support for quitting smoking. ACM Trans Comput Hum Interact 2017;2017:3057-3070 [FREE Full text] [doi: 10.1145/3025453.3025725] [Medline: 29123362]
9. Vilardaga R, Casellas-Pujol E, McClernon JF, Garrison KA. Mobile applications for the treatment of tobacco use and dependence. Curr Addict Rep 2019 Jun;6(2):86-97 [FREE Full text] [doi: 10.1007/s40429-019-00248-0] [Medline: 32010548]
10. Dar R. Effect of real-time monitoring and notification of smoking episodes on smoking reduction: a pilot study of a novel smoking cessation app. Nicotine Tob Res 2018 Nov 15;20(12):1515-1518. [doi: 10.1093/ntr/ntx223] [Medline: 29126209]
11. McFall RM. Effects of self-monitoring on normal smoking behavior. J Consult Clin Psychol 1970 Oct;35(2):135-142. [doi: 10.1037/h0030087] [Medline: 5474283]
12. Lipinski D, Black JL, Nelson RO, Ciminero AR. Influence of motivational variables on the reactivity and reliability of self-recording. J Consult Clin Psychol 1975 Oct;43(5):637-646. [doi: 10.1037//0022-006x.43.5.637] [Medline: 1176677]
13. Sillett RW, Wilson MB, Malcolm RE, Ball KP. Deception among smokers. Br Med J 1978 Oct 28;2(6146):1185-1186 [FREE Full text] [doi: 10.1136/bmj.2.6146.1185] [Medline: 719343]
14. Connor Gorber S, Schofield-Hurwitz S, Hardt J, Levasseur G, Tremblay M. The accuracy of self-reported smoking: a systematic review of the relationship between self-reported and cotinine-assessed smoking status. Nicotine Tob Res 2009 Jan;11(1):12-24. [doi: 10.1093/ntr/ntn010] [Medline: 19246437]
15. Chandra S, Shiffman S, Scharf DM, Dang Q, Shadel WG. Daily smoking patterns, their determinants, and implications for quitting. Exp Clin Psychopharmacol 2007 Feb;15(1):67-80. [doi: 10.1037/1064-1297.15.1.67] [Medline: 17295586]
16. Shiffman S, Dunbar MS, Li X, Scholl SM, Tindle HA, Anderson SJ, et al. Smoking patterns and stimulus control in intermittent and daily smokers. PLoS One 2014;9(3):e89911 [FREE Full text] [doi: 10.1371/journal.pone.0089911] [Medline: 24599056]
17. Benowitz NL. Nicotine addiction. N Engl J Med 2010 Jun 17;362(24):2295-2303 [FREE Full text] [doi: 10.1056/NEJMra0809890] [Medline: 20554984]
18. Kabat‐Zinn J. Mindfullness-Based Interventions in Context: Past, Present, and Future. Clinical Psychology: Science and Practice 2006 May 11;10(2):144-156. [doi: 10.1093/clipsy.bpg016]
19. Bishop SR. Mindfulness: a proposed operational definition. Clin Psychol Sci Pract 2004 Aug 01;11(3):230-241. [doi: 10.1093/clipsy/bph077]
20. Hölzel BK, Lazar SW, Gard T, Schuman-Olivier Z, Vago DR, Ott U. How does mindfulness meditation work? Proposing mechanisms of action from a conceptual and neural perspective. Perspect Psychol Sci 2011 Nov;6(6):537-559. [doi: 10.1177/1745691611419671] [Medline: 26168376]
21. Brewer JA, Elwafi HM, Davis JH. Craving to quit: psychological models and neurobiological mechanisms of mindfulness training as treatment for addictions. Psychol Addict Behav 2013 Jun;27(2):366-379 [FREE Full text] [doi: 10.1037/a0028490] [Medline: 22642859]
22. Cropley M, Ussher M, Charitou E. Acute effects of a guided relaxation routine (body scan) on tobacco withdrawal symptoms and cravings in abstinent smokers. Addiction 2007 Jun;102(6):989-993. [doi: 10.1111/j.1360-0443.2007.01832.x] [Medline: 17523994]

23. Davis JM, Manley AR, Goldberg SB, Smith SS, Jorenby DE. Randomized trial comparing mindfulness training for smokers to a matched control. J Subst Abuse Treat 2014 Sep;47(3):213-221 [FREE Full text] [doi: 10.1016/j.jsat.2014.04.005] [Medline: 24957302]
24. Davis JM, Fleming MF, Bonus KA, Baker TB. A pilot study on mindfulness based stress reduction for smokers. BMC Complement Altern Med 2007 Jan 25;7:2 [FREE Full text] [doi: 10.1186/1472-6882-7-2] [Medline: 17254362]
25. Brewer JA, Mallik S, Babuscio TA, Nich C, Johnson HE, Deleone CM, et al. Mindfulness training for smoking cessation: results from a randomized controlled trial. Drug Alcohol Depend 2011 Dec 01;119(1-2):72-80 [FREE Full text] [doi: 10.1016/j.drugalcdep.2011.05.027] [Medline: 21723049]
26. Vidrine JI, Spears CA, Heppner WL, Reitzel LR, Marcus MT, Cinciripini PM, et al. Efficacy of mindfulness-based addiction treatment (MBAT) for smoking cessation and lapse recovery: a randomized clinical trial. J Consult Clin Psychol 2016 Sep;84(9):824-838. [doi: 10.1037/ccp0000117] [Medline: 27213492]
27. Garrison KA, Pal P, O'Malley SS, Pittman BP, Gueorguieva R, Rojiani R, et al. Craving to quit: a randomized controlled trial of smartphone app-based mindfulness training for smoking cessation. Nicotine Tob Res 2020 Mar 16;22(3):324-331 [FREE Full text] [doi: 10.1093/ntr/nty126] [Medline: 29917096]
28. Janes AC, Datko M, Roy A, Barton B, Druker S, Neal C, et al. Quitting starts in the brain: a randomized controlled trial of app-based mindfulness shows decreases in neural responses to smoking cues that predict reductions in smoking. Neuropsychopharmacology 2019 Aug;44(9):1631-1638 [FREE Full text] [doi: 10.1038/s41386-019-0403-y] [Medline: 31039580]
29. Luberto CM, McLeish AC. The effects of a brief mindfulness exercise on state mindfulness and affective outcomes among adult daily smokers. Addict Behav 2018 Feb;77:73-80. [doi: 10.1016/j.addbeh.2017.09.013] [Medline: 28965070]
30. Bowen S, Marlatt A. Surfing the urge: brief mindfulness-based intervention for college student smokers. Psychol Addict Behav 2009 Dec;23(4):666-671. [doi: 10.1037/a0017127] [Medline: 20025372]
31. Ruscio AC, Muench C, Brede E, Waters AJ. Effect of brief mindfulness practice on self-reported affect, craving, and smoking: a pilot randomized controlled trial using ecological momentary assessment. Nicotine Tob Res 2016 Jan;18(1):64-73. [doi: 10.1093/ntr/ntv074] [Medline: 25863520]
32. Elwafi HM, Witkiewitz K, Mallik S, Thornhill TA, Brewer JA. Mindfulness training for smoking cessation: moderation of the relationship between craving and cigarette use. Drug Alcohol Depend 2013 Jun 01;130(1-3):222-229 [FREE Full text] [doi: 10.1016/j.drugalcdep.2012.11.015] [Medline: 23265088]
33. Brewer JA, Davis JH, Goldstein J. Why is it so hard to pay attention, or is it? Mindfulness, the factors of awakening and reward-based learning. Mindfulness (N Y) 2013 Mar 01;4(1):75 [FREE Full text] [doi: 10.1007/s12671-012-0164-8] [Medline: 24244224]
34. Bodhi B. In the Buddha's Words: An Anthology of Discourses From the Pali Canon. Somerville, MA: Wisdom Publications; Aug 10, 2005.
35. Bowen DJ, Kreuter M, Spring B, Cofta-Woerpel L, Linnan L, Weiner D, et al. How we design feasibility studies. Am J Prev Med 2009 May;36(5):452-457 [FREE Full text] [doi: 10.1016/j.amepre.2009.02.002] [Medline: 19362699]
36. Arain M, Campbell MJ, Cooper CL, Lancaster GA. What is a pilot or feasibility study? A review of current practice and editorial policy. BMC Med Res Methodol 2010 Jul 16;10:67 [FREE Full text] [doi: 10.1186/1471-2288-10-67] [Medline: 20637084]
37. Rollnick S, Heather N, Gold R, Hall W. Development of a short 'readiness to change' questionnaire for use in brief, opportunistic interventions among excessive drinkers. Br J Addict 1992 May;87(5):743-754. [doi: 10.1111/j.1360-0443.1992.tb02720.x] [Medline: 1591525]
38. Craving to Quit. URL: https://www.cravingtoquit.com/ [accessed 2021-10-05]
39. Shiffman S, Gwaltney CJ, Balabanis MH, Liu KS, Paty JA, Kassel JD, et al. Immediate antecedents of cigarette smoking: an analysis from ecological momentary assessment. J Abnorm Psychol 2002 Nov;111(4):531-545. [doi: 10.1037//0021-843x.111.4.531] [Medline: 12428767]
40. Garrison KA, Pal P, Rojiani R, Dallery J, O'Malley SS, Brewer JA. A randomized controlled trial of smartphone-based mindfulness training for smoking cessation: a study protocol. BMC Psychiatry 2015 Apr 14;15:83 [FREE Full text] [doi: 10.1186/s12888-015-0468-z] [Medline: 25884648]
41. Dallery J, Raiff BR, Grabinski MJ. Internet-based contingency management to promote smoking cessation: a randomized controlled study. J Appl Behav Anal 2013 Dec;46(4):750-764 [FREE Full text] [doi: 10.1002/jaba.89] [Medline: 24114862]
42. Suh H, Shahriaree N, Hekler EB, Kientz JA. Developing and validating the User Burden Scale: a tool for assessing user burden in computing systems. In: Proceedings of the 2016 CHI Conference on Human Factors in Computing Systems. 2016 May Presented at: CHI '16; May 7-12, 2016; San Jose, CA p. 3988-3999. [doi: 10.1145/2858036.2858448]
43. Lewis JR. The System Usability Scale: past, present, and future. Int J Hum–Computer Interaction 2018 Mar 30;34(7):577-590. [doi: 10.1080/10447318.2018.1455307]
44. Stoyanov SR, Hides L, Kavanagh DJ, Wilson H. Development and validation of the user version of the Mobile Application Rating Scale (uMARS). JMIR Mhealth Uhealth 2016 Jun 10;4(2):e72 [FREE Full text] [doi: 10.2196/mhealth.5849] [Medline: 27287964]

45. Weiner BJ, Lewis CC, Stanick C, Powell BJ, Dorsey CN, Clary AS, et al. Psychometric assessment of three newly developed implementation outcome measures. Implement Sci 2017 Aug 29;12(1):108 [FREE Full text] [doi: 10.1186/s13012-017-0635-3] [Medline: 28851459]
46. Sobell L, Sobell M. Timeline follow-back a technique for assessing self-reported alcohol consumption. In: Litten RZ, Allen JP, editors. Measuring Alcohol Consumption Psychosocial and Biochemical Methods. Totowa, NJ: Humana Press; 1992:41-72.
47. West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. Addiction 2005 Mar;100(3):299-303. [doi: 10.1111/j.1360-0443.2004.00995.x] [Medline: 15733243]
48. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. Br J Addict 1991 Sep;86(9):1119-1127. [doi: 10.1111/j.1360-0443.1991.tb01879.x] [Medline: 1932883]
49. Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. Arch Gen Psychiatry 1986 Mar;43(3):289-294. [doi: 10.1001/archpsyc.1986.01800030107013] [Medline: 3954551]
50. Baer RA, Smith GT, Hopkins J, Krietemeyer J, Toney L. Using self-report assessment methods to explore facets of mindfulness. Assessment 2006 Mar;13(1):27-45. [doi: 10.1177/1073191105283504] [Medline: 16443717]
51. Bohlmeijer E, ten Klooster PM, Fledderus M, Veehof M, Baer R. Psychometric properties of the five facet mindfulness questionnaire in depressed adults and development of a short form. Assessment 2011 Sep;18(3):308-320. [doi: 10.1177/1073191111408231] [Medline: 21586480]
52. Hamilton CM, Strader LC, Pratt JG, Maiese D, Hendershot T, Kwok RK, et al. The PhenX Toolkit: get the most from your measures. Am J Epidemiol 2011 Aug 01;174(3):253-260 [FREE Full text] [doi: 10.1093/aje/kwr193] [Medline: 21749974]
53. Robinson SM, Sobell LC, Sobell MB, Leo GI. Reliability of the Timeline Followback for cocaine, cannabis, and cigarette use. Psychol Addict Behav 2014 Mar;28(1):154-162. [doi: 10.1037/a0030992] [Medline: 23276315]
54. Etter JF, Bergman MM, Humair JP, Perneger TV. Development and validation of a scale measuring self-efficacy of current and former smokers. Addiction 2000 Jun;95(6):901-913. [doi: 10.1046/j.1360-0443.2000.9569017.x] [Medline: 10946439]
55. Norman CD, Skinner HA. eHEALS: The eHealth Literacy Scale. J Med Internet Res 2006 Nov 14;8(4):e27 [FREE Full text] [doi: 10.2196/jmir.8.4.e27] [Medline: 17213046]
56. Fiore M, JaÈn C, Baker T, Bailey W, Benowitz N, Curry S. Treating Tobacco Use and Dependence: 2008 Update - Clinical Practice Guidelines. Rockville, MD: US Department of Health and Human Services; 2008:101-103.

Abbreviations

CO: carbon monoxide
CPD: cigarettes per day
EMA: ecological momentary assessment
mHealth: mobile health
RAIN: recognize, allow, investigate, nonidentification
VAS: visual analog scale

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Protocol

Harnessing Neuroplasticity to Promote Brain Health in Aging Adults: Protocol for the MOVE-Cog Intervention Study

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Abstract

Background: Extensive evidence supports a link between aerobic exercise and cognitive improvements in aging adults. A major limitation with existing research is the high variability in cognitive response to exercise. Our incomplete understanding of the mechanisms that influence this variability and the low adherence to exercise are critical knowledge gaps and major barriers for the systematic implementation of exercise for promoting cognitive health in aging.

Objective: We aimed to provide an in-person and remotely delivered intervention study protocol with the main goal of informing the knowledge gap on the mechanistic action of exercise on the brain by characterizing important mechanisms of neuroplasticity, cardiorespiratory fitness response, and genetics proposed to underlie cognitive response to exercise.

Methods: This is an open-label, 2-month, interventional study protocol in neurologically healthy sedentary adults. This study was delivered fully in-person and in remote options. Participants underwent a total of 30 sessions, including the screening session, 3 pretest (baseline) assessments, 24 moderate-to-vigorous aerobic exercise sessions, and 3 posttest assessments. We recruited participants aged 55 years and above, sedentary, and cognitively healthy. Primary outcomes were neuroplasticity, cognitive function, and cardiorespiratory fitness. Secondary outcomes included genetic factors, endothelium function, functional mobility and postural control, exercise questionnaires, depression, and sleep. We also explored study feasibility, exercise adherence, technology adaptability, and compliance of both in-person and remote protocols.

Results: The recruitment phase and data collection of this study have concluded. Results are expected to be published by the end of 2021 or in early 2022.

Conclusions: The data generated in these studies will introduce tangible parameters to guide the development of personalized exercise prescription models for maximal cognitive benefit in aging adults. Successful completion of the specific aims will enable researchers to acquire the appropriate expertise to design and conduct studies by testing personalized exercise interventions in person and remotely delivered, likely to be more effective at promoting cognitive health in aging adults.

Trial Registration: ClinicalTrials.gov NCT03804528; http://clinicaltrials.gov/ct2/show/NCT03804528

International Registered Report Identifier (IRRID): RR1-10.2196/33589

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KEYWORDS

exercise; neuroplasticity; cognition; brain health; cardiorespiratory fitness; cardiovascular function; trophic factors; telehealth; aging adult

Introduction

Cognitive Aging

Individuals aged 65 years and older will compose 30% of the global population over the next 30 years, totaling approximately 2 billion people [1]. This increase in human longevity has unfortunately not been accompanied by a comparable increase in healthy longevity (health span). Age-related cognitive decline impacts healthy longevity by leading to substantial disability and decreased quality of life. Cognitive health is critical for healthy longevity because it is highly linked to one's functional independence in managing important aspects of life such as living independently in one's home and managing health care and finances. Pharmacological approaches to treating age-related cognitive decline in midlife to later life have been limited [2]. In contrast, interventions that increase levels of physical activity have been effective in improving cognitive function in aging adults [3-5]. But there is considerable interindividual variability in cognitive outcomes after exercise. Greater understanding of this variability and the underpinning mechanisms are necessary to improve the effectiveness of exercise in prevention and remediation of age-related cognitive decline.

Variability in Cognitive Response to Exercise

Extensive evidence supports a link between aerobic exercise and cognitive improvements in aging adults. Heterogeneity in exercise-induced cognitive improvements remains the most significant barrier to achieving optimal efficacy of exercise for brain health in aging. Some individuals show robust cognitive benefits from exercise, while others show less pronounced improvements. To answer this question, measures that capture the effects of exercise at the brain level and knowledge of factors explaining the differences in cognitive response to exercise are needed. For example, the optimal and necessary exercise dose and regimen required to achieve cognitive benefits are unknown. Likewise, it is unclear which cognitive domains show most reliable and consistent improvements following exercise. Similarly, it is unclear which neuropsychological outcomes are most sensitive to capture exercise-induced cognitive gains. Advancing understanding of differences in cognitive response to exercise requires concurrent examination of associated neuroplasticity and cardiovascular changes after exercise. Aerobic exercise, with its cardiorespiratory gains, contributes to cognition by optimizing cerebrovascular function, ultimately leading to more efficient neural processing [6]. At the brain level, neuroplasticity is an important mechanism and driver of aerobic exercise–induced cognitive improvements.

Evaluating Mechanisms of Neuroplasticity to Capture the Effects of Exercise in the Brain

Neuroplasticity is broadly defined as a change in neural structure and function in response to experience or environmental stimuli. A critical component of neuroplasticity in response to exercise is long-lasting synaptic potentiation. Direct electrical recordings of hippocampal neurons show synaptic enhancement (ie, long-term potentiation) [7] after exercise that correlates with improved cognitive outcomes [8-14]. Prior studies using transcranial magnetic stimulation (TMS) demonstrated a substantial long-term potentiation–like neuroplasticity response to exercise that was relevant for exercise-induced cognitive gains [15]. Importantly, it is possible to assess neuroplasticity noninvasively and remotely by using transcranial alternating current stimulation (tACS) combined with electroencephalography (EEG). In this paradigm, small electrodes placed on the scalp deliver a short burst of tACS, which induces a controlled perturbation in the brain that is measured by EEG changes. The magnitude and duration of tACS-induced spectral EEG changes in EEG enable an assessment of neuroplastic mechanisms that is akin to the TMS/intermittent theta-burst stimulation (iTBS) approach [16,17]. tACS/EEG is uniquely suited for a home-based intervention as it can be delivered with a device designed for home use. Using established procedures via a secure video platform, the participant is instructed on how to appropriately place the EEG cap, and the study investigators conduct the assessment via remote neurophysiological monitoring. Thus, evaluation of tACS-induced spectral EEG changes is relevant to advance understanding of exercise-mediated cognitive benefits, with the important advantage of being suitable for home-based interventions.

Low Adherence to Exercise Is a Major Obstacle

In addition to all mechanisms that influence the variability of cognitive gains in response to exercise, an important limitation of existing research is that adhering to supervised in-person exercise can be challenging for many aging adults. Given the increasing use of ubiquitous mobile technologies by aging adults, a remotely delivered exercise research program may facilitate recruitment and retention, address barriers to exercise participation, and accelerate the translation of our findings to a broader audience. This is especially relevant considering the post–COVID-19 pandemic and living in the new normal social practices.

Thus, our incomplete understanding of the mechanisms that influence this variability and low adherence to exercise are critical knowledge gaps and major barriers for the systematic implementation of exercise for promoting cognitive health in aging. The major goal of this study is to inform the knowledge gap on the mechanistic action of exercise on the brain by characterizing important mechanisms of neuroplasticity, cardiorespiratory fitness, mobility, endothelium function, and genetic factors proposed to underlie cognitive response to exercise. Addressing this gap with methods of clinical and translational research will aid the development of exercise interventions that can be individually tailored to establish maximal effectiveness.

Specific Aims of the Study

Aim 1: Quantify improvements in cognitive performance after 8 weeks (150 minutes per week) of in-person and remotely delivered moderate-to-vigorous intensity aerobic exercise in sedentary aging adults aged 55 years and older. Hypothesis 1: We hypothesize improvements in overall cognitive performance after exercise and greater improvements in specific cognitive domains (eg, in executive function, as opposed to memory or language).

Aim 2: Quantify improvements in mechanisms of neuroplasticity and cardiorespiratory fitness response after 8 weeks (150 minutes per week) of in-person and remotely delivered moderate-to-vigorous intensity aerobic exercise in sedentary adults aged 55 years and older. Hypothesis 2: We hypothesize increased response in the mechanisms of neuroplasticity (as assessed by TMS-iTBS and tACS-induced spectral EEG changes) and increased cardiorespiratory response.

Aim 3: Determine an association between changes in neuroplasticity, cognitive performance, and cardiorespiratory fitness response after 8 weeks of moderate-to-vigorous intensity aerobic exercise in sedentary adults aged 55 years and older. Hypothesis 3: We hypothesize that a greater neuroplasticity response will be associated with greater improvement in cognitive performance and better cardiorespiratory response.

Aim 4: Determine whether postexercise cognitive gains, neuroplasticity, and cardiorespiratory response are moderated by baseline endothelial function and genetic factors. Hypothesis 4: Postexercise cognitive gains in neuroplasticity and cardiorespiratory response will be greater among individuals with greater endothelial function (brain-derived neurotrophic factors [BDNF] and vascular endothelial growth factor [VEGF]) and greater among individuals with an absence of apolipoprotein E e4 allele and Met BDNF allele.

Exploratory Aims

Aim 5. To examine and compare the feasibility and adherence of an in-person and remotely delivered exercise trial consisting of 8 weeks of moderate-to-vigorous intensity aerobic exercise (150 minutes per week). Hypothesis 5: We predict that this study will be feasible, defined by successful recruitment of 40 participants in the in-person group and 40 participants in the remote group, and will demonstrate at least 80% adherence to the program.

Aim 6. To examine the adaptability and technology compliance of an in-person and remotely delivered exercise intervention and remote testing procedures, including neuroplasticity assessment, neurophysiological testing, cardiorespiratory fitness, and mobility in sedentary aging adults aged 55 years and older. Hypothesis 6: We hypothesize that it would be feasible to adapt and compare the exercise intervention and testing procedures and participants will have at least an 80% technology compliance.

Methods

Ethical Aspects and Study Design

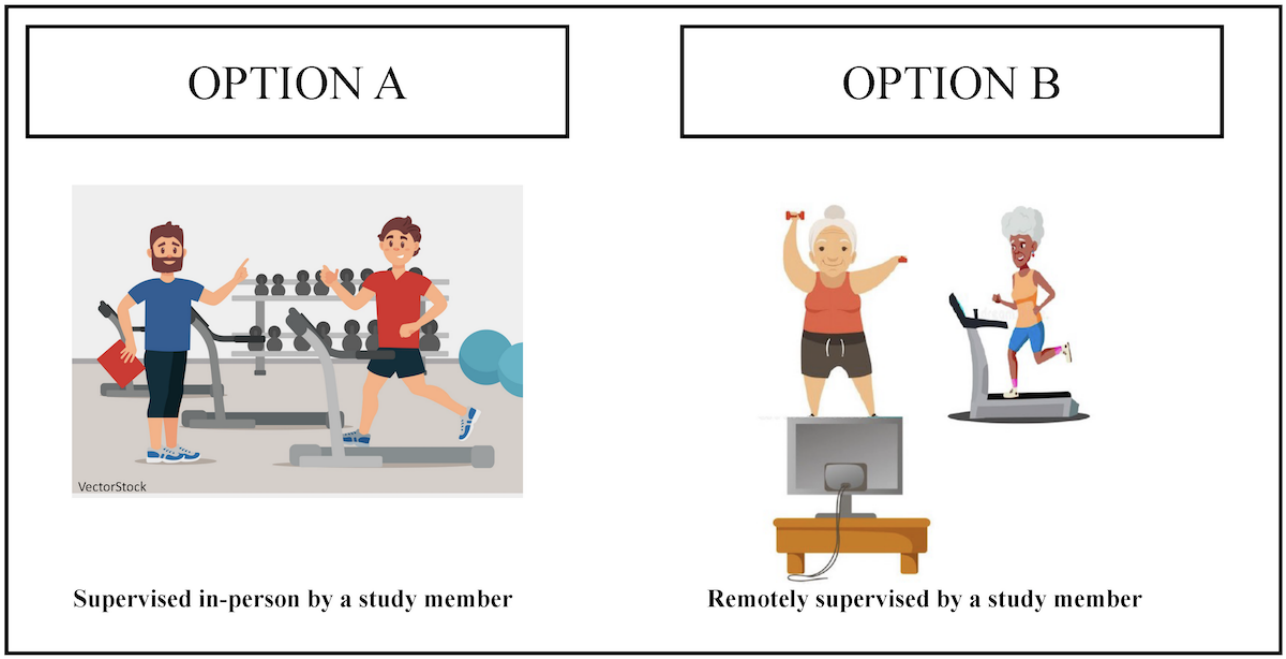
This is an open label, 2-month, interventional study protocol in neurologically healthy sedentary adults. Participants underwent a total of 30 sessions, including the screening session, 3 pretest (baseline) assessments, 24 aerobic exercise sessions, and 3 posttest assessments. This study was conceptualized a priori to be delivered fully in-person. Due to challenges posed by the COVID-19 pandemic, social distancing practices, and aiming to create a feasible scenario to continue this study, we propose an additional option to safely adapt study methods to deliver the study in a home-based, fully remote manner. Importantly, this scenario also presented as an opportunity to collect meaningful data on our specific aims while translating this successful research program into a remote/home-based mode of delivery. A remote/home-based option may also yield valuable preliminary data relevant for planning future exercise studies in aging adults in the present new normal. Proposed changes included: (1) screening and additional inclusion criteria, (2) informed consent form and consenting procedures, (3) addition of a study kit, (4) remote testing procedures, (5) remote exercise intervention, and (6) additional safety plan.

All participants provided written informed consent prior to participation, and all forms and procedures were approved by the University of Miami institutional review board (IRB). This protocol and all protocol modifications were approved by the IRB.

Therefore, this research project was offered using a 2-option design (Figure 1) consisting of the following:

- Option A: supervised in-person exercise intervention. This option was offered between February 2019 and March 2020
- Option B: home-based remotely supervised option of current methods to maximize recruitment. This option was offered between August 2020 and April 2021

Figure 1. Study design options.



Recruitment and Consent

Participants were recruited using an open enrollment process. A total of 74 adults aged 55 years or older were recruited from August 2019 to April 2021. Participants for this study were recruited by advertising recruitment flyer on the Miller School of Medicine campus, University of Miami Coral Gables campus, and greater Miami community (eg, public libraries). In addition, an online research database tool (eg, ResearchMatch.org), the social media platform Nextdoor.com, and the University Research Informatics Data Environment were used as recruitment methods, and potential participants were identified and contacted via the Consent to Contact Initiative. Individuals who were interested in participating in the study were instructed to contact study staff via email or telephone to discuss the study details. At this time, the study was explained to the potential participants, who were screened to eligibility criteria. Participants who fulfilled preliminary eligibility criteria and showed further interest in participating were scheduled to proceed with a consent visit in-person or virtually via Zoom for Healthcare (Zoom Video Communications Inc) and Research Electronic Data Capture (REDCap) e-consent. During this meeting, individuals signed the consent form and followed the procedures for the study. Participants were compensated for their participation in the study.

Eligibility Criteria

Participants were screened by collecting information to ensure their eligibility in the study. Inclusion criteria included individuals age 55 years and older, no clinically detectable cognitive impairment (Montreal Cognitive Assessment score ≥24), sedentary (defined as low category using the International Physical Activity Questionnaire–short form last 7 days), and English as primary language. An additional inclusion criterion for the remote group was basic computer skills (accessing an email or using the internet).

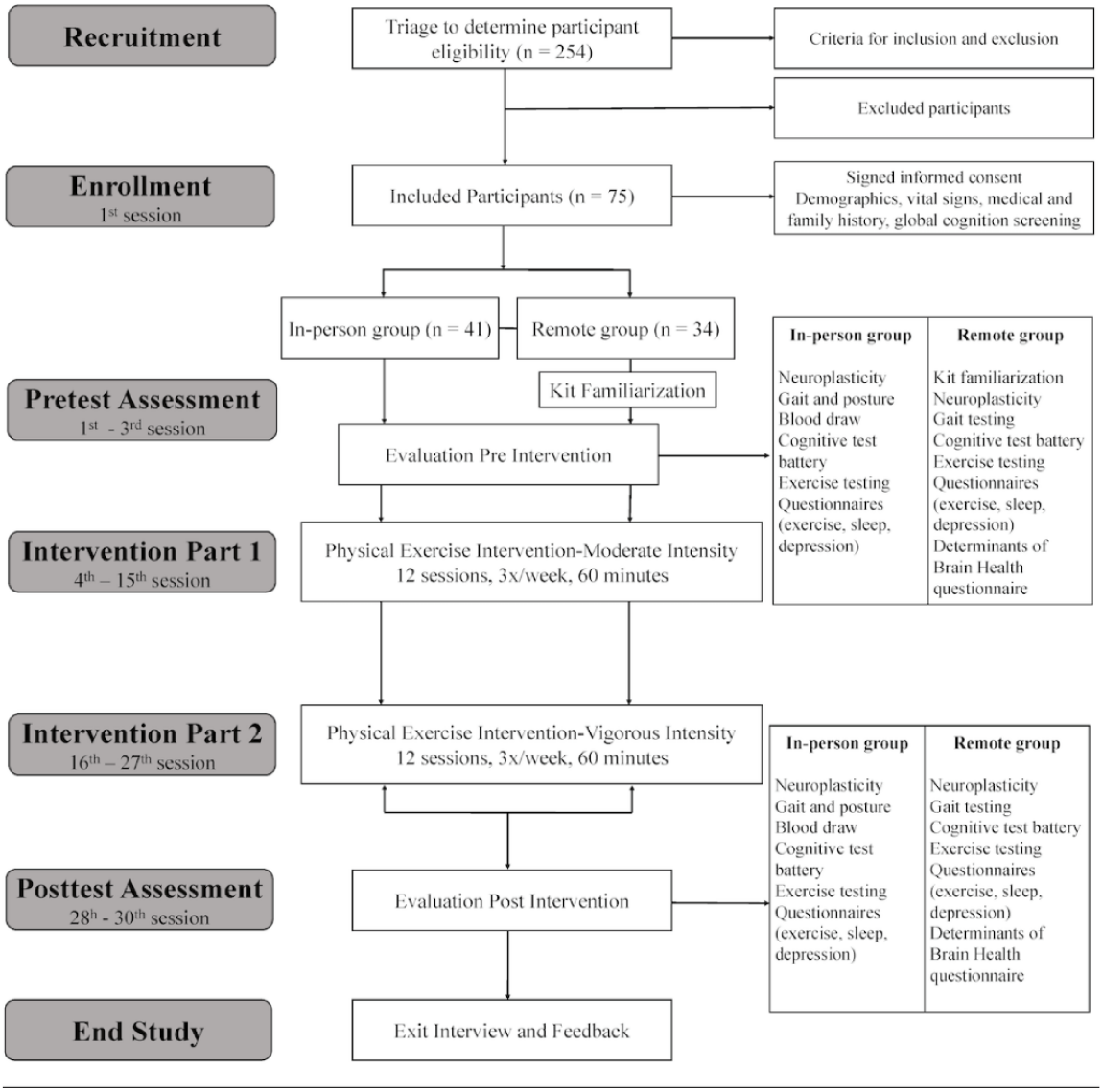
Exclusion criteria included any unstable medical condition (ie, uncontrolled hypertension or uncontrolled diabetes), medical contraindication to physical exercise, and contraindication to neuroplasticity assessment (TMS and tACS) [18]. No medication is an absolute exclusion from TMS and tACS. The decision to include a person in the study was made upon a review of the potential participant's medical history, drug dose, history of recent medication changes or duration of treatment, vital signs sheet, physical ability readiness questionnaire, and a systems review performed by a licensed physical therapist who was member of the laboratory. Based on the results of this evaluation, if the participant was found to require further medical clearance, they were referred to their physician for further evaluation and assessment of potential eligibility in this study.

Procedures

Study Timeline

The total time for a participant to complete this study varied based on participant availability, but it was feasible to complete within 10 weeks (the intervention portion of the study was 8 weeks, with week 1 designated for pretesting and week 10 for posttesting). The following timeline was used to guide and track the intervention based on participant visit/session number and study delivery option (in-person vs remote) available as described in Figure 2.

Figure 2. Study flowchart.



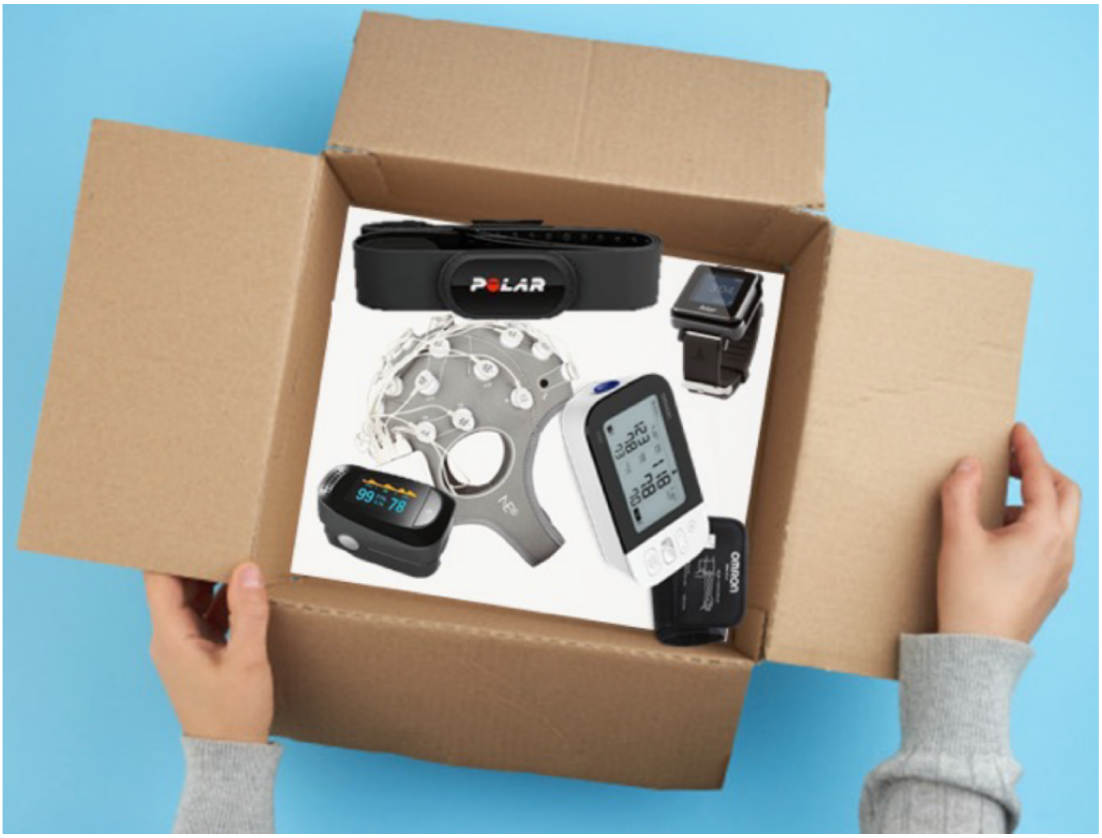
In-Person Procedures

Screening was partially done during a phone interview but required 1 visit in person during week 1 to consent and collect physical measures (eg, vital signs), demographics, and medical and family history. All assessments were conducted by a study member who received specific training for each test. The assessments were divided into 3 different visits. Blood draw and neuroplasticity assessment were performed on the first visit, cognitive test battery and questionnaires were performed on the second visit, and gait and postural control assessment and exercise fitness testing were performed on the third visit. All testing procedures were conducted in the same order after the intervention with the same study member.

Remote Procedures

This option was an adaptation of the in-person methods that included an updating testing timeline to include a kit familiarization session. We updated our assessment to include outcome measures that were appropriate for remote delivery. We eliminated our genetic testing, as it was not possible to perform remotely. In this option, in-person visits were replaced with remote sessions. Upon signing informed consent to participate in the study, participants received a study kit delivered by a study member or through the mail (Figure 3) containing the devices that would be used during the pre- and postassessment tests and exercise intervention. The study kit included a (1) sphygmomanometer (OMRON BP7350, Omron Healthcare Inc); (2) heart rate monitor (Polar H10, Polar Electro Inc); (3) pulse oximeter (Diagnostix 2100 fingertip pulse oximeter, American Diagnostic Corp); (4) physical activity monitor (ActiGraph GT9X-BT Link, ActiGraph LLC); (5) tape measure, masking tape, and alcohol prep pads (isopropyl alcohol 70%); (6) noninvasive brain stimulation/EEG hybrid Starstim-Home (Neuroelectrics), including a tablet; (7) participant study booklet; and (8) prepaid shipping label to return the kit.

Figure 3. Items included in the study kit.



When the study kit arrived, before beginning any assessments or intervention, we scheduled a remote meeting using Zoom for Healthcare to familiarize the participant with all the tools in the study kit. The participant learned various Zoom platform functions; how to take their own blood pressure and oxygen saturation, put on the heart rate monitor and EEG cap, and set up the activity monitor; and proper safety and cleaning procedures. If needed, we scheduled multiple meetings to ensure the participant was properly familiarized with all the materials in the study kit. Participants also received a study booklet (Multimedia Appendix 1) containing specific recommendations on how to follow the study procedures, set up the study devices, and prepare for the assessment; definitions of important terms, and daily exercise sheets to be completed during the exercise sessions.

All assessments visits were monitored remotely using a secure, video platform through Zoom and were conducted by the study team members in the same order as the in-person study protocol.

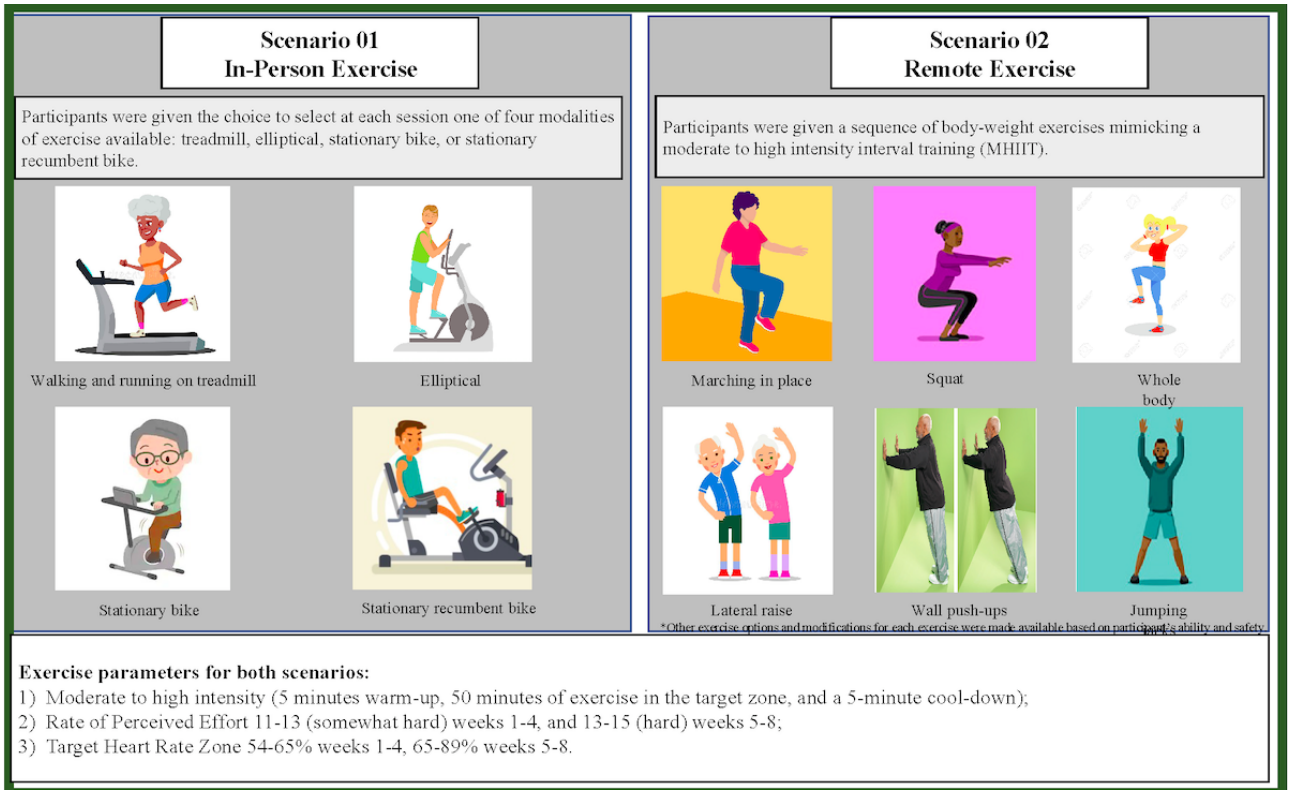
Intervention

In-Person Exercise Protocol

The physical exercise intervention was administered at the University of Miami Miller School of Medicine Wellness Center. Participants were given a time slot for the duration of the study, but flexibility with the intervention time frame was provided. Participants were supervised by a member of the study team (licensed physical therapists) at all times. Each participant engaged in 60-minute daily sessions delivered 3 times per week for 8 consecutive weeks (a total of 24 sessions).

Participants could select 1 of 4 modalities of exercise available (treadmill, elliptical, stationary bike, or stationary recumbent bike) at each session. They were fitted with a heart rate monitor and were instructed to maintain 55% to 64% of maximal heart rate (determined by the Karvonen method) for the first 4 weeks of exercise and 65% to 89% of maximal heart rate for the second 4 weeks of exercise. During the sessions, heart rate and participant's exerted effort (measured with the Borg scale) [19] were monitored prior to the session, every 5 minutes of the 50 minute session, and 5 minutes after the end of the session. The Borg scale is a numerical scale where 6 represents rest (no effort) and 20 represents maximal effort. Blood pressure was measured with participant seated for 5 minutes prior to the session and after completing the session. The session was discontinued if participant reported excessive discomfort (eg, musculoskeletal pain), and an appropriate referral was made as necessary. Participants were offered the opportunity to make up a missed session. Figure 4 shows a sample of exercise types for the in-person and remote protocols.

Figure 4. In-person and remote exercise protocol scenarios.



Remote Exercise Protocol

We have modified our 8-week, 3 per week in-person exercise intervention to be safely delivered as a home-based exercise program. Exercise sessions follow standard physical therapy protocols with existing safety procedures from the in-person sessions adapted to a virtual setting. Additional safety procedures included oxygen saturation measure, daily signs and symptoms questionnaire, daily geographical location, and daily emergency phone number. Home-based exercise sessions were monitored remotely by a physical therapist using Zoom for Healthcare. Participants were given the choice of exercise mode. Participants who had access to aerobic exercise equipment at home (treadmill, elliptical, or stationary bike) were able to use them in the same manner as scenario 1 (see Figure 4, scenario 1) with a remote investigator monitoring and instructing. Participants who did not have exercise equipment at home were given a routine of exercises that did not require any equipment and could be done safely in their homes. The body weight exercise program was developed by a group of 4 physical therapists formed by the principal investigator and study team members. Modifications for each exercise were tailored individually based on participant ability levels, available resources, and safety.

Exercises followed a standard format to ensure safety and adherence to study goals (Table 1). All participants completed a guided 5-minute warm-up. The intervention was structured in five 10-minute timed blocks consisting of 8 minutes of exercise and 2 minutes of rest. For the body weight protocol, participants were showed 2 exercises. They performed exercise A for 1 minute, exercise B for 1 minute, and then rested for 20 seconds. Participant then repeated the A-B sequence 3 more times for a total of 8 minutes of exercise and took an additional rest and water break for 1 minute to complete block 1. Participant completed 5 blocks using this format, completing a total of 10 unique exercises, and was then guided through a cool down where they slowly decreased exercise vigor to bring their heart rate down to baseline levels. Following exercise, the participant was asked to take their blood pressure, heart rate, and oxygen saturation and were monitored until they returned to within 20% of their baseline measurement. Each day of the week (eg, Monday, Wednesday, and Friday) had a different sequence of exercises.

The remote protocol followed the same intensity as the in-person protocol with an adaptation to mimic moderate-to-high intensity interval training (relative to their age-predicted maximal heart rate determined by the Karvonen method [heart rate (HR) = HRrest + ((intended fraction) * (HRmax – HRrest))], where HRmax = 220 – age, and intended fraction was 54% to 65% on weeks 1 to 4 and 65% to 90% on weeks 5 to 8). For participants taking β-blocker medication, an adjusted formula was used to estimate HRmax (HRmax = 119 + 0.5 [resting HR] − 0.5 [age]) [20]. We assessed perceived effort using the 20-point Borg scale. Table 1 shows the protocol of exercise for both groups.

Table 1. Remote exercise protocols.

Time	Steady state aerobic (personal equipment)	Body weight (no equipment)
0:00-4:59 (5 min)	Warm-up	Warm-up
5:00-14:59 (10 min) Work: 8 min, rest and water: 2 min	Block 1	Block 1: A/B
15:00-24:59 (10 min) Work: 8 min, rest and water: 2 min	Block 2	Block 2: C/D
25:00-34:59 (10 min) Work: 8 min, rest and water: 2 min	Block 3	Block 3: E/F
35:00-44:59 (10 min) Work: 8 min, rest and water: 2 min	Block 4	Block 4: G/H
45:00-54:59 (10 min) Work: 8 min, rest and water: 2 min	Block 5	Block 5: I/J
55:00-60:00 (5 min)	Cool down	Cool down

Outcome Measures

All assessment measures were performed at baseline and after the 8-week exercise intervention. Table 2 shows the summary of assessments used in the in-person and remote groups.

Table 2. Outcomes and assessments.

Outcome measures	In-person assessment	Both	Remote assessment
Primary			
Neuroplasticity			
	TMS/iTBS[a]	—[b]	tACS/EEG[c]
Cognitive function			
	—	Digit span subtest of the WAIS-4th[d]	—
	—	Trail-Making Test Part B	—
	—	RBANS[e]	—
	—	DKEFS[f]	—
	Stroop color-word test	—	TestMyBrain.org
Cardiorespiratory fitness			
	Incremental shuttle walking test	—	1-minute sit-to-stand test
Secondary			
Functional mobility and postural control			
	—	Timed Up-and-Go test (single and dual task)	—
	Wireless accelerometer	—	—
	90-second trials of walking	—	—
	Standing postural control	—	—
Blood collection and genetic testing			
	Endothelium function (BDNF[g], VEGF[h], and CRP[i] levels) and genetic factors (BDNF genes, and APOE[j] e4 allele)	—	—
Physical activity and exercise			
	—	Lifetime Physical Activity questionnaire	—
	—	Exercise Self-Efficacy, and Barriers and Motivators to Exercise	—
	—	Physical Activity Self-Regulation Scale	—
	—	—	ActiGraph GT9X Link
Depression			
	—	GDS[k]	—
Sleep			
	—	PSQI[l]	—
	—	—	ActiGraph GT9X Link
Brain health index			
	—	—	BBHI[m] determinants of brain health
Study feasibility			
	—	Exercise adherence and technology compliance	—
	—	Exercise intensity adherence	—
	—	Adaptability of the intervention and assessments methods	—

Outcome measures	In-person assessment	Both	Remote assessment
Participant self-evaluation, study feedback, and plans for exercise			
	Exit interview survey	—	Exit interview survey with additional questions

[a]TMS/iTBS: transcranial magnetic stimulation/intermittent theta-burst stimulation.
[b]Not applicable.
[c]tACS/EEG: transcranial alternating current stimulation/electroencephalography.
[d]WAIS-4th: Wechsler Adult Intelligence Scale, 4th Edition.
[e]RBANS: Repeatable Neuropsychological Battery.
[f]DKEFS: Delis-Kaplan Executive Function System.
[g]BDNF: brain-derived neurotrophic factor.
[h]VEGF: vascular endothelial growth factor.
[i]CRP: C reactive protein.
[j]APOE: apolipoprotein E.
[k]GDS: Geriatric Depression Scale.
[l]PSQI: Pittsburgh Sleep Quality Index.
[m]BBHI: Barcelona Brain Health Institute.

Primary Outcome Measures

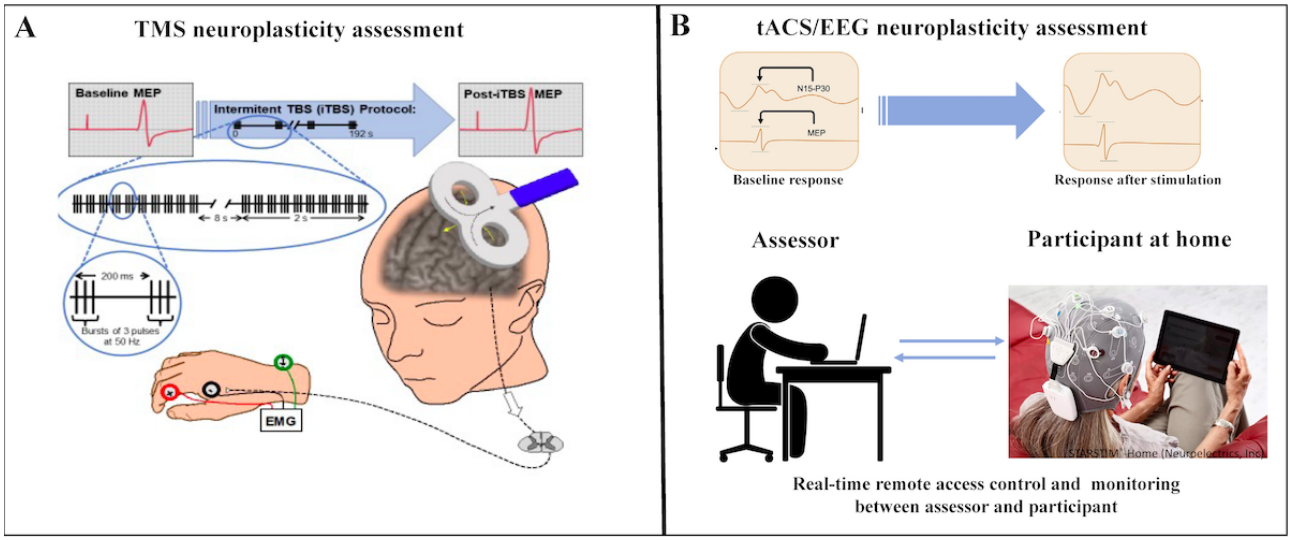
Neuroplasticity Measures

TMS Plasticity

An index of the duration of the theta-burst stimulation (TBS)-induced modulation of corticospinal excitability was defined for each participant. Participants were set up in a chair with electromyography (EMG) electrodes placed on the first dorsal interosseus on the dominant hand to measure motor threshold in the corresponding (contralateral) motor cortex (Figure 5A). The motor threshold serves as the basis for the following TMS measures over the motor cortex. When administering TMS, the figure of 8 coil was placed tangentially to the scalp with the handle pointing posterior for all stimulations. We proceeded with determining motor threshold and conducted TMS (single pulse TMS and TBS) over the dominant motor cortex. After removing the EMG equipment from the participant, a post-TMS safety evaluation was conducted. During each of the TMS/plasticity visits, the following procedures took place:

- Single pulse TMS was delivered using a biphasic figure of 8 coil. This stimulation phase consisted of 3 batches of 30 TMS pulses delivered every 5 to 7 seconds at 120% of resting motor threshold prior to TBS stimulation as a baseline. Resting motor threshold was defined as the minimum stimulus intensity that produced a small motor evoked potential (MEP; about 50 µV in 50% of 10 trials) during relaxation of the tested muscles.
- For this study, participants received iTBS over the motor cortex. iTBS consists of bursts of 3 pulses at 50 Hz repeated at intervals of 200 ms for a total of 2 seconds (1 train); each train were repeated every 10 seconds for 20 times for a total of 600 stimuli. After TBS is applied to the motor cortex in an intermittent fashion (iTBS), TMS-induced potentials show increased amplitude for a period of 20 to 30 minutes. Stimulation intensity was delivered at 80% of active motor threshold, defined as the minimum stimulus intensity that produces a small MEP (about 200 µV in 50% of 10 trials) during isometric contraction of the tested muscles, at about 20% of maximum voluntary contraction. After iTBS has been administered, batches of single pulse TMS were administered at timed intervals for 30 minutes over the motor cortex (T5, T10, T20, and T30). The degree of potentiation of MEPs (ie, the percentage change in peak-to-peak MEP amplitude from baseline at each post-iTBS time point (T5, T10, T20, and T30) was considered as a TMS index of neuroplasticity [21-23].

Figure 5. Experimental setup for transcranial magnetic stimulation (TMS) and transcranial alternating current stimulation/electroencephalography (tACS/EEG) neuroplasticity assessment. EMG: electromyography; MEP: motor evoked potential; TBS: theta-burst stimulation.



tACS/EEG Plasticity

All visits were monitored remotely using a secure, video platform through Zoom and conducted by the study team members of the laboratory, with appropriate oversight. In this paradigm, small electrodes placed on the scalp deliver a short burst of tACS, which induces a controlled perturbation in the brain that is measured by EEG changes (Figure 5B). tACS/EEG is uniquely suited for a home-based intervention as it can be delivered with a device designed for home use. Using established procedures via a secure video platform, the participant was instructed on how to appropriately place the EEG cap, and the study investigators conducted the assessment via remote neurophysiological monitoring. An index of change in the tACS-induced modulation of cortical excitability was defined for each participant, and brain functional connectivity and interregional coordination were directly estimated from EEG. We used established tACS/EEG procedures to measure neuroplasticity [16,17]. We used the noninvasive brain stimulation/EEG hybrid Starstim-Home system (Neuroelectrics) and recorded EEG before (5 minutes), during (3 minutes), and after (5 minutes) tACS stimulation. Participants received tACS stimulation (3 minutes, 40-60 Hz, 1-2 mA) targeting the motor and prefrontal cortices through remote neurophysiologic monitoring by the study team. We used published methods of artifact removal and event detection algorithms to extract the magnitude and duration of post-tACS gamma EEG power changes from the EEG signals [16,17]. In accordance with the safe application of neurophysiological measures recommended by the International Federation of Clinical Neurophysiology, we collected and monitored adverse events.

Cognitive Function

Visuomotor Processing Speed and Cognitive Flexibility and Task Switching

This was assessed using the Trail Making Test Part B [24,25]. Trail Making Test Part B consists of encircled numbers (1-13) and letters (A-L). Individuals were asked to connect the circles alternating between numbers and letters as quickly as they could without making mistakes. The test was scored according to the number of errors made and the time (in seconds) to completion.

Response Inhibition, Mental Flexibility, and Attentional Control

This was assessed using the Stroop Color and Word Test [26]. The test consists of 3 components, each component consisting of 100 items, presented in 5 columns. In the first portion, participants were asked to read words printed in black ink (RED/GREEN/BLUE). In the second portion, participants were asked to identify the color of ink in which a series of Xs are printed. In the final section, participants were asked to identify the color of ink the color words were printed in. Participants were asked to complete each component as quickly and accurately as possible. Each section was scored based on number of items completed accurately within a 45-second period.

For the remote group, the same cognitive battery minus the Stroop color and word test and with the addition of a TestMyBrain.org [27] battery of Digit Symbol Matching, Simple and Choice Reaction Time, and Gradual Onset Continuous Performance Test was used via a secured Zoom for Healthcare platform.

Attention and Working Memory

The Digit Span subtest of the Wechsler Adult Intelligence Scale, 4th Edition [28] was used to asses this construct. This measure consists of 3 parts: Digit Span Forward, Digit Span Backward, and Digit Span Sequencing. Participants were read increasingly longer lists of numbers (starting with 2 digits and increasing in difficulty up to 9 digits) and asked to repeat them verbatim, in backward order, and sequentially (ie, from smallest to largest) on Digit Span Forward, Digit Span Backward, and Digit Span Sequencing, respectively. Each portion was discontinued when participants could not accurately repeat 2 consecutive trials of equal difficulty.

Global Cognition

The Repeatable Battery for the Assessment of Neuropsychological Status Update [29] is a brief battery used to measure an individual's cognitive state. The assessment was

completed in approximately 25 minutes. The battery was composed of 5 cognitive domains:

- Immediate memory was assessed through a list learning task of 10 words and a short story. Participants were asked to repeat a list of 10 words over a series of 4 learning trials. The score was dependent on the number of correctly recalled words over the 4 trials. Participants were then read a short story and asked to recall as many details as possible from the story that they could remember over 2 trials. The score was based on the number of correct key details the participant could recall.
- Visuospatial was assessed using a figure copy and line orientation task. Participants were asked to copy a figure as accurately as they could while being timed. The score was based solely on the exactness of the copy of the figure. Participants were then shown 13 lines that were numbered 1 to 13 and arranged in a fan shape that were 15 degrees apart from each other at the top of a page. Participants were shown a series of 2 lines, isolated from the fan shape, and asked to identify what numbers they corresponded to on the fan shape. Participants were awarded 1 point for each time they correctly match the lines.
- Language was assessed through picture naming and semantic fluency. Participants were asked to identify the name of 10 different figures. The score was based on the number of figures the participant named correctly. Participants were then asked to name as many items from a specific category as they could for 1 minute. One point was awarded for each unique response.
- Attention was composed of a digit span and coding task. Participants were read a series of numbers increasing in length that they were asked to repeat. Participants were awarded 1 point for each series of number they correctly recalled. Coding was comprised of a key of 9 symbols that were associated with a number 1 through 9. The participant was then asked to use the key to assign numbers to a list of matching symbols below, where the numbers were missing. One point was given for each symbol correctly assigned to a number based on the key.
- Delayed memory was measured by recalling the 10 words and short story from the immediate memory task, recalling the figure copied during the visual spatial constructional task, and identifying the 10 words from the list learning task among 20 other words.

Verbal Fluency

The Verbal Fluency subtest of the Delis-Kaplan Executive Function System [30] was used to assess verbal fluency. This subtest comprised letter fluency, category fluency, and category switching. During the letter fluency portion, participants were asked to name as many words as they could that began with a certain letter of the alphabet within 1 minute. There were 3 trials with 3 different letters, and the participant was awarded 1 point for each unique, appropriate response. For category fluency, participants were asked to name as many items as they could that corresponded to the category provided within 1 minute. Participants completed 2 trials with 2 different categories and were awarded 1 point for each unique, appropriate response. During the category switching, the participant was asked to switch between naming items from 2 different categories within 1 minute. Participants were awarded 1 point for each unique, appropriate response given for each category as well as each time they correctly switched between categories.

TestMyBrain.org

As there were some tests that were not appropriately delivered via Zoom, a few additional tests were used for option B. A TestMyBrain link was sent to participants during their assessment visit, and the investigator guided them through the test. Overall, this portion of the test required 10 minutes. The test comprised the following:

- Processing speed was assessed using the TestMyBrain Digit Symbol Matching. Participants were shown symbols that matched a corresponding number. Participants quickly and accurately selected the appropriate number. They had 90 seconds to complete as many symbols as possible.
- Basic psychomotor response speed was measured with TestMyBrain Simple Reaction Time. Participants were shown either GO! or WAIT! Participants pressed the space bar on the computer as rapidly as possible only when the word GO! was presented.
- Choice Reaction Time was used to measure processing speed, response inhibition, and attention. Participants were shown 3 boxes with arrows inside of them. Two boxes had the same color, and one was different (odd color). Participants must rapidly select the direction of the arrow in the odd colored box.
- Sustained attention, response inhibition, and cognitive control was measured with the Gradual Onset Continuous Performance Test. Participants were asked to press a key when a city picture appeared and to not press when a mountain image appeared. The images rapidly transition from one to the next with mountains appearing only 10% to 20% of the time.

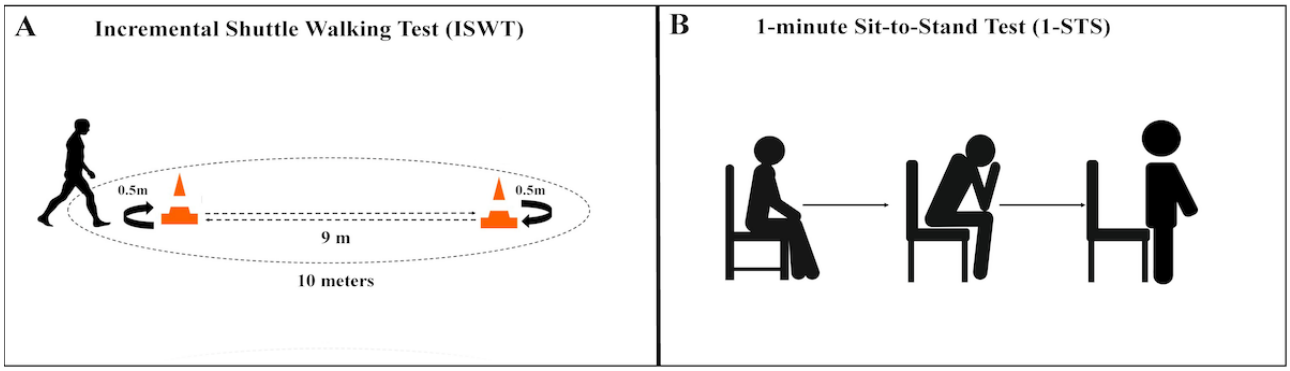
Cardiorespiratory Fitness

Incremental Shuttle Walking Test

The Incremental Shuttle Walking Test was performed to determine cardiorespiratory fitness by evaluating maximal walking velocity and walking distance during the test (Figure 6A) [31]. These values were used to estimate peak oxygen consumption (VO_2 peak) changes over time as a measure of aerobic capacity [32]. Prior to the test, participants were fitted a heart rate monitor (Polar H10, Polar Electro Inc), seated in a comfortable chair for 5 minutes, and we measured blood pressure, heart rate, rate of perceived effort, and oxygen saturation. Participants were screened for signs and symptoms (eg, dizziness, nausea, chest pain) and a list of medications taken before the test. Participants were then instructed to walk progressively a distance of a 10-meter course around a marking between 2 cones, keeping to the speed indicated by the bleeps on the audio recording. At every minute, the participants had to increase their speed to keep up with the test. We recorded reasons for termination, and these included the following: (1) participant became too breathless to maintain the required speed or could no longer keep up with the set pace, (2) operator determined that the participant was not fit to continue (eg,

reached 85% of predicted maximum heart rate), or (3) operator assessed that the patient was unable to sustain the speed and cover the distance to the cone prior to the beep sounding. Participants were closely monitored upon completion and 5 minutes after test cessation, including blood pressure measurement, heart rate, oxygen saturation, and rate of perceived effort. Heart rate recovery was also recorded at minute 1 and minute 2 after test cessation.

Figure 6. Cardiorespiratory fitness assessment.



1-Minute Sit-to-Stand Test

We adapted our exercise assessment to a submaximal aerobic capacity assessment using the 1-Minute Sit-to-Stand Test (Figure 6B) [33], which could be completed in the participant's home and monitored securely through the Zoom platform. The 1-Minute Sit-to-Stand Test was performed to determine maximal repetitions completed in 1 minute. Participants were asked to join a Zoom meeting where they were asked to confirm their current geographical location and emergency phone number. Prior to the start of the test, the investigator requested participant place a sturdy chair in the camera view range in a safe location for proper monitoring, preferably an armless chair of standard height (45.0 to 48.0 cm) placed against a wall for stability. The participant was asked to don the Polar Heart Rate monitor and an activity monitor (ActiGraph GT9X Link) and have a seat in the chair. After this, vitals were taken after 3 to 5 minutes of seated rest, and the investigator completed a signs and symptoms check. Blood pressure, heart rate, perceived exertion, and oxygen saturation were documented by the investigator. The participant was then asked to stand up and sit down from a sturdy chair for 1 minute while being monitored by a trained study member. The number of sit-to-stands performed in 1 minute was recorded. The participant's heart rate was monitored continuously throughout the test, and heart rate and blood pressure was taken and documented immediately after the assessment and after 5 minutes of seated rest and was continued monitored until the participant returned within 20% of their baseline measurement. Heart rate recovery was also recorded at minute 1 and minute 2 after test cessation.

In the remote group, we were also able to measure heart rate variability. Heart rate variability was assessed at rest and during the 1-minute Sit-to-Stand Test using the ActiGraph GT9X Link, paired with a wireless heart rate monitor (POLAR Inc) that generated beat to beat intervals (RR interval), an approach demonstrated to be comparable to an electrocardiogram for heart rate variability measurement [34]. For analysis, data will be then transferred to a computer using the CentrePoint system. All RR data will be manually reviewed by trained team members. Heart rate variability measures will include time and frequency domains and spectral and nonlinear indices [35,36], calculated offline using Kubios and Cardioedit/Cardiobatch software [37].

Secondary Outcome Measures

Functional Mobility and Postural Control

Participants underwent a functional evaluation to assess the influence of physical exercise on gait and mobility, postural control, and cognitive-motor interference.

Functional Assessment (Gait and Mobility)

Participants were outfitted with wireless accelerometers (Mobility Lab System, APDM Wearable Technologies Inc) secured with Velcro straps to the wrists, ankles, sternum, and lower back. Then, the Timed Up-and-Go (TUG) test, 90-second trials of walking, and standing postural control were administered following these procedures:

- The TUG test is a valid and reliable test of mobility [38] that requires participants to stand from a chair on command, walk 3 meters, turn around, walk back to the chair, and sit back down. The TUG was performed under 3 conditions: 2 trials of normal walking (regular pace) TUG single-task, 2 trials of fast walking TUG single task, and 2 trials of TUG dual task. For the TUG dual task, the participants were given a 3-digit number at the beginning of the trial and were instructed to perform serial 7 subtractions while walking during the test. For the TUG dual task, a dual-task effect was computed as the percentage change of the TUG dual task from the TUG single task, and the cost of the cognitive task in combination of the motor task was used to reflect a cognitive-motor interference [39].
- Four trials of the 90-second walking were completed along a 35×4 m indoor hallway to assess gait under normal and cognitive dual-task conditions. Cognitive dual-task conditions included dual-task walk, dual-task walk with priority on walking, and dual task with priority on the cognitive task. The cognitive dual task was to verbalize serial subtractions of 7 from a random 3-digit number.
- Postural control was assessed by measuring postural sway (ie, center-of-pressure fluctuations) during six 30-second trials of standing—2 with eyes open, 2 with eyes closed,

and 2 while performing the serial 7 subtraction cognitive task.

Remote Group

For the remote option, we performed the TUG test as a measure of functional mobility in all 3 conditions described above: normal TUG single task, fast TUG single task, and TUG dual task. The test was completed and supervised via a secured Zoom platform. The participant was instructed to set up the chair and measure a 3-meter space with the provided tape measure and masking tape to complete the assessment in their home. The investigator guided the TUG procedures and recorded their performance.

Blood Collection and Genetic Testing

Blood samples were collected to assess peripheral BDNF levels (pg/mL), VEGF (pg/mL), and high-sensitivity C-reactive protein (mg/L) concentrations. We also evaluated DNA to assess BDNF, Val66Met polymorphism, and the presence of apolipoprotein E e4 allele. We stored blood samples for future examination of other potential genetic, epigenetic, metabolic, or proinflammatory markers. Blood samples were delivered to the lab on ice within 2 hours of collection, centrifuged, and stored at –80 °C until processing. The blood collection was only performed on the in-person participants.

Physical Activity and Exercise

The following physical activity and exercise questionnaires were applied for both in-person and remote groups.

Lifetime Physical Activity Questionnaire

The Lifetime Physical Activity Questionnaire [40] uses questions about participant physical activity at various times in the participants' life. Participants were asked to estimate the average amount of time each week and the average number of months each year spent in moderate, vigorous, and other activities.

Exercise Self-Efficacy

The Exercise Self-efficacy Questionnaire [41] assessed how sure participants were that they would perform exercise under different conditions or constraints (eg, how sure you are that you will exercise when you are feeling tired). Each item responses varied from 1 (not at all sure) to 4 (very sure).

Exercise Barriers and Motivators

Exercise Barriers Questionnaire [42] assessed participant agreement of a list of statements about barriers to physical exercise (eg, I am not sufficiently physically active because I haven't any time for physical activity.). Each item responses varied from 1 (disagree), 2 (partially agree), and 3 (agree). Participants were also asked to give reasons that help them remain sufficiently physically active (eg, I have exercise equipment at home).

Remote Group

Questionnaires were completed by the participant using a REDCap link sent via a secured email. We also objectively collected physical activity data with the ActiGraph GT9X-BT Link.

Physical Activity

An objective measurement of overall physical activity was collected using the activity monitor ActiGraph GT9X-BT Link, the gold standard, research-grade, activity monitor. The device includes a 3-axis gyroscope, magnetometer, and accelerometer and provided raw data on a variety of objective physical activity, wear compliance, and sleep measures using validated algorithms through the CentrePoint platform. The physical activity raw data included (1) daily activity profile (steps taken, kcals, and activity counts), (2) activity and sedentary bouts (bouts of sustained physical activity), and (3) activity intensity (the time spent within different categories of activity intensity (sedentary, light, moderate-to-vigorous). The CentrePoint is a cloud-based data capture and management platform technology that permits participants to transfer data to the cloud via computer or mobile, and investigators had the ability to monitor patients remotely and in near real time to assure they were engaged and compliant with the protocol. The device was worn on the waist. We collected data at baseline during 3 to 5 days before exercise intervention and daily activity data during the intervention.

Wear Compliance

The participants were advised to use the activity monitor all day long, including sleep time, and only remove it when taking a shower or swimming. Wear compliance was monitored with the daily amount and percentage of time the participant wore the activity monitor. The data were validated if the participant wore the monitor for a minimum of 12 hours.

Sleep

The Pittsburgh Sleep Quality Index is a valid and reliable measure broadly used in clinical and research setting that evaluates sleep quality over the last month, providing an index of severity and nature of the sleep disorder [43,44].The Pittsburgh Sleep Quality Index was assessed in both in-person and remote protocols.

In the remote group, sleep quality was assessed using the ActiGraph GT9X-BT Link. Daily raw data were collected at baseline and during the intervention. Sleep data included total sleep time, wake after sleep onset, and sleep efficiency.

Brain Health Index

We expanded the questionnaires to include a structured survey used to assess the 7 pillars of brain health (cognitive function, physical exercise, nutrition, comprehensive health, socialization, sleep, and vital plan [perceived meaning in life]) developed by the Barcelona Brain Health Initiative [45]. The questionnaire includes 52 items with yes or no responses. A percentage weighted score was used to indicate the brain health index of the participants.

Depression

For both options (remote and in-person), we used the full version of the Geriatric Depression Scale. The Geriatric Depression Scale is a valid and reliable self-reported measure of depression in older adults and contains a total of 30 items [46].

Study Feasibility and Adaptability

Adherence to the Intervention

The adherence rate was calculated in both groups by the (1) proportion of participants who initiated the intervention out of the total allocated, (2) proportion of participants who completed the whole planned intervention out of the participants who initiated the intervention, and (3) total number of days to complete the intervention from exercise session 1 to session 24. In both groups, we also assessed the proportion of participants lost to follow-up, proportion of participants who withdrew, and proportion of participants who rescheduled sessions and the average number of rescheduled sessions.

Exercise Intensity Adherence

We calculated the proportion of time spent within the planned target heart zone (moderate and vigorous intensity) for each session (24 in total), for each participant, and the average of participants for each group.

Adaptability of the Intervention and Assessment Methods

This was assessed by comparing the outcome results of both groups, and the feedback of the participants. At the end of the study, participants completed an exit interview that included questions on their feedback about the intervention and methods. Examples of specific questions: How difficult was it for you to use Zoom for testing and exercise sessions? Did you have any difficulties with the remote program, connectivity, or any of the technology used within the study?

Technology Compliance

This was assessed in the remote group by evaluating the compliance report of the activity monitor ActiGraph GT9X Link generated by the CentrePoint platform: (1) daily use at baseline and during the intervention, (2) daily validated data (minimum of 12 hours), and (3) average of daily hours.

Participant Self-Evaluation, Study Feedback, and Plans for Exercise

After study completion, participants completed an exit interview containing questions in the following domains: (1) motivation to join the study, (2) likelihood they would continue exercise, (3) their plan to continue exercising, (4) types of exercise they planned to do, (5) confidence to exercise on their own, (6) dietary changes during the study, and (7) changes experienced during the course of the intervention (eg, energy level, thinking, memory, motivation, fitness, and others).

We also asked their feedback about the study. Questions related to (1) health problems experienced, (2) importance of procedures adopted by the study team (eg, trainer, interactions during session, flexibility of schedule), and (3) what they liked about the study (eg, being a part of a research study, making a commitment to exercise).

For the remote group, we asked about their experience with this modality of study, including (1) difficulty with the remote procedures (eg, using the computer and other technologies) and (2) recommendations and suggestions.

Sample Size

With a significance level of .05, an estimated sample of 80 individuals would provide 80% power to detect a Cohen effect size of 0.36 using a 2-sided paired *t* test for aim 1, the effect size associated with improvements in executive function in a recent meta-analysis of healthy adults aged older than 55 years [47], and an attrition of 20%, not uncommon in exercise intervention trials. In addition, a sample of 80 participants would provide 80% power to detect a correlation of 0.34 between the change in TMS neuroplasticity and the change in cognitive performance for aims 2 and 3 and 80% power to detect an R^2 of .11 attributed to a genetic modification in the change in cognitive performance using an *F* test for aim 4.

Statistical Analysis

Baseline characteristics will be summarized as means and standard deviations or medians and interquartile ranges for continuous variables and as frequency and percentage for categorical variables. Normality for the distributions of continuous variables will be visually assessed and statistically tested. If the normality assumption is questionable, Box-Cox transformation, a logarithmic or square root transformation, will be used to reduce the skewness in the indicated analyses or nonparametric tests such as Wilcoxon rank test will be used. All statistical tests will be conducted against a 2-sided alternative hypothesis with a significance level of .05.

In the univariate analysis, we will compare the cognitive performance (overall and by domain) before and after exercise using paired *t* test to test for specific aim 1. For specific aim 2, we will compare neuroplasticity response and cardiorespiratory response before and after exercise using a mixed effects repeated measures model. To account for potentially important covariates in the model (eg, age, sex, race/ethnicity, education), supporting analyses will control for these factors in a non–time-varying fashion. For specific aims 3 and 4, we will compare mean change in cognitive performance across subgroups by genotype using an *F* test. In the multivariable analyses, we will adjust for baseline characteristics (age, sex, race/ethnicity, education) using mixed effect modeling to quantify improvements in cognitive performance after exercise (specific aim 1) and determine an association between changes in neuroplasticity, cognitive performance, and changes in cardiorespiratory response (specific aim 3). We will use modification models by including interaction terms (time-by-genotype) to explore the relationship between change in cognitive performance after exercise and BDNF levels, Val66Met, and APOE e4 status (specific aim 4).

All data entry will be coded and double-entered into an Excel (Microsoft Corp) spreadsheet for analysis. Exploratory analyses, plotting, and mixed effects regression analyses will be performed using Stata statistical software (version 17 or later, StataCorp LLC).

Results

This study was funded by award number KL2TR002737 from the National Center For Advancing Translational Sciences of the National Institutes of Health in September 2018 for 2 years,

and the protocol was first approved by the University of Miami IRB in November 2018. The modification of the study adaptation for a remote version was approved by the IRB in July 2020. Participants were recruited using an open enrollment process. A total of 254 individuals were screened for eligibility, and 75 adults aged 55 years or older were recruited from August 2019 to April 2021. A total of 41 individuals were enrolled in the in-person protocol, and data were collected between February 2019 and March 2020. A total of 34 individuals were enrolled in the remote study, and data were collected between August 2020 and April 2021. Currently, data are being processed and analyzed. Results are expected to be published in 3 major papers in 2021 and 2022.

Discussion

The research proposed in this investigation will advance the field of exercise and cognition by generating evidence on the mechanistic action of 8 weeks of moderate to high exercise on cognitive performance, neuroplasticity and cardiorespiratory function, and examining potential effect modification of cognitive response to exercise by endothelial function and genetic factors. The data generated in these studies will introduce tangible parameters to guide the development of personalized exercise prescription models for maximal cognitive benefit in aging adults. Successful completion of the specific aims will enable researchers to acquire the appropriate expertise to design and conduct studies testing personalized exercise interventions in person and remote delivered, likely to be more effective at promoting cognitive health in aging adults.

Neuroplasticity assessments are critical to understanding why some people show greater cognitive response to exercise than others do, which will then facilitate development of optimal exercise doses and regimens to achieve maximal cognitive benefits for each person. Exercise is a low-cost intervention with an established safety profile, so in addition to advancing scientific knowledge, the results of the proposed study have the potential for direct translation into community settings and eventually to health care policy.

With the addition of the remote group to the study, we intended to gain valuable data in exercise adherence and feasibility of the introduction of effective technology aimed at improving cognitive brain health in the aging population. Given the increasing use of ubiquitous mobile technologies in aging and older adults, especially considering the post–COVID-19 pandemic effects, the addition of a remotely delivered clinical research program facilitated recruitment, addressed barriers to participation, and accelerated the translation of findings to a broader audience and clinical application.

Acknowledgments

JGO was supported by award number KL2TR002737 from the National Center for Advancing Translational Sciences of the National Institutes of Health

Conflicts of Interest

APL is a cofounder of Linus Health and TI Solutions AG; serves on the scientific advisory boards for Starlab Neuroscience, Magstim Inc, and MedRhythms; and is listed as an inventor on several issued and pending patents on the real-time integration of noninvasive brain stimulation with electroencephalography and magnetic resonance imaging. JGO works as Director of Interventional Therapy at Linus Health.

Multimedia Appendix 1
Study booklet sample.
[PDF File (Adobe PDF File), 12953 KB - resprot_v10i11e33589_app1.pdf]

Multimedia Appendix 2
Peer-review report from the Miami CTSI KL2 Award Committee.
[PDF File (Adobe PDF File), 66 KB - resprot_v10i11e33589_app2.pdf]

References

1. World population prospects: the 2017 revision, key findings and advance tables. United Nations. 2017. URL: https://population.un.org/wpp/Publications/Files/WPP2017_KeyFindings.pdf [accessed 2021-10-05]
2. Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimers Res Ther 2014;6(4):37 [FREE Full text] [doi: 10.1186/alzrt269] [Medline: 25024750]
3. Gomes-Osman J, Cabral D, Morris T, McInerney K, Cahalin L, Rundek T, et al. Exercise for cognitive brain health in aging: A systematic review for an evaluation of dose. Neurol Clin Pract 2018 Jun;8(3):257-265 [FREE Full text] [doi: 10.1212/CPJ.0000000000000460] [Medline: 30105166]
4. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci 2003 Mar;14(2):125-130. [doi: 10.1111/1467-9280.t01-1-01430] [Medline: 12661673]

5. Etnier JL, Nowell PM, Landers DM, Sibley BA. A meta-regression to examine the relationship between aerobic fitness and cognitive performance. Brain Research Reviews 2006 Aug 30;52(1):119-130. [doi: 10.1016/j.brainresrev.2006.01.002] [Medline: 16490256]
6. Gorelick P, Furie K, Iadecola C, Smith E, Waddy S, Lloyd-Jones D, American Heart Association/American Stroke Association. Defining optimal brain health in adults: a presidential advisory from the American Heart Association/American Stroke Association. Stroke 2017 Oct;48(10):e284-e303 [FREE Full text] [doi: 10.1161/STR.0000000000000148] [Medline: 28883125]
7. Barnes CA. Long-term potentiation and the ageing brain. Philos Trans R Soc Lond B Biol Sci 2003 Apr 29;358(1432):765-772 [FREE Full text] [doi: 10.1098/rstb.2002.1244] [Medline: 12740124]
8. van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc Natl Acad Sci U S A 1999 Nov 09;96(23):13427-13431 [FREE Full text] [doi: 10.1073/pnas.96.23.13427] [Medline: 10557337]
9. van Praag H. Neurogenesis and exercise: past and future directions. Neuromolecular Med 2008;10(2):128-140. [doi: 10.1007/s12017-008-8028-z] [Medline: 18286389]
10. Christie B, Eadie B, Kannangara T, Robillard J, Shin J, Titterness A. Exercising our brains: how physical activity impacts synaptic plasticity in the dentate gyrus. Neuromolecular Med 2008;10(2):47-58. [doi: 10.1007/s12017-008-8033-2] [Medline: 18535925]
11. Christie B, Swann S, Fox C, Froc D, Lieblich S, Redila V, et al. Voluntary exercise rescues deficits in spatial memory and long-term potentiation in prenatal ethanol-exposed male rats. Eur J Neurosci 2005 Mar;21(6):1719-1726. [doi: 10.1111/j.1460-9568.2005.04004.x] [Medline: 15845099]
12. Zhao G, Liu H, Zhang H, Tong X. Treadmill exercise enhances synaptic plasticity, but does not alter β-amyloid deposition in hippocampi of aged APP/PS1 transgenic mice. Neuroscience 2015 Jul 09;298:357-366. [doi: 10.1016/j.neuroscience.2015.04.038] [Medline: 25917310]
13. Liu H, Zhao G, Cai K, Zhao H, Shi L. Treadmill exercise prevents decline in spatial learning and memory in APP/PS1 transgenic mice through improvement of hippocampal long-term potentiation. Behav Brain Res 2011 Apr 15;218(2):308-314. [doi: 10.1016/j.bbr.2010.12.030] [Medline: 21192984]
14. Dao AT, Zagaar MA, Salim S, Eriksen JL, Alkadhi KA. Regular exercise prevents non-cognitive disturbances in a rat model of Alzheimer's disease. Int J Neuropsychopharmacol 2014 Apr;17(4):593-602 [FREE Full text] [doi: 10.1017/S1461145713001351] [Medline: 24229510]
15. Gomes-Osman J, Cabral DF, Hinchman C, Jannati A, Morris TP, Pascual-Leone A. The effects of exercise on cognitive function and brain plasticity—a feasibility trial. Restor Neurol Neurosci 2017;35(5):547-556 [FREE Full text] [doi: 10.3233/RNN-170758] [Medline: 28984621]
16. Ozdemir RA, Tadayon E, Boucher P, Momi D, Karakhanyan KA, Fox MD, et al. Individualized perturbation of the human connectome reveals reproducible biomarkers of network dynamics relevant to cognition. Proc Natl Acad Sci U S A 2020 Apr 07;117(14):8115-8125 [FREE Full text] [doi: 10.1073/pnas.1911240117] [Medline: 32193345]
17. Vink JJT, Klooster DCW, Ozdemir RA, Westover MB, Pascual-Leone A, Shafi MM. EEG functional connectivity is a weak predictor of causal brain interactions. Brain Topogr 2020 Mar;33(2):221-237 [FREE Full text] [doi: 10.1007/s10548-020-00757-6] [Medline: 32090281]
18. Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009 Dec;120(12):2008-2039 [FREE Full text] [doi: 10.1016/j.clinph.2009.08.016] [Medline: 19833552]
19. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14(5):377-381. [doi: 10.1249/00005768-198205000-00012]
20. Keteyian S, Kitzman D, Zannad F, Landzberg J, Arnold J, Brubaker P, et al. Predicting maximal HR in heart failure patients on β-blockade therapy. Med Sci Sports Exerc 2012 Mar;44(3):371-376 [FREE Full text] [doi: 10.1249/MSS.0b013e318234316f] [Medline: 21900844]
21. Oberman L, Pascual-Leone A. Changes in plasticity across the lifespan: cause of disease and target for intervention. Prog Brain Res 2013;207:91-120 [FREE Full text] [doi: 10.1016/B978-0-444-63327-9.00016-3] [Medline: 24309252]
22. Freitas C, Farzan F, Pascual-Leone A. Assessing brain plasticity across the lifespan with transcranial magnetic stimulation: why, how, and what is the ultimate goal? Front Neurosci 2013;7:42 [FREE Full text] [doi: 10.3389/fnins.2013.00042] [Medline: 23565072]
23. Fried PJ, Schilberg L, Brem A, Saxena S, Wong B, Cypess AM, et al. Humans with type-2 diabetes show abnormal long-term potentiation-like cortical plasticity associated with verbal learning deficits. J Alzheimers Dis 2017;55(1):89-100 [FREE Full text] [doi: 10.3233/JAD-160505] [Medline: 27636847]
24. Giovagnoli AR, Del Pesce M, Mascheroni S, Simoncelli M, Laiacona M, Capitani E. Trail making test: normative values from 287 normal adult controls. Ital J Neurol Sci 1996 Aug;17(4):305-309. [doi: 10.1007/BF01997792] [Medline: 8915764]
25. Reitan RM, Hom J, Wolfson D. Verbal processing by the brain. J Clin Exp Neuropsychol 1988 Aug;10(4):400-408. [doi: 10.1080/01688638808408248] [Medline: 3403703]

26. Morrow SA. Normative data for the Stroop color word test for a North American population. Can J Neurol Sci 2013 Nov;40(6):842-847. [doi: 10.1017/s0317167100015997] [Medline: 24257227]
27. Germine L, Nakayama K, Duchaine BC, Chabris CF, Chatterjee G, Wilmer JB. Is the Web as good as the lab? Comparable performance from Web and lab in cognitive/perceptual experiments. Psychon Bull Rev 2012 Oct;19(5):847-857. [doi: 10.3758/s13423-012-0296-9] [Medline: 22829343]
28. LaBelle DR, Lee BG, Miller JB. Dissociation of executive and attentional elements of the digit span task in a population of older adults: a latent class analysis. Assessment 2019 Oct;26(7):1386-1398. [doi: 10.1177/1073191117714556] [Medline: 28621146]
29. Randolph C, Tierney M, Mohr E, Chase T. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. J Clin Exp Neuropsychol 1998 Jun;20(3):310-319. [doi: 10.1076/jcen.20.3.310.823] [Medline: 9845158]
30. Delis D, Kaplan EK, Kramer J. Delis-Kaplan Executive Function System: Technical Manual. San Antonio: The Psychological Corporation; 2001.
31. Singh SJ, Morgan MD, Scott S, Walters D, Hardman AE. Development of a shuttle walking test of disability in patients with chronic airways obstruction. Thorax 1992 Dec;47(12):1019-1024 [FREE Full text] [doi: 10.1136/thx.47.12.1019] [Medline: 1494764]
32. Dourado VZ, Vidotto MC, Guerra RLF. Reference equations for the performance of healthy adults on field walking tests. J Bras Pneumol 2011;37(5):607-614 [FREE Full text] [doi: 10.1590/s1806-37132011000500007] [Medline: 22042392]
33. Bohannon R, Crouch R. 1-Minute sit-to-stand test: systematic review of procedures, performance, and clinimetric properties. J Cardiopulm Rehabil Prev 2019 Jan;39(1):2-8. [doi: 10.1097/HCR.0000000000000336] [Medline: 30489442]
34. Quintana DS, Heathers JAJ, Kemp AH. On the validity of using the Polar RS800 heart rate monitor for heart rate variability research. Eur J Appl Physiol 2012 Dec;112(12):4179-4180. [doi: 10.1007/s00421-012-2453-2] [Medline: 22790488]
35. Routledge FS, Campbell TS, McFetridge-Durdle JA, Bacon SL. Improvements in heart rate variability with exercise therapy. Can J Cardiol 2010;26(6):303-312 [FREE Full text] [doi: 10.1016/s0828-282x(10)70395-0] [Medline: 20548976]
36. Malik M. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use: task force of The European Society of Cardiology and the North American Society for Pacing and Electrophysiology. Ann Noninv Electrocard 1996 Apr;1(2):151-181. [doi: 10.1111/j.1542-474x.1996.tb00275.x]
37. Tarvainen MP, Niskanen J, Lipponen JA, Ranta-Aho PO, Karjalainen PA. Kubios HRV—heart rate variability analysis software. Comput Methods Programs Biomed 2014;113(1):210-220. [doi: 10.1016/j.cmpb.2013.07.024] [Medline: 24054542]
38. Podsiadlo D, Richardson SJ. The timed “up & go”: a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc 1991 Feb;39(2):142-148. [doi: 10.1111/j.1532-5415.1991.tb01616.x] [Medline: 1991946]
39. Kelly VE, Janke AA, Shumway-Cook A. Effects of instructed focus and task difficulty on concurrent walking and cognitive task performance in healthy young adults. Exp Brain Res 2010 Nov;207(1-2):65-73 [FREE Full text] [doi: 10.1007/s00221-010-2429-6] [Medline: 20931180]
40. Chasan-Taber L, Erickson J, McBride J, Nasca P, Chasan-Taber S, Freedson P. Reproducibility of a self-administered lifetime physical activity questionnaire among female college alumnae. Am J Epidemiol 2002 Feb 01;155(3):282-289. [doi: 10.1093/aje/155.3.282] [Medline: 11821254]
41. Neupert SD, Lachman ME, Whitbourne SB. Exercise self-efficacy and control beliefs: effects on exercise behavior after an exercise intervention for older adults. J Aging Phys Act 2009 Jan;17(1):1-16 [FREE Full text] [doi: 10.1123/japa.17.1.1] [Medline: 19299835]
42. Booth ML, Owen N, Bauman A, Clavisi O, Leslie E. Social-cognitive and perceived environment influences associated with physical activity in older Australians. Prev Med 2000 Jul;31(1):15-22. [doi: 10.1006/pmed.2000.0661] [Medline: 10896840]
43. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989 May;28(2):193-213. [doi: 10.1016/0165-1781(89)90047-4] [Medline: 2748771]
44. Mollayeva T, Thurairajah P, Burton K, Mollayeva S, Shapiro CM, Colantonio A. The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: a systematic review and meta-analysis. Sleep Med Rev 2016 Feb;25:52-73. [doi: 10.1016/j.smrv.2015.01.009] [Medline: 26163057]
45. Cattaneo G, Bartrés-Faz D, Morris T, Sánchez J, Macià D, Tarrero C, et al. The Barcelona Brain Health Initiative: a cohort study to define and promote determinants of brain health. Front Aging Neurosci 2018;10:321 [FREE Full text] [doi: 10.3389/fnagi.2018.00321] [Medline: 30405394]
46. Yesavage JA, Brink T, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982;17(1):37-49. [doi: 10.1016/0022-3956(82)90033-4] [Medline: 7183759]
47. Scherder E, Scherder R, Verburgh L, Königs M, Blom M, Kramer A, et al. Executive functions of sedentary elderly may benefit from walking: a systematic review and meta-analysis. Am J Geriatr Psychiatry 2014 Aug;22(8):782-791. [doi: 10.1016/j.jagp.2012.12.026] [Medline: 23636004]

Abbreviations

BDNF: brain-derived neurotrophic factor
EEG: electroencephalography
EMG: electromyography
HR: heart rate
IRB: institutional review board
iTBS: intermittent theta-burst stimulation
MEP: motor evoked potential
REDCap: Research Electronic Data Capture
tACS: transcranial alternating current stimulation
TBS: theta-burst stimulation
TMS: transcranial magnetic stimulation
TUG: Timed Up-and-Go
VEGF: vascular endothelial growth factor

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Protocol

Using Methods From Computational Decision-making to Predict Nonadherence to Fitness Goals: Protocol for an Observational Study

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Abstract

Background: Can methods from computational models of decision-making be used to build a predictive model to identify individuals most likely to be nonadherent to personal fitness goals? Such a model may have significant value in the global battle against obesity. Despite growing awareness of the impact of physical inactivity on human health, sedentary behavior is increasingly linked to premature death in the developed world. The annual impact of sedentary behavior is significant, causing an estimated 2 million deaths. From a global perspective, sedentary behavior is one of the 10 leading causes of mortality and morbidity. Annually, considerable funding and countless public health initiatives are applied to promote physical fitness, with little impact on sustained behavioral change. Predictive models developed from multimodal methodologies combining data from decision-making tasks with contextual insights and objective physical activity data could be used to identify those most likely to abandon their fitness goals. This has the potential to enable development of more targeted support to ensure that those who embark on fitness programs are successful.

Objective: The aim of this study is to determine whether it is possible to use decision-making tasks such as the Iowa Gambling Task to help determine those most likely to abandon their fitness goals. Predictive models built using methods from computational models of decision-making, combining objective data from a fitness tracker with personality traits and modeling from decision-making games delivered via a mobile app, will be used to ascertain whether a predictive algorithm can identify digital personae most likely to be nonadherent to self-determined exercise goals. If it is possible to phenotype these individuals, it may be possible to tailor initiatives to support these individuals to continue exercising.

Methods: This is a siteless study design based on a *bring your own device* model. A total of 200 healthy adults who are novice exercisers and own a Fitbit (Fitbit Inc) physical activity tracker will be recruited via social media for this study. Participants will provide consent via the study app, which they will download from the Google Play store (Alphabet Inc) or Apple App Store (Apple Inc). They will also provide consent to share their Fitbit data. Necessary demographic information concerning age and sex will be collected as part of the recruitment process. Over 12 months, the scheduled study assessments will be pushed to the subjects to complete. The Iowa Gambling Task will be administered via a web app shared via a URL.

Results: Ethics approval was received from Dublin City University in December 2020. At manuscript submission, study recruitment was pending. The expected results will be published in 2022.

Conclusions: It is hoped that the study results will support the development of a predictive model and the study design will inform future research approaches.

Trial Registration: ClinicalTrials.gov NCT04783298; https://clinicaltrials.gov/ct2/show/NCT04783298

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KEYWORDS

decision-making games; computational psychology; fitness goals; advanced analytics; mobile app; computational modeling; fitness tracker; mobile phone

Introduction

Background

As a society, we are becoming more sedentary. In some countries, inactivity levels can be as high as 70%, with 1 in 4 adults and 3 in 4 adolescents not achieving the recommended World Health Organization (WHO) activity levels [1]. Recommendations for adults are as follows: "at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity" [2]. In a press release issued to celebrate world health data on April 7, 2020, the WHO stated that approximately 2 million deaths per year are due to low physical activity. From a global perspective, sedentary behavior is one of the 10 leading causes of mortality and morbidity [1]. Physical inactivity can significantly affect an individual's health and quality of life and increase the probability of developing several chronic diseases such as heart disease, obesity, high blood cholesterol, and type 2 diabetes.

Every year, a large section of the global population makes resolutions that are focused on improved fitness. Unfortunately, these resolutions are not sustained, with both popular media and peer-reviewed journals reporting on the low number that maintain behavioral changes. Popular media report dramatic figures, including an analysis by Strava of their global membership data, revealing that January 17, 2020, was *quitters day*, the day individuals are most likely to give up their New Year's resolutions [3]. Similar statistics have been reported for gym membership and use. A review by Sperandei et al [4] of over 5240 gym members revealed a dropout rate of 47% by the second month, 86% by the sixth month, and 96% by the 12th month. These figures were reinforced by a Spanish study of 14,522 gym members, which revealed that between 47.3% and 56% dropped out over the course of a year [5].

Nevertheless, despite the health impacts and our good intentions, the questions remain: why do so many start but abandon their fitness regimens? What factors impact this nonadherence to self-made fitness goals, and can we use computational models of decision-making to predict those most likely to give up? Does the issue reside in the resolution itself and tied to that specific goal-setting activity? Is it down to motivation, behavioral change, and personality traits, or is it a complex combination of the aforementioned factors? This study's unique value is the combination of computational psychology methods, personality traits that have been shown to correlate with *healthy behaviors*, and behavioral change with objective physical measurement using a fitness tracker. The study hypothesis hopes to show that using a decision-making game, combined with contextual insights from personality traits, a predictive behavioral model can be built that can be used to identify individuals most likely to give up personal physical activity goals. The ability to predict a specific phenotype based on results from the decision-making tasks, Type D personality, and self-efficacy will allow targeted motivational health interventions. These personality traits will be described in greater detail in the following sections.

Goal-Setting

Goal-setting is seen as an essential factor in commencing and sustaining health behaviors [6]. A significant body of work focuses on goal-setting as a strategy for promoting sustained physical activity. The best-known and most widely implemented is the goal-setting theory developed by Locke and Latham [7], which is based on the premise that human behavior is purposefully regulated by an individual's goal. The successful outcome of sustained healthy behavioral change is impacted by the individual constructs of goal-setting theory, such as effort toward goal-related activities, persistence, and commitment [8]. In a recent reflection, Locke and Latham reviewed 50 years of the development of the goal-setting theory and reaffirmed that the approach has "generality across participants, tasks, nationality, goal source, settings, experimental designs, outcome variables, levels of analysis, and time spans" [9]. However, the current school of thought has further refined this approach and dissected goal-setting into two separate domains of performance goals and learning goals, with the former more appropriate for those who are already physically active and the latter more impactful on novices or those new to physical activity [10].

Self-efficacy

Self-efficacy has been defined as *the belief in one's capabilities to organize and execute the courses of action required to manage prospective situations* [11]. There has been a considerable interest in the impact of low self-efficacy on human behavior, particularly its effects on physical activity levels [12]. A 2012 review by Bauman et al [13] explored 5 separate categories, which are demographic or biological, psychosocial, behavioral, social and cultural, and environmental factors, and identified a positive correlation between self-efficacy and physical activity. Self-efficacy has been identified as a core belief that affects each of the basic *processes of personal change.* Bandura further described how individuals with low self-efficacy were more likely to give up [14]. He developed a targeted questionnaire to measure self-efficacy associated with reduced physical activity, the 5-item Self-Efficacy for Physical Activity [15].

Type D Personality

A Type D personality is a term used to describe a personality type that tends to have negative affectivity and social inhibition [16]. Denollet [17] developed the DS14, a validated psychometric measure for assessing negative affectivity, social inhibition, and Type D personality types, and as early as 1998, it showed a demonstrable link between Type D personality and coronary heart disease. According to a 2005 study of over 3800 subjects, this 14-item questionnaire was observed to be stable over 3 months and not dependent on mood and health status

[16]. Type D personality has been associated with medication nonadherence and heart failure [18], coronary heart disease [19], and type 2 diabetes [20,21]. Several studies have linked Type D personalities with sedentary lifestyles, including a 2009 study of 564 healthy men that showed that Type D personality was more common in men with a sedentary lifestyle (45%) than men who exercised regularly (14%) [20]. Compared with non-Type D personality types, Type D personality types have been associated with decreased walking and total exercise [22]. This study of 189 healthy volunteers looked at the relationship between Type D personality, physical activity, and self-efficacy and determined that Type D personalities had lower levels of self-efficacy and engaged in significantly less walking and total exercise compared with non-Type D personalities [22].

Low self-efficacy has been associated with Type D personalities in populations with chronic diseases such as type 2 diabetes [23] and acute coronary syndrome [19].

Status of Change

When exploring physical activity, particularly those individuals who are embarking on a new exercise program, understanding an individual's perspective concerning their status of change will provide critical contextual insights. The current understanding regarding behavior change suggests that individuals need to progress through several changes. The most widely used model is the status of change model, which forms part of the 10-stage transtheoretical model [24]. The status of change model consists of 5 separate stages: "(1) precontemplation where no intention to change is intended within the next 6 months, (2) contemplation where change is intended sometime in the future (usually defined as between 1 and 6 months), (3) preparation where change is intended in the immediate future (1 month) and steps are taken to help prepare for change, (4) action where the target behavior has been modified for <6 months, and (5) maintenance that is the stage characterized by temporally robust behavior change extending beyond 6 months" [25]. Individuals are believed to transition progressively through the various stages. They can regress to the previous stages. Perhaps it is not surprising that self-efficacy, a situation-specific construct [26], is believed to change as the individual moves through the status of change [15,25]. We selected the WHO physical activity recommendations as a guideline for this study [27].

Computational Psychology and Decision-making Games

There has been a growing interest in applying computational modeling to understand human behavior. The ability to predict human behavior and understand that drivers behind the decision-making process have significant application in adherence to physical activity behavior and relevance when predicting medication adherence in health care. Decision-making tasks have evolved within computational psychology to simulate real-life decision-making and sensitivity to reward and punishment. As described by Ahn et al [28], the performance of simulated gambling tasks represents a conglomerate of psychological processes such as reinforcement learning and motivational strategies. One of the best-known games is the Iowa Gambling Task (IGT), developed by Bechara et al in 1994 [29], and has been used extensively to evaluate the decision-making process. This assessment uses 4 decks of cards labeled A, B, C, and D. Two decks are good, and 2 are bad. If the good decks are selected, there are positive outcomes. If the bad decks are selected, there are corresponding negative outcomes. Throughout the game, the player learns to select the positive decks.

In a study by Bechara, a discernible difference in deck selection was identified when performance of healthy participants was compared with that of a clinical population. Although initially, the IGT was used in subjects with damage to the ventromedial prefrontal cortex, it has been used in a broader range of clinical patients and healthy populations to detect risky decision-making. Within the clinical context, the IGT has been used in several populations where decision-making is impaired, such as gambling, substance abuse, and several neurological conditions such as schizophrenia and psychopathy [30] and eating disorders [31]. Regarding healthy populations, some work has been done to show a differential response depending on whether individuals self-select as either an intuitive (affective) decision-making style or deliberate (planned) decision-making style, potentially those with a more intuitive decision-making style having greater success on the IGT [32]. Research in the '80s and '90s suggested a possible link between negative mood and decision-making behavior [33,34]. Suhr et al [35] built on these findings and investigated the impact personality traits have on the IGT's performance. In 2007, they published the research results on 87 nonclinical participants, which showed that higher negative mood correlated with risky performance on the IGT. In 2013, the team identified a correlation among mood, personality variables, and deck selection. Although this study did not identify a link between positivity and a specific deck selection, less advantageous decks were selected by individuals in a more negative mood [36]. Although not without distractors, these findings were supported by the Somatic Marker Hypothesis, which postulates that emotional defects significantly impact what is understood as the normal decision-making process [37]. The hypothesis also specifies the number of structures and operations required for the normal decision-making operations.

Although this is one of the best-known decision-making games, some limitations have been reported, with some researchers reporting both interstudy and interindividual variability in healthy participants. It has been proposed that the IGT lacks *an integrated sensitivity measure* [38]. Other contradictory findings have been reported, which are against the premise that healthy subjects learn to select decks that yield the highest returns, the good expected value decks. Several studies have shown that participants select the less favorable decks with larger penalties and that there may be a drive to choose more frequent gains and immediacy of reward rather than long-term outcomes. This is referred to as *gain-loss frequency* [39,40] and healthy participants are influenced by the frequency of losses rather than the long-term outcomes [41]. In 2013, Steingroever et al [41] suggested that performance inconsistencies impacted the value of IGT to measure real-life decision-making. However, in their aptly named paper, "Who Fails the Iowa Gambling Test (IGT)?" Suhr et al [42] ascribed several plausible explanations

to the IGT *failed performance* in normal populations, including personality and negative mood.

Several groups have developed strategies to overcome the limitations of the IGT. There have been numerous evolutions of decision-making games, such as the Soochow Gambling task [43]. This is a more symmetrically designed game, with a more defined expected value between the good and bad decks. Participants were offered only a single net payoff for each trial. According to the team that developed the Soochow Gambling Task, *gain-loss frequency rather than expected values guide decision-makers*, this desire for instant gain may explain some impulsive behaviors in real life [43].

Many researchers have focused on modifying the empirical cognitive modeling used to identify meaningful signals to characterize the underlying human behavior behind the tasks' choices. The established Reinforcement Learning model includes the Expectancy-Valence Learning model [44] and the Prospect Valence Learning (PVL) model [45]. Modifications include PVL-Delta [46], PVL-DecayRI [47], PVL2 [48], and the Value-Plus-Perseverance model [49]. In 2018, Haines [50] proposed a model called the Outcome-Representation Learning model that provided the best compromise among competing models [50]. This model has been tested in a healthy nonclinical population and will be one of the leading models used in this study. Steingroever [51] proposed other novel Bayesian analyses. To date, most of the models have been trained and tested in clinical subjects, with few applied to normal nonclinical populations.

Decision-making games based on game-theoretical ideas, such as the Prisoner's dilemma game and the Trust game, which are reciprocal games involving social decision-making, were deemed to be outside the scope of this study.

Study Hypothesis

The hypothesis of this study is as follows: combining results from decision-making tasks, such as the IGT with contextual insights gleaned from personality trait assessments and objective data from the physical activity tracker, we can develop a predictive model that can identify those most likely to give up their fitness goals. This information has the potential to be used to create more targeted support to ensure that those who embark on fitness programs are successful. This study also acts as a feasibility model to test the deployment of questionnaires and the IGT using a *bring your own device* (BYOD) model. The intention is to incorporate feedback from compliance and acceptance testing to inform future studies.

Methods

Study Design

This multimodal observational study combines objective sensor data with decision-making games and contextual personality traits to identify patterns in exercise decay. The data generated will build computational models to predict digital personas, who are most likely to abandon exercise goals.

Recruitment

The study will be advertised on social media, commencing in 2021. This is an entirely virtual, BYOD study design, and interested individuals without any underlying health issues and over the age of 18 years will be invited to download the study app from the Google Play store (Alphabet Inc) and Apple App Store (Apple Inc). Those who are willing to consent to the study and own a Fitbit (Fitbit Inc) will be requested to participate in the study. Once consent is given to participate in the study, participants will be asked to share their Fitbit data. Physical activity, sleep, and heart rate data will be shared using an anonymized token system to ensure that only pseudonymized data are included in the study. Once the individuals provide consent to participate in the study and share their Fitbit data, they will be asked to complete the following assessments: demographics, Type D personality, goal-setting, and self-efficacy questionnaire. They will also be asked to perform decision-making games based on the IGT.

Metrics concerning compliance with each assessment will be quantified. Data will be captured over 12 months. At the end of the study period, participants will be sent a notification to thank them for their participation and a link to where the study results will be shared once available.

Research Participants

Healthy adults (self-certified) over the age of 18 years who are embarking on a physical activity regime will be invited to participate in the study. These subjects need to own their own Fitbit and smartphone and be willing to participate in the study.

Study Interventions

Study App

The study app was developed by Dublin City University (AthenaCX, DCU). It allows researchers to rapidly design and deploy mobile experience sampling apps (iOS and Android), including integrated consenting and wearable data collection devices. This will provide the participants with a study overview in the form of plain language statements and privacy statements and facilitate the participants e-consent into the study. The app was designed to ensure that subjects have read the study details and consented to the study before completing the study assessments (Multimedia Appendix 1 includes a text sample from the plain language statement and informed consent in the mobile app). The participants have the right to withdraw from the study at any time. The app will be used to deliver the assessments and provide a link to the decision-making game. Push notifications will be sent to the participants during the study, requesting them to complete the assessments at the required time intervals, as detailed below.

Fitbit

The use of fitness trackers in this study will facilitate the objective assessment of the participants' activity patterns and behavioral changes in exercise. It will also enable the identification of individuals who already have a well-established exercise regime. A BYOD approach will be used, and data from each participant's Fitbit will be captured. Fitbit devices are a range of physical activity trackers and smartwatches that

combine integrated accelerometers and photoplethysmograph sensors to measure motion and heart rate. Proprietary algorithms convert the accelerometer data into sleep and activity patterns. Fitbit devices use Bluetooth low energy technology to synchronize with the individual's mobile device and produce various metrics, including step count, floors climbed, distance covered, calories burned, active minutes, sleep time and stages, and heart rate. In this study, a high-frequency intraday data will be collected using a web-based application programming interface. These data are highly granular and include 1 minute and 15 minutes for activity and 1 second and 1 minute for heart rate.

Assessments

Demographic Information

Participants will be requested to provide details of their age and sex. The following classifiers will be used: male, female, self-defined, and prefer not to say.

Self-efficacy Questionnaire

The self-efficacy questionnaire for exercise was based on the Bandura Exercise Self-Efficacy scale initially developed in 2006 [26], and the original 0 to 100 numerical rating scale was used (Multimedia Appendix 1). Participants were asked to rate their degree of confidence by moving a widget across a scale on the app. A rating of 0 equates to *cannot do at all* and a rating of 100 reflects complete confidence and participants are *highly certain* they can engage in physical activity. Participants will be requested to complete the self-efficacy questionnaire at the start of the study and 6 months after the study commencement (Multimedia Appendix 2 includes the self-efficacy questionnaire and screenshots of the app).

Status of Change

To ensure that all participants were able to assess their current activity levels against the same criteria, the WHO physical activity guidance [27] was included in the instructions for the *stages of change* questionnaire. Participants were asked to consider only planned physical activities aimed at improving or maintaining physical fitness and health. Active periods should consist of 150 minutes of moderate-intensity physical activity (such as a brisk walk) in a week or 75 minutes of vigorous-intensity physical activity (such as a jog or run) over the course of a week. Participants will be asked to complete the status of changes questionnaire at the start of the study and 6 months after study commencement (Multimedia Appendix 3 includes details of the stages of change questionnaire and screenshots of the app).

Type D Personality Questionnaire

The 14-question Type D personality questionnaire developed by Denollet [16] will be used in this study. A total of 7 questions pertain to the negative affectivity domain and 7 to the social inhibition domain. Each question will be scored on a scale of 0 to 4. The questionnaire will be scored as individual negative affectivity and social inhibition domains and a composite Type D personality score. Participants will be asked to complete the Type D personality questionnaire at the start of the study and 6 months after the study commencement (Multimedia Appendix 4 includes details of the Type D personality questionnaire and screenshots of the app).

Decision-making Tasks

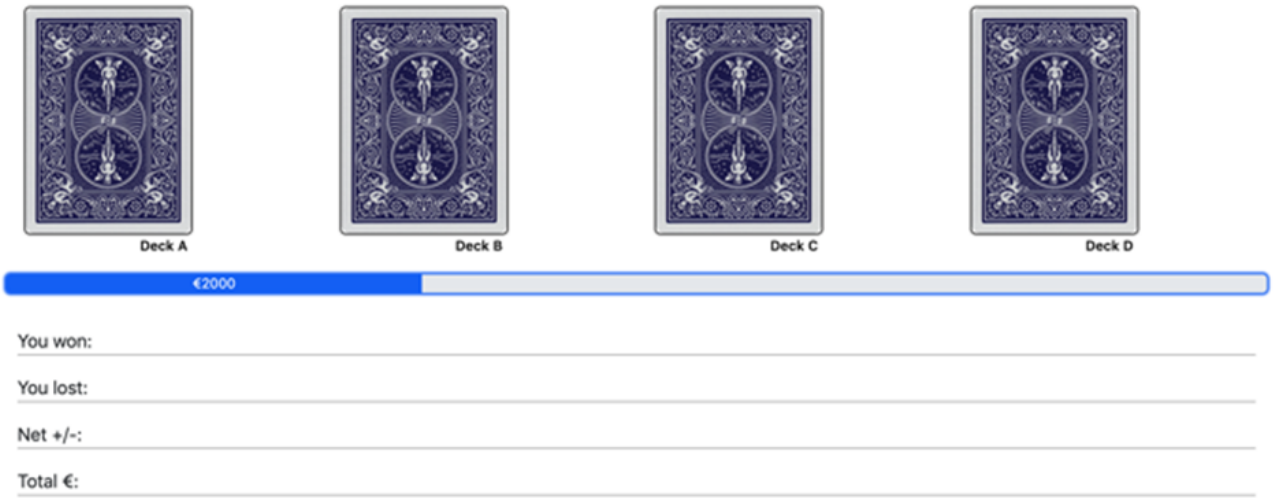
These tasks will be performed twice during the study. The IGT will be deployed within the first 3 months and at 6 months. Participants in the IGT will be given €2000 (US $2314) virtual money and presented with 4 decks of cards labeled A, B, C, and D. Each card in these decks can generate wins and can sometimes cause losses. Participants must choose 1 card from these 4 decks consecutively until the task shuts off automatically after 100 trials. In each trial, feedback on rewards and losses of their choice and the running tally over all trials so far are given to the participants, but no information is given regarding how many trials they will play and how many trials they have completed during the task. Participants will be instructed to choose cards from any deck and switch decks at any time. They will also be told to make as much money as possible, minimizing losses.

Table 1 presents the payoff for the 4 decks. As seen in the table, decks A and B are 2 "bad decks" that generate high immediate, constant rewards but even higher unpredictable, occasional losses. Thus, the long-term net outcome associated with decks A and B is negative. In contrast, decks C and D are 2 "good decks" that generate low immediate, constant rewards but even lower unpredictable, occasional losses. Thus, the long-term net outcome associated with decks C and D is positive. In addition to the payoff magnitudes, the 4 decks also differ in the frequency of losses, that is, decks A and C are associated with a higher frequency of losses, whereas decks B and D are associated with a lower frequency of losses. The key to obtaining a higher long-term net outcome in this task is to explore all the decks in the initial stage and then exploit the 2 good decks (Figure 1 shows a screenshot of the web-based IGT implemented).

Table 1. Summary of the payoff of the Iowa Gambling Task.

Characteristics	Deck A (bad deck with frequent losses)	Deck B (bad deck with infrequent losses)	Deck C (good deck with frequent losses)	Deck D (good deck with infrequent losses)
Reward/trial	100	100	50	50
Number of losses/10 cards	5	1	5	1
Loss/10 cards	−1250	−1250	−250	−250
Net outcome/10 cards	−250	−250	250	250

Figure 1. Screenshot of the web-based Iowa Gambling Task.



Data Analysis and Computational Modeling

This study aims to investigate whether we can predict adherence to self-made fitness goals and identify potential behavioral phenotypes based on the changes in the participants' responses to a series of validated instruments, including self-efficiency, status of change, and Type D personality, and their behavioral performance on the IGT over 6 months. A range of data analysis techniques will be applied to the collected data to achieve this goal.

We term the results obtained from questionnaires and decision-making tasks as predictor variables, whereas the adherence levels of the participants to fitness goals as target variables for convenience of description. The first problem that must be addressed before predicting and clustering is to quantify both the predictor variables and target variables.

Self-efficiency was measured by an instrument including 18 items using the original 0 to 100 numerical rating scale, where 0 represents *cannot do at all* and 100 represents *high certainty to do*. The Type D personality questionnaire also uses numerical rating scales, although with different ranges from 0 representing *false* to 4 representing *true*. However, for the Status of Change questionnaire, the answers were categorical scales of *yes* or *no*. Thus, the one-hot encoding technique, one of the most common encoding methods in machine learning, will convert the categorical answers to numerical formats.

To evaluate participants' performance on the IGT, both superficial behavioral variables and underlying cognitive parameters will be summarized and estimated from the behavioral data set. Specifically, 2 parameters will be measured in the behavioral summary analysis. The first parameter will be the total amount of gain by the end of the task, and this parameter will be used to measure the overall performance of the IGT. The second parameter will be the IGT learning scores across the task, that is, the difference between the number of good deck selections and that of bad deck selections across the task, used to reflect the learning process in the task. The 100 trial choices will first be divided into five blocks of 20 trials, each without overlap, and the learning score will be calculated for each block. As a result, 5 variables (learning scores) will be created for this measure.

Cognitive parameters that drive the behavioral performance will be extracted from the cognitive models designed for the IGT. As mentioned earlier, multiple models have been proposed for the IGT, including the Expectancy-Valence Learning model, the PVL-Delta model, the PVL-Decay model, the Value-Plus-Perseverance model, and the latest proposed Outcome-Representation Learning model (Table 2 presents the parameter specifications of the 4 IGT models). The hierarchical Bayesian modeling method, where both individual and group parameters (ie, posterior distributions) are estimated simultaneously in a mutually constraining fashion, will be used to estimate the cognitive parameters for each model. The models will be implemented in a newly developed probabilistic programing language STAN, which uses a specific Markov Chain Monte Carlo sampler called Hamiltonian Monte Carlo, to efficiently perform sampling from high dimensional posterior distributions as specified by the user. After obtaining the fitting results, model validation will be executed to determine the winning model, including a one-step-ahead leave-one-out information criterion and a posterior predictive check. The parameters of the winning model will then be used as predictor variables to predict adherence behavior. Thus, the number of variables obtained here for predicting adherence depends on which model best fits the data set.

Table 2. Parameter specifications of the 4 Iowa Gambling Task models.

Model	NP[a]	Parameters							
PVL[b]_delta	4	Outcome sensitivity (α)	Loss aversion (λ)	Learning rate (*A*)	Response consistency (c)	N/A[c]	N/A	N/A	N/A
PVL_decay	4	Outcome sensitivity (α)	Loss aversion (λ)	Decay parameter (*A*)	Response consistency (c)	N/A	N/A	N/A	N/A
VPP[d]	8	Outcome sensitivity (α)	Loss aversion (λ)	Learning rate (*A*)	Decay parameter (*K*)	Gain impact parameter (EP_P)	Loss impact parameter (EP_N)	Weight parameter (*w*)	Response consistency (c)
ORL[e]	5	Reward learning rate (A_+)	Punishment learning rate (A_-)	Decay parameter (*K*)	Outcome frequency weight ($ß_F$)	Perseverance weight ($ß_p$)	N/A	N/A	N/A

[a]NP: number of parameters.

[b]PVL: Prospect Valence Learning.

[c]N/A: not applicable.

[d]VPP: Value-Plus-Perseverance.

[e]ORL: Outcome-Representation Learning.

Finally, the question arises of how to quantify the target variable, that is, the adherence behavior, given that various types of objective fitness data will be collected. We will mainly rely on the data set of activity patterns and the step counts. According to the WHO physical activity guidelines, to improve or maintain physical fitness and health, active periods should consist of 150 minutes of moderate-intensity brisk walking or 75 minutes of vigorous-intensity jogging or running over the course of a week. If the participant completes this minimum exercise in a particular week, their adherence score for this week will be 1; otherwise, the score is 0. The scores for all weeks will be summed to obtain a total score to represent the overall adherence level of this participant.

Making Predictions and Clustering

It is apparent that the numerical predictor variables are measured at different scales; therefore, a standardization process is necessary to make the numerical features identical regarding the range. *Z* score normalization that scales the value while considering the SD will be adopted in this case. Finally, a list of regression algorithms in machine learning will be applied to the cleaned data set, in which we characterize each participant with a vector of a certain length. The possible algorithms include linear regression, rigid regression, lasso regression, and neural network regression.

In addition, unsupervised learning algorithms that can work independently to discover patterns and information will be applied to the data set to identify potential behavioral phenotypes. The K-means clustering algorithm, one of the simplest unsupervised learning algorithms, can be used to solve this problem.

Risks

Participation in this study presents no identifiable risk to the participants.

Results

This study was funded by the Irish Research Council as part of an employment-based PhD scholarship. Ethics approval was obtained from Dublin City University in December 2020. At manuscript submission, study recruitment was pending. The expected results will be published in 2022.

Discussion

Overview

The rationale for this study is to determine whether data from decision-making games and personality traits could predict individuals most likely to give up on self-determined physical activity goals. The ability to identify the digital persona of those most likely to abandon exercise goals has significant value to those involved in developing targeted support to encourage and adhere to fitness goals.

Methodological Limitations

Recruitment

Participants will not be incentivized to join the study, and as such, it may be challenging to reach the recruitment goals. A rolling strategy will be adopted with regular push notifications to social media and a dedicated study page established on Facebook to maximize recruitment. These pages will have details of the study, the app, and a YouTube instructional video.

Loss of Fitbit Data

All Fitbit devices have a finite internal memory, and intraday data are stored for 5 to 7 days, depending on the tracker (daily totals are generally retained for 30 days). If participants do not regularly synchronize their devices, the data can be overwritten.

Participants may fail to complete the required number of tests in the IGT to facilitate parameter modeling and derive the required insights.

Depending on the number of participants recruited for the study, the application of deep learning approaches may be limited owing to the participant numbers and may result in overfitting.

Acknowledgments

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Conflicts of Interest

MM is an employee of ICON Plc and is in receipt of a grant from the Irish Research Council.

Multimedia Appendix 1
Text sample from the plain language statement and informed consent in the mobile app.
[DOCX File , 125 KB - resprot_v10i11e29758_app1.docx]

Multimedia Appendix 2
Self-efficacy questionnaire.
[DOCX File , 94 KB - resprot_v10i11e29758_app2.docx]

Multimedia Appendix 3
Status of change.
[DOCX File , 117 KB - resprot_v10i11e29758_app3.docx]

Multimedia Appendix 4
Type D personality questionnaire.
[DOCX File , 106 KB - resprot_v10i11e29758_app4.docx]

References

1. World Health Organization. Global Action Plan on Physical Activity 2018–2030: More Active People for a Healthier World. Geneva: World Health Organization; 2018:1-101.
2. Physical activity. World Health Organization. URL: https://www.who.int/news-room/fact-sheets/detail/physical-activity [accessed 2021-10-21]
3. Strava reveals 2020 quitters day. Sports Insight. 2020. URL: https://www.sports-insight.co.uk/news/strava-reveals-2020-quitters-day [accessed 2021-10-21]
4. Sperandei S, Vieira MC, Reis AC. Adherence to physical activity in an unsupervised setting: explanatory variables for high attrition rates among fitness center members. J Sci Med Sport 2016 Nov;19(11):916-920. [doi: 10.1016/j.jsams.2015.12.522] [Medline: 26874647]
5. Emeterio I, García-Unanue J, Iglesias-Soler E, Felipe J, Gallardo L. Prediction of abandonment in Spanish fitness centres. Eur J Sport Sci 2019 Mar 22;19(2):217-224. [doi: 10.1080/17461391.2018.1510036] [Medline: 30132378]
6. Shilts MK, Horowitz M, Townsend MS. Goal setting as a strategy for dietary and physical activity behavior change: a review of the literature. Am J Health Promot 2004 Aug 26;19(2):81-93. [doi: 10.4278/0890-1171-19.2.81] [Medline: 15559708]
7. Tosi HL, Locke EA, Latham GP. A theory of goal setting and task performance. Acad Manag Rev 1991 Apr;16(2):480. [doi: 10.2307/258875]
8. Locke EA, Latham GP. Building a practically useful theory of goal setting and task motivation: a 35-year odyssey. Am Psychol 2002 Sep;57(9):705-717. [doi: 10.1037/0003-066x.57.9.705]
9. Locke EA, Latham GP. The development of goal setting theory: a half century retrospective. Motivat Sci 2019 Jun;5(2):93-105. [doi: 10.1037/mot0000127]
10. Swann C, Rosenbaum S, Lawrence A, Vella SA, McEwan D, Ekkekakis P. Updating goal-setting theory in physical activity promotion: a critical conceptual review. Health Psychol Rev 2021 Mar 27;15(1):34-50. [doi: 10.1080/17437199.2019.1706616] [Medline: 31900043]
11. Bandura A. Self-Efficacy in Changing Societies. Cambridge, MA: Cambridge University Press; 1995.
12. Daniali S, Darani F, Eslami A, Mazaheri M. Relationship between self-efficacy and physical activity, medication adherence in chronic disease patients. Adv Biomed Res 2017;6(1):63 [FREE Full text] [doi: 10.4103/2277-9175.190997] [Medline: 28603704]

13. Bauman AE, Reis RS, Sallis JF, Wells JC, Loos RJ, Martin BW. Correlates of physical activity: why are some people physically active and others not? Lancet 2012 Jul;380(9838):258-271. [doi: 10.1016/s0140-6736(12)60735-1]
14. Bandura A. Health promotion by social cognitive means. Health Educ Behav 2004 Apr 30;31(2):143-164. [doi: 10.1177/1090198104263660] [Medline: 15090118]
15. Marcus BH, Selby VC, Niaura RS, Rossi JS. Self-efficacy and the stages of exercise behavior change. Res Q Exerc Sport 1992 Mar;63(1):60-66. [doi: 10.1080/02701367.1992.10607557] [Medline: 1574662]
16. Denollet J. DS14: standard assessment of negative affectivity, social inhibition, and Type D personality. Psychosom Med 2005;67(1):89-97. [doi: 10.1097/01.psy.0000149256.81953.49] [Medline: 15673629]
17. Denollet J, Brutsaert DL. Personality, disease severity, and the risk of long-term cardiac events in patients with a decreased ejection fraction after myocardial infarction. Circulation 1998 Jan 20;97(2):167-173. [doi: 10.1161/01.cir.97.2.167] [Medline: 9445169]
18. Wu J, Moser DK. Type D personality predicts poor medication adherence in patients with heart failure in the USA. Int J Behav Med 2014 Nov 6;21(5):833-842 [FREE Full text] [doi: 10.1007/s12529-013-9366-2] [Medline: 24198039]
19. Molloy G, Randall G, Wikman A, Perkins-Porras L, Messerli-Bürgy N, Steptoe A. Type D personality, self-efficacy, and medication adherence following an acute coronary syndrome. Psychosom Med 2012 Jan;74(1):100-106. [doi: 10.1097/PSY.0b013e31823a5b2f] [Medline: 22155940]
20. Li X, Zhang S, Xu H, Tang X, Zhou H, Yuan J, et al. Type D personality predicts poor medication adherence in chinese patients with type 2 diabetes mellitus: a six-month follow-up study. PLoS One 2016 Feb 19;11(2):e0146892 [FREE Full text] [doi: 10.1371/journal.pone.0146892] [Medline: 26894925]
21. Conti C, Carrozzino D, Patierno C, Vitacolonna E, Fulcheri M. The clinical link between type D personality and diabetes. Front Psychiatry 2016 Jun 21;7:113 [FREE Full text] [doi: 10.3389/fpsyt.2016.00113] [Medline: 27445869]
22. Wiencierz S, Williams L. Type D personality and physical inactivity: the mediating effects of low self-efficacy. J Health Psychol 2017 Jul 01;22(8):1025-1034. [doi: 10.1177/1359105315622557] [Medline: 26837688]
23. Shao Y, Yin H, Wan C. Type D personality as a predictor of self-efficacy and social support in patients with type 2 diabetes mellitus. Neuropsychiatr Dis Treat 2017 Mar;Volume 13:855-861. [doi: 10.2147/ndt.s128432]
24. Prochaska JO, Velicer WF. The transtheoretical model of health behavior change. Am J Health Promot 1997 Aug 26;12(1):38-48. [doi: 10.4278/0890-1171-12.1.38] [Medline: 10170434]
25. Bridle C, Riemsma RP, Pattenden J, Sowden AJ, Mather L, Watt IS, et al. Systematic review of the effectiveness of health behavior interventions based on the transtheoretical model. Psychol Health 2007 Feb 01;20(3):283-301. [doi: 10.1080/08870440512331333997]
26. Bandura A. Self-efficacy mechanism in human agency. Am Psychol 1982;37(2):122-147. [doi: 10.1037/0003-066x.37.2.122]
27. World Health Organization. Global Recommendations on Physical Activity for Health. Geneva: World Health Organization; 2010:1-58.
28. Ahn W, Dai J, Vassileva J, Busemeyer J, Stout J. Computational modeling for addiction medicine: from cognitive models to clinical applications. Prog Brain Res 2016;224:53-65. [doi: 10.1016/bs.pbr.2015.07.032] [Medline: 26822353]
29. Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 1994 Apr;50(1-3):7-15. [doi: 10.1016/0010-0277(94)90018-3]
30. Buelow MT, Suhr JA. Construct validity of the Iowa Gambling Task. Neuropsychol Rev 2009 Mar 5;19(1):102-114. [doi: 10.1007/s11065-009-9083-4] [Medline: 19194801]
31. Cavedini P, Bassi T, Ubbiali A, Casolari A, Giordani S, Zorzi C, et al. Neuropsychological investigation of decision-making in anorexia nervosa. Psychiatry Res 2004 Jul 15;127(3):259-266. [doi: 10.1016/j.psychres.2004.03.012] [Medline: 15296825]
32. Steingroever H, Pachur T, Šmíra M, Lee MD. Bayesian techniques for analyzing group differences in the Iowa Gambling Task: a case study of intuitive and deliberate decision-makers. Psychon Bull Rev 2018 Jun 6;25(3):951-970 [FREE Full text] [doi: 10.3758/s13423-017-1331-7] [Medline: 28685273]
33. Arkes HR, Herren LT, Isen AM. The role of potential loss in the influence of affect on risk-taking behavior. Organizat Behav Hum Decis Proc 1988 Oct;42(2):181-193. [doi: 10.1016/0749-5978(88)90011-8]
34. Nygren TE. Reacting to perceived high- and low-risk win–lose opportunities in a risky decision-making task: is it framing or affect or both? Motivat Emot 1998:73-98. [doi: 10.1023/A:1023096709380]
35. Suhr JA, Tsanadis J. Affect and personality correlates of the Iowa Gambling Task. Personal Indiv Diff 2007 Jul;43(1):27-36. [doi: 10.1016/j.paid.2006.11.004]
36. Buelow MT, Suhr JA. Personality characteristics and state mood influence individual deck selections on the Iowa Gambling Task. Personal Indiv Diff 2013 Apr;54(5):593-597. [doi: 10.1016/j.paid.2012.11.019]
37. Bechara A, Damasio H, Damasio A. Emotion, decision making and the orbitofrontal cortex. Cereb Cortex 2000 Mar;10(3):295-307. [doi: 10.1093/cercor/10.3.295] [Medline: 10731224]
38. Bull PN, Tippett LJ, Addis DR. Decision making in healthy participants on the Iowa Gambling Task: new insights from an operant approach. Front Psychol 2015 Apr 07;6:391 [FREE Full text] [doi: 10.3389/fpsyg.2015.00391] [Medline: 25904884]

39. Lin C, Song T, Chen Y, Lee W, Chiu Y. Reexamining the validity and reliability of the clinical version of the iowa gambling task: evidence from a normal subject group. Front Psychol 2013;4:220 [FREE Full text] [doi: 10.3389/fpsyg.2013.00220] [Medline: 23755026]
40. Aram S, Levy L, Patel JB, Anderson AA, Zaragoza R, Dashtestani H, et al. The Iowa Gambling Task: a review of the historical evolution, scientific basis, and use in functional neuroimaging. SAGE Open 2019 Jul 02;9(3):215824401985691. [doi: 10.1177/2158244019856911]
41. Steingroever H, Wetzels R, Horstmann A, Neumann J, Wagenmakers E. Performance of healthy participants on the Iowa Gambling Task. Psychol Assess 2013 Mar;25(1):180-193. [doi: 10.1037/a0029929] [Medline: 22984804]
42. Suhr J, Hammers D. Who fails the Iowa Gambling Test (IGT)? Personality, neuropsychological, and near-infrared spectroscopy findings in healthy young controls. Arch Clin Neuropsychol 2010 Jun 17;25(4):293-302. [doi: 10.1093/arclin/acq017] [Medline: 20237050]
43. Chiu Y, Lin C, Huang J, Lin S, Lee P, Hsieh J. Immediate gain is long-term loss: are there foresighted decision makers in the Iowa Gambling Task? Behav Brain Funct 2008 Mar 19;4(1):13 [FREE Full text] [doi: 10.1186/1744-9081-4-13] [Medline: 18353176]
44. Busemeyer JR, Stout JC. A contribution of cognitive decision models to clinical assessment: decomposing performance on the Bechara gambling task. Psychol Assess 2002;14(3):253-262. [doi: 10.1037/1040-3590.14.3.253]
45. Ahn W, Busemeyer J, Wagenmakers E, Stout J. Comparison of decision learning models using the generalization criterion method. Cogn Sci 2008 Dec;32(8):1376-1402 [FREE Full text] [doi: 10.1080/03640210802352992] [Medline: 21585458]
46. Fridberg DJ, Queller S, Ahn W, Kim W, Bishara AJ, Busemeyer JR, et al. Cognitive mechanisms underlying risky decision-making in chronic cannabis users. J Math Psychol 2010 Feb 01;54(1):28-38 [FREE Full text] [doi: 10.1016/j.jmp.2009.10.002] [Medline: 20419064]
47. Ahn W, Krawitz A, Kim W, Busmeyer JR, Brown JW. A model-based fMRI analysis with hierarchical Bayesian parameter estimation. J Neurosci Psychol Econ 2011 May;4(2):95-110 [FREE Full text] [doi: 10.1037/a0020684] [Medline: 23795233]
48. Dai J, Kerestes R, Upton DJ, Busemeyer JR, Stout JC. An improved cognitive model of the Iowa and Soochow Gambling Tasks with regard to model fitting performance and tests of parameter consistency. Front Psychol 2015 Mar 12;6:229 [FREE Full text] [doi: 10.3389/fpsyg.2015.00229] [Medline: 25814963]
49. Worthy DA, Pang B, Byrne KA. Decomposing the roles of perseveration and expected value representation in models of the Iowa Gambling Task. Front Psychol 2013;4:640 [FREE Full text] [doi: 10.3389/fpsyg.2013.00640] [Medline: 24137137]
50. Haines N, Vassileva J, Ahn W. The outcome-representation learning model: a novel reinforcement learning model of the iowa gambling task. Cogn Sci 2018 Nov 05;42(8):2534-2561 [FREE Full text] [doi: 10.1111/cogs.12688] [Medline: 30289167]
51. Steingroever H, Wetzels R, Wagenmakers E. Absolute performance of reinforcement-learning models for the Iowa Gambling Task. Decision 2014;1(3):161-183. [doi: 10.1037/dec0000005]

Abbreviations

BYOD: bring your own device
IGT: Iowa Gambling Task
PVL: Prospect Valence Learning
WHO: World Health Organization

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Protocol

Evaluating the Impact of Incentives on Clinical Trial Participation: Protocol for a Mixed Methods, Community-Engaged Study

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Abstract

Background: Monetary incentives in research are frequently used to support participant recruitment and retention. However, there are scant empirical data regarding how researchers decide upon the type and amount of incentives offered. Likewise, there is little guidance to assist study investigators and institutional review boards (IRBs) in their decision-making on incentives. Monetary incentives, in addition to other factors such as the risk of harm or other intangible benefits, guide individuals' decisions to enroll in research studies. These factors emphasize the need for evidence-informed guidance for study investigators and IRBs when determining the type and amount of incentives to provide to research participants.

Objective: The specific aims of our research project are to (1) characterize key stakeholders' views on and assessments of incentives in biomedical HIV research; (2) reach consensus among stakeholders on the factors that are considered when choosing research incentives, including consensus on the relative importance of such factors; and (3) pilot-test the use of the guidance developed via aims 1 and 2 by presenting stakeholders with vignettes of hypothetical research studies for which they will choose corresponding incentive types.

Methods: Our 2-year study will involve monthly, active engagement with a stakeholder advisory board of people living with HIV, researchers, and IRB members. For aim 1, we will conduct a nationwide survey (N=300) among people living with HIV to understand their views regarding the incentives used in HIV research. For aim 2, we will collect qualitative data by conducting focus groups with people living with HIV (n=60) and key informant interviews with stakeholders involved in HIV research (people living with HIV, IRB members, and biomedical HIV researchers: n=36) to extend and deepen our understanding of how incentives in HIV research are perceived. These participants will also complete a conjoint analysis experiment to gain an understanding of the relative importance of key HIV research study attributes and the impact that these attributes have on study participation. The data from the nationwide survey (aim 1) will be triangulated with the qualitative and conjoint analysis data (aim 2) to create 25 vignettes that describe hypothetical HIV research studies. Finally, individuals from each stakeholder group will select the most appropriate incentive that they feel should be used in each of the 25 vignettes (aim 3).

Results: The stakeholder advisory board began monthly meetings in March 2021. All study aims are expected to be completed by December 2022.

Conclusions: By studying the role of incentives in HIV clinical trial participation, we will establish a decision-making paradigm to guide the choice of incentives for HIV research and, eventually, other types of similar research and facilitate the ethical recruitment of clinical research participants.

Trial Registration: ClinicalTrials.gov NCT04809636; https://clinicaltrials.gov/ct2/show/NCT04809636

International Registered Report Identifier (IRRID): DERR1-10.2196/33608

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KEYWORDS

incentives; ethics; research participation; stakeholder advisory board; HIV

Introduction

Background

Providing incentives, which are defined as "payment[s] (including money, gifts, and services) to research volunteers for participation in studies" [1], is a widely accepted and common practice in HIV clinical research [2-6]. Although some research suggests that altruism is a primary motivation for research participation [3,5,6], incentives are typically necessary for ensuring sufficient participant enrollment in research [7-9], including high-risk trials and other studies that may result in negative health outcomes for participants [10,11]. Although it is known that the incentives provided among similar studies can vary greatly [9,12], little research exists on the factors that are considered important for determining appropriate incentives. This raises concerns about the possibility of unduly influencing participation in research due to the type and quality of the incentives provided [8,13-16].

Many factors influence the type and quality of incentives, including risks, benefits, burdens, historical precedents, study procedures, time commitments, study budgets, institutional review board (IRB) recommendations, advice from other investigators, and local regulations [9,12-14]. In the field of HIV treatment and cure-related research, additional factors regarding incentives are considered, since participants can face greater than minimal risk (eg, the risk of interrupting HIV treatment). In HIV cure research, the outlook for direct individual benefit is low, and participants may face additional social vulnerabilities (eg, belonging to a sexual minority group and having a lower socioeconomic status), which can affect motivations to participate in such research [6,13,16,17]. These factors emphasize the need for ethical incentive decision-making guidelines, especially in biomedical HIV research.

Ideally, incentives encourage participation and participant retention in clinical and behavioral research without causing undue inducement [9,15,18,19]. However, balance for incentive types and amounts can be difficult to establish when significant variability exists across studies. It is important to consider the spectrum of researchers' attitudes regarding the ethics of incentives as well as beliefs about what IRBs permit. This is reflected by the varying monetary amounts that are approved by IRBs and issued across similar protocols, especially those that are issued at the same institution [9]. Other factors could include study procedures, participants' setting characteristics (eg, local norms and the cost of living), and variabilities in institutional practices [9].

The documentation of incentive types and amounts in consideration of these factors is lacking [20,21]. The most recent comprehensive study of payment in US-based research (conducted in 2005) described 467 publications of clinical studies, of which fewer than 25% reported payment amounts [9]. Furthermore, a review by Dickert and colleagues [22] showed that less than one-fifth of US institutions knew which of their studies provided payment.

An important topic that will be addressed in our study is the characterization of undue inducement. Even when institutions track payments, significant differences often exist in IRBs' understanding of undue influence, which is sparsely studied [9,15,21,23]. The Council for International Organizations of Medical Sciences Guidelines state that "[c]ompensation is not meant to compensate for the risk that participants agree to undertake" [24]. However, it is possible that stakeholders (research participants, IRB members, and study investigators) may nonetheless believe that an incentive should compensate for risk and that providing payments is a way of making risks acceptable to participants [3]. We will explore ethical issues related to this topic and consider incentives that may be viewed as too small.

Little is known about the actual effect that incentives have on clinical research participation. In large part, this is due to a lack of comprehensive tracking, a lack of mandates for investigators to record participant payments, and the inconsistent reporting of incentives in published research manuscripts [25-29]. Even in multisite or multinational research, wide variability in incentivizing has been observed. For example, to control over- and underincentivizing, South Africa developed standardized payments for participants [30], while Brazil prohibited the provision of monetary payments for clinical trials [31]. Outside of these rare cases, the absence of a reference for comparison burdens researchers with the need to determine appropriate incentives on a case-by-case basis.

Decisions on acceptable payment should not be made without a clear understanding of currently offered incentives, or else we will continue to develop personal biases that are not critically assessed. Our study aims to lay the groundwork that will guide this emerging area of inquiry toward the establishment of a more systematic study that will develop a framework for

determining incentives. Ultimately, we will provide a resource so that decisions on incentive types and amounts are guided by transparent, concrete, and evidence-based decision-making. In the absence of an incentive decision-making tool, it will continue to be impossible to determine the equity of incentives that are offered across similar studies [27].

We are interested to know if stakeholders perceive incentives as a benefit of research participation. Federal law expressly prohibits the consideration of providing compensation to offset risks [1,32]. This is because of concerns that a very risky study may be perceived as having an acceptable risk-benefit ratio simply because it pays a lot of money. It is possible however that participants still consider money to be a benefit of research participation, at least beyond reimbursement. We seek to determine if incentives make the perceived risk-benefit ratio more favorable or acceptable and if they affect the perceived balance of risks and potential benefits [3,33]. There may be ethical issues when incentives sway the decision-making capacities of individuals by making them ignore the risks involved rather than balance the risks and benefits [17,19,33]. We will also ask stakeholders for specific recommendations to improve the description of payments in the informed consent process.

Specific Aims

The specific aims of our project are to (1) characterize key stakeholders' views on and assessments of incentives, (2) reach consensus among stakeholders on the factors that are considered important when choosing incentives and on the relative importance of these factors, and (3) pilot-test the use of the guidance developed via aims 1 and 2 by using vignettes of hypothetical research studies. These vignettes will present a variety of HIV research studies that differ in risks, procedures, and incentives.

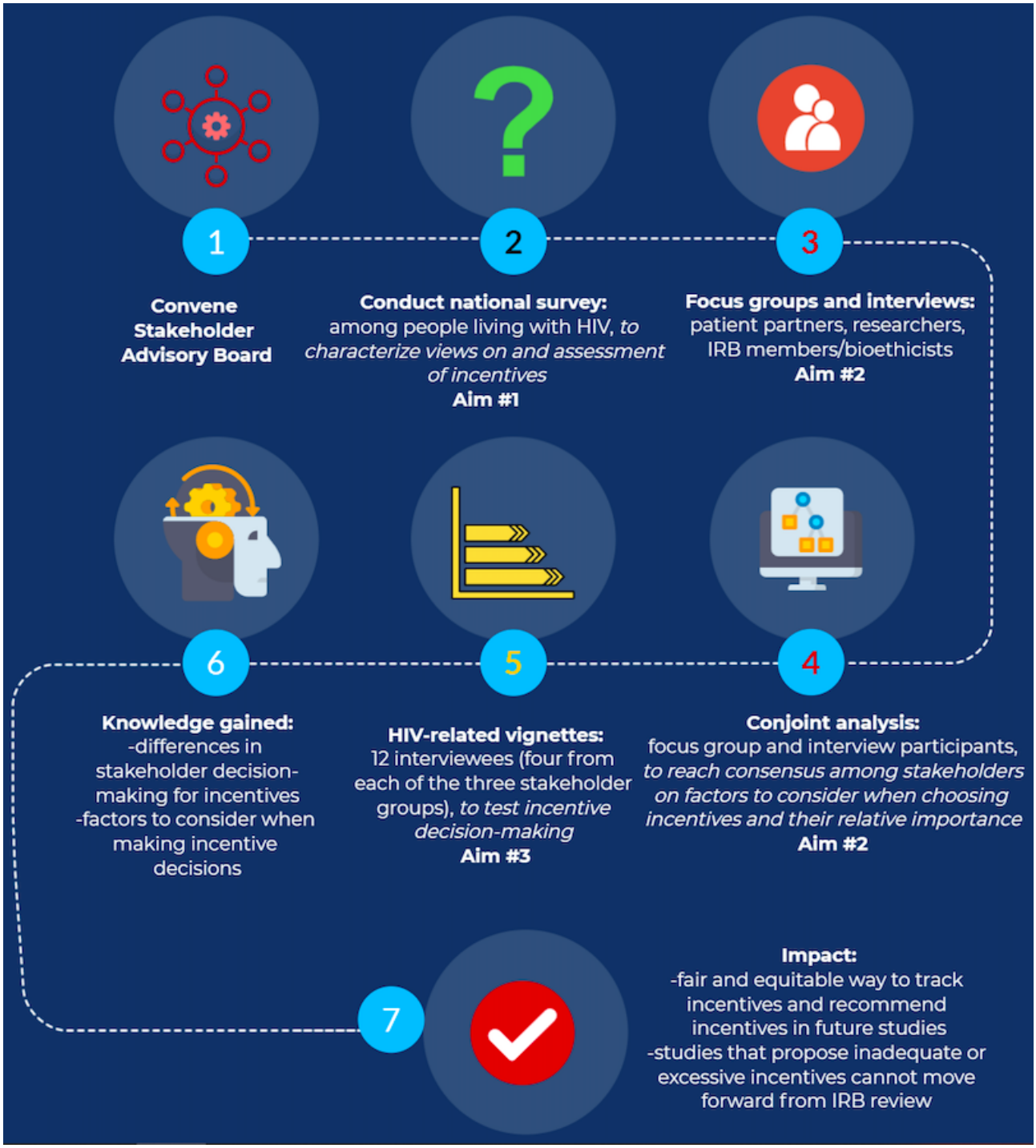
The projected outcomes from these aims include the determination of different stakeholder groups' views about incentives, shared decision-making on relevant study factors to consider when deciding on an ethical incentive, and an understanding of how well our chosen factors predict incentive decision-making. We hypothesize that potential study participants make trade-offs based on the characteristics of a research study when deciding on whether to participate. For example, after a study's risks are weighed against the benefits and incentives offered, a decision to participate will be made.

Methods

Overview

We will use an explanatory, sequential, mixed methods study design to address each study aim. Specific study activities will include the establishment of a stakeholder advisory board (SAB); a national survey of people living with HIV; focus groups and interviews with key stakeholders; a consumer marketing experiment (conjoint analysis [CJA]) to understand the relative importance of different incentive types and amounts in research participation decision-making; and finally, a pilot test of ethical decision-making, which will be conducted by providing case vignettes to stakeholders to determine appropriate incentives (Figure 1). The study will last 24 months (Table S1 in Multimedia Appendix 1).

Figure 1. Study aims and process. IRB: institutional review board.



Develop an SAB

We will convene a national, 12-member SAB comprised of people living with HIV, IRB members, and HIV researchers to review and provide ongoing feedback and suggestions for the implementation of each study component. The SAB will meet each month via Zoom (Zoom Video Communications Inc) for 90 minutes throughout the study period and receive US $30 for each meeting attended. SAB members will provide their stakeholder perspective to review and amend proposed study materials, help make decisions on study procedures, pilot study activities, and assist with participant recruitment.

Aim 1: Conduct a National Survey of People Living With HIV

We will conduct a single, internet-based survey with English-speaking US residents who identify as people living with HIV. The 20-minute survey will assess demographic characteristics and how incentives affect the willingness to participate in HIV research. We will include screening questions to ensure that each survey respondent meets our inclusion criteria (Table S2 in Multimedia Appendix 1). Participants who pass the screening questions and complete the survey will be compensated with US $7.

Participants will be recruited through Amazon Mechanical Turk, and the survey will be programmed into Qualtrics (Qualtrics International Inc). Amazon Mechanical Turk is a commonly used platform for recruiting targeted populations and collecting high-quality data, and it is comparable to US web-based survey panels [34-36]. We expect that the purposive national sample will represent people living with HIV who are diverse with respect to their ages, genders, sexual orientations, races and ethnicities, times since diagnosis, and histories of participation in clinical studies. We will analyze survey data by using Stata/SE 17 (StataCorp LLC). We will calculate descriptive statistics for all study variables and use linear, logistic, and multinomial regression models to identify any significant associations between demographic characteristics and key dependent variables.

Aim 2: Facilitate Focus Groups and Interviews With Key Stakeholders

We will conduct 6 focus groups with people living with HIV (6-10 people per group; up to 60 people in total) to obtain perceptions on the ethics of incentives in research. We especially hope to capture the views of historically underrepresented populations, including older men and women aging with HIV, cisgender and transgender women living with HIV, and adults (aged ≥18 years) of color. We will also focus on recruiting people living with HIV who have comorbid diagnoses of depression, heart disease, and arthritis to ensure that our results are applicable beyond HIV research.

Focus groups will last approximately 1 hour and 40 minutes, will be conducted via videoconferencing, and will be recorded. Participants without sufficient technology for video streaming will be permitted to join discussions via phone. Each participant will receive a US $25 gift card. A key advantage of focus groups is that they help evoke conversations, but they may also foster groupthink [37]. We will mitigate this drawback by having a strong leader who is trained in effective focus group facilitation. By doing so, we will also ensure the receipt of input from all participants, help minimize the amount of irrelevant discussions, and prevent people from speaking over each other. Furthermore, having a strong focus group leader will help transcriptions run smoothly and increase the decipherability of audio data. Our focus group questioning route, as shown in Table S3 in Multimedia Appendix 1, will mirror the key domains in the national survey and the interviews to allow for the triangulation of data. The SAB will review the focus group script prior to IRB submission and implementation.

To obtain perceptions on the ethics of incentives in research, we will conduct 12 key informant interviews (with up to 36 informants in total or until thematic saturation is achieved) with each of the following three stakeholder groups: people living with HIV from across the United States, biomedical HIV researchers, and IRB members and bioethicists. Each interview will last approximately 1 hour, will be conducted via videoconferencing, and will be recorded. Interview participants will receive a US $25 gift card.

Professional informants (eg, biomedical researchers and IRB members and bioethicists) will be individually interviewed one-on-one, as we believe that they will be more likely to share information that they might not openly share with other participants. Key informant interviews have high data yields, are easier to coordinate and transcribe, and provide the flexibility to explore emerging themes while collecting information from knowledgeable individuals [38,39]. We will develop and adapt informed consent forms and interview guides for each category of key informants. The SAB will review the guides prior to IRB submission and implementation.

The main goal of the data analysis will be to generate a list of factors that are deemed the most important to consider when thinking about incentives in HIV research. The qualitative analysis will rely primarily on grounded theory, which seeks to understand the realities grounded in the views of study participants [40]. We will develop a codebook to systematically analyze the data and identify data-driven (or emergent and latent) codes [41]. Code development will be an inductive and iterative process. As relationships among different themes and subthemes become evident, narratives will be combined into general concepts to summarize key informants' perceptions. We will perform analyses by using MAXDQA software (version 12.1.3; VERBI Software GmbH).

Aim 2: CJA

CJA is a consumer market-based methodology that was designed to determine the relative "weight" of the characteristics that influence a consumer's decision to purchase a product or service. CJA follows 2 fundamental assumptions. First, when choosing among very similar products or services, consumers make choices based on the interconnected (ie, conjoined) characteristics that make up products and services and make trade-offs among the characteristics, leading to a product preference. Second, consumers' product and service preferences are created in a rational way, and consumers preferentially select products and services that increase personal benefits and minimize personal costs. This is referred to as *the theory of random utility maximization* [42]. We consider patient partners to be "consumers" and research studies to be "products" or "services." When deciding whether to participate in a research study, potential participants make trade-offs among the various study characteristics in a rational way to increase their personal benefits and decrease their personal costs.

CJA is methodologically well suited to help us determine which factors stakeholders consider the most important when choosing incentives and the relative importance of these factors, as this type of analysis can be conducted to efficiently measure the degrees of influence that different factors have on a respondent's decision-making [43]. Furthermore, CJA has been used to effectively predict preferences for and the acceptability of a wide range of medical services and constructs, including disease treatments and health care systems [44-53]. It has also been used to predict real-world outcomes, such as patients' actual HIV medication choices [54], and in the assessment of hypothetical biomedical HIV interventions [55,56].

The ability of CJA to accurately reflect and predict consumer preferences is heavily dependent on the type of people participating in the CJA experiment and the selection of study characteristics. The participants in our CJA experiments will be people who have participated or would consider participating

in biomedical research, thereby increasing the generalizability of the results to a real-world setting. Each attribute will have different values (referred to as *levels* in CJA) from which participants must choose. For example, the risk characteristic may have 3 levels—no risk, minimal risk, and moderate risk—whereas the incentive received per clinical study interaction may have the values none, US $50, or US $100. The attributes and levels used in our CJA exercises will be determined via extensive consultation with our SAB, people living with HIV, IRB members and bioethicists, and researchers and after a thorough review of relevant research literature.

The selected attributes and levels will be programmed into Sawtooth Software's choice-based conjoint program (Lighthouse Studio 9, version 9.11.0). Participants in the CJA will be asked to complete an exercise in which they are presented with multiple hypothetical studies or scenarios and must decide whether they would consider participating. Each hypothetical study will be presented as a finite set of attributes that vary in value, as depicted in Table S4 in Multimedia Appendix 1. Participants will demonstrate their preferences for these studies by completing exercises that force trade-offs among similar studies with the same attributes, but the attributes will differ in value across the studies. Scenarios will be presented randomly to prevent order effect bias.

This exercise will allow us to estimate the relative influence that each attribute has on the decisions of each person participating in each hypothetical study. For example, the level of risk associated with participating in a research study may carry a greater "weight" than that of the frequency of required study site visits. Data from the CJA exercises will be used to construct hypothetical scenarios for aim 3.

Aim 3: Develop HIV-Related Vignettes

By using the data collected via aim 2 and the final number of levels (2-3) per attribute, we will use a factorial design to create 25 hypothetical scenarios (hereafter referred to as *vignettes*). For each vignette, the incentive amounts will not be so large or so small that the answers will be almost unanimous and therefore predictable. The three research incentive amounts that we specify will be reasonable choices. A range of US $0 to US $20,000 is consistent with the studies that we identified in the literature [57-60].

By using the information collected via aims 1 and 2, the SAB will help develop the vignettes. We will contrast different types of HIV studies while being mindful of their parameters, such as study interventions, perceived risks, participant populations, and the inconvenience of study visits. We will also integrate 3 comorbidities (depression, heart disease, and arthritis) into the vignettes to observe differences in decision-making that are beyond the context of HIV. Four key informant interviewees from each of the three stakeholder groups (people living with HIV, IRB members and bioethicists, and researchers: n=12) will pilot-test the 25 vignettes. Participants will select what they believe is the most appropriate incentive for each hypothetical HIV-related vignette (Table S5 in Multimedia Appendix 1). Research participants will receive US $50 as compensation for participating in this portion of the study. A linear mixed model [61] will be used to analyze vignette data, and possible censoring will be handled by using a maximum likelihood approach.

Demographic Data

Demographic information will be obtained from the national survey respondents, including age, race and ethnicity, the state of residence, and the level of educational attainment. Interview, focus group, and hypothetical study scenario participants will provide demographic data, which will be linked to their confidential responses for the purpose of understanding differences in study data based on key demographic variables. The demographic survey will be completed after consent is provided and immediately before beginning the interviews, focus groups, or hypothetical study scenarios. We will perform standard descriptive, bivariate, and multivariate analyses on survey data.

Results

We have convened monthly meetings with the SAB since March 2021, and they helped to cocreate all of the study instruments and informed consent documents. SAB members are currently assisting with participant recruitment for focus groups and key informant interviews. We are also collaborating with the SAB to develop the attributes and levels that will be programmed into the CJA software. Data collection and analysis are expected to be completed by December 2022. The dissemination of our findings will be accomplished through conferences, community presentations, the sharing of slide sets, and publications.

Discussion

Given the lack of guidelines that can assist researchers in ethically incentivizing research participants, it is our hope that the results of our study will establish a paradigm for all future clinical research. Integrating HIV comorbidities into our study will assist in this regard. We will gather pertinent information by interviewing people living with HIV, IRB members, bioethicists, and HIV researchers and by conducting a CJA to determine the relative importance that they place on various study attributes. We will be able to evaluate what factors influence an individual's decision to participate in a research study by testing decision-making in relation to ethical incentives via HIV-related vignettes. We hope that our findings will provide robust empirical data that will guide future ethical incentive practices in clinical research.

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Authors' Contributions

BB, JTG, KD, and ZZ conceived and designed the study. KYG, JTG, and BB wrote the first draft of the manuscript that BN, ANP, JT, CC, and ZZ edited. All authors approved the final version of the manuscript submitted for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary tables.
[DOCX File , 71 KB - resprot_v10i11e33608_app1.docx]

Multimedia Appendix 2
Peer-reviewer report from the Patient-Centred Outcomes Research Institute (PCORI).
[PDF File (Adobe PDF File), 126 KB - resprot_v10i11e33608_app2.pdf]

References

1. Payment and reimbursement to research subjects. U.S. Food & Drug Administration. 2018 Jan 25. URL: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/payment-and-reimbursement-research-subjects [accessed 2021-09-13]
2. Lee R, Cui RR, Muessig KE, Thirumurthy H, Tucker JD. Incentivizing HIV/STI testing: a systematic review of the literature. AIDS Behav 2014 May;18(5):905-912 [FREE Full text] [doi: 10.1007/s10461-013-0588-8] [Medline: 24068389]
3. Largent E. For love and money: the need to rethink benefits in HIV cure studies. J Med Ethics 2017 Feb;43(2):96-99 [FREE Full text] [doi: 10.1136/medethics-2015-103119] [Medline: 27193021]
4. Arnold MP, Evans D, Vergel N. Recruitment and ethical considerations in HIV cure trials requiring treatment interruption. J Virus Erad 2015 Jan 01;1(1):43-48 [FREE Full text] [Medline: 27482394]
5. Dubé K, Evans D, Sylla L, Taylor J, Weiner BJ, Skinner A, et al. Willingness to participate and take risks in HIV cure research: survey results from 400 people living with HIV in the US. J Virus Erad 2017 Jan 01;3(1):40-50.e21 [FREE Full text] [Medline: 28275457]
6. London AJ, Borasky Jr DA, Bhan A, Ethics Working Group of the HIV Prevention Trials Network. Improving ethical review of research involving incentives for health promotion. PLoS Med 2012 Mar;9(3):e1001193. [doi: 10.1371/journal.pmed.1001193] [Medline: 22479154]
7. Brown JA, Serrato CA, Hugh M, Kanter MH, Spritzer KL, Hays RD. Effect of a post-paid incentive on response rates to a web-based survey. Surv Pract 2016 Jan 31;9(1):1-9 [FREE Full text] [doi: 10.29115/sp-2016-0001]
8. Webinar follow-up: compensation or inducement? What IRBs need to know about paying subjects for participation. Amp&rsand. 2017 May 8. URL: https://blog.primr.org/webinar-follow-compensation-inducement/ [accessed 2021-09-13]
9. Grady C. Payment of clinical research subjects. J Clin Invest 2005 Jul;115(7):1681-1687 [FREE Full text] [doi: 10.1172/JCI25694] [Medline: 16007244]
10. Bentley JP, Thacker PG. The influence of risk and monetary payment on the research participation decision making process. J Med Ethics 2004 Jun;30(3):293-298 [FREE Full text] [doi: 10.1136/jme.2002.001594] [Medline: 15173366]
11. Lo B, Grady C, Working Group on Ethics of the International AIDS Society. Ethical considerations in HIV cure research: points to consider. Curr Opin HIV AIDS 2013 May;8(3):243-249 [FREE Full text] [doi: 10.1097/COH.0b013e32835ea1c5] [Medline: 23422260]
12. Ripley EBD. A review of paying research participants: It's time to move beyond the ethical debate. J Empir Res Hum Res Ethics 2006 Dec;1(4):9-20. [doi: 10.1525/jer.2006.1.4.9] [Medline: 19385834]
13. Brown B, Marg L, Michels E, Zhang Z, Kuzmanović D, Dubé K, et al. Comparing payments between sociobehavioral and biomedical studies in a large research university in Southern California. J Empir Res Hum Res Ethics 2021;16(1-2):117-124. [doi: 10.1177/1556264620987773] [Medline: 33535867]
14. Gelinas L, Largent EA, Cohen IG, Kornetsky S, Bierer BE, Lynch HF. A framework for ethical payment to research participants. N Engl J Med 2018 Feb 22;378(8):766-771. [doi: 10.1056/NEJMsb1710591] [Medline: 29466147]
15. Kamuya DM, Marsh V, Njuguna P, Munywoki P, Parker M, Molyneux S. "When they see us, it's like they have seen the benefits!": experiences of study benefits negotiations in community-based studies on the Kenyan Coast. BMC Med Ethics 2014 Dec 24;15(1):90 [FREE Full text] [doi: 10.1186/1472-6939-15-90] [Medline: 25539983]
16. Largent EA, Grady C, Miller FG, Wertheimer A. Money, coercion, and undue inducement: attitudes about payments to research participants. IRB 2012;34(1):1-8 [FREE Full text] [Medline: 22338401]
17. Groth SW. Honorarium or coercion: use of incentives for participants in clinical research. J N Y State Nurses Assoc 2010;41(1):11-3; quiz 22 [FREE Full text] [Medline: 20882821]
18. Dubé K, Henderson GE, Margolis DM. Framing expectations in early HIV cure research. Trends Microbiol 2014 Oct;22(10):547-549 [FREE Full text] [doi: 10.1016/j.tim.2014.08.003] [Medline: 25280965]

19. Resnik DB. Bioethical issues in providing financial incentives to research participants. Medicoleg Bioeth 2015 Jun 24;5:35-41 [FREE Full text] [doi: 10.2147/MB.S70416] [Medline: 26807399]
20. Booker CL, Harding S, Benzeval M. A systematic review of the effect of retention methods in population-based cohort studies. BMC Public Health 2011 Apr 19;11:249 [FREE Full text] [doi: 10.1186/1471-2458-11-249] [Medline: 21504610]
21. Anderson EE, Brown B. A call for radical transparency regarding research payments. Am J Bioeth 2021 Mar;21(3):45-47. [doi: 10.1080/15265161.2020.1870763] [Medline: 33616491]
22. Dickert N, Emanuel E, Grady C. Paying research subjects: an analysis of current policies. Ann Intern Med 2002 Mar 05;136(5):368-373. [doi: 10.7326/0003-4819-136-5-200203050-00009] [Medline: 11874309]
23. Grant RW, Sugarman J. Ethics in human subjects research: do incentives matter? J Med Philos 2004 Dec;29(6):717-738. [doi: 10.1080/03605310490883046] [Medline: 15590518]
24. Foster CG. International ethical guidelines for biomedical research involving human subjects. J Med Ethics 1994 Jun 01;20(2):123-124. [doi: 10.1136/jme.20.2.123]
25. Henderson GE. The ethics of HIV "cure" research: what can we learn from consent forms? AIDS Res Hum Retroviruses 2015 Jan;31(1):56-63 [FREE Full text] [doi: 10.1089/AID.2014.0219] [Medline: 25406579]
26. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? JAMA 2000 May;283(20):2701-2711. [doi: 10.1001/jama.283.20.2701] [Medline: 10819955]
27. Brown B, Galea JT, Dubé K, Davidson P, Khoshnood K, Holtzman L, et al. The need to track payment incentives to participate in HIV research. IRB 2018;40(4):8-12. [Medline: 30387975]
28. Brown B, Galea JT, Davidson P, Khoshnood K. Transparency of participant incentives in HIV research. Lancet HIV 2016 Oct;3(10):e456-e457 [FREE Full text] [doi: 10.1016/S2352-3018(16)30150-3] [Medline: 27687034]
29. Brown B, Merritt MW. A global public incentive database for human subjects research. IRB 2013;35(2):14-17. [Medline: 23672146]
30. Emanuel EJ, Currie XE, Herman A, Project Phidisa. Undue inducement in clinical research in developing countries: is it a worry? Lancet 2005 Jul;366(9482):336-340. [doi: 10.1016/S0140-6736(05)66992-9] [Medline: 16039339]
31. Lobato L, Bethony JM, Pereira FB, Grahek SL, Diemert D, Gazzinelli MF. Impact of gender on the decision to participate in a clinical trial: a cross-sectional study. BMC Public Health 2014 Nov 06;14:1156 [FREE Full text] [doi: 10.1186/1471-2458-14-1156] [Medline: 25377601]
32. Department of Health, Education, and Welfare, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report. Ethical principles and guidelines for the protection of human subjects of research. J Am Coll Dent 2014;81(3):4-13. [Medline: 25951677]
33. Cryder CE, London AJ, Volpp KG, Loewenstein G. Informative inducement: study payment as a signal of risk. Soc Sci Med 2010 Feb;70(3):455-464. [doi: 10.1016/j.socscimed.2009.10.047] [Medline: 19926187]
34. Weinberg J, Freese J, McElhattan D. Comparing data characteristics and results of an online factorial survey between a population-Based and a crowdsource-recruited sample. Sociol Sci 2014 Aug 04;1:292-310 [FREE Full text] [doi: 10.15195/v1.a19]
35. Shank DB. Using crowdsourcing websites for sociological research: The case of Amazon Mechanical Turk. Am Sociol 2015 Mar 14;47(1):47-55. [doi: 10.1007/s12108-015-9266-9]
36. Sheehan KB. Crowdsourcing research: Data collection with Amazon's Mechanical Turk. Commun Monogr 2017 Jul 04;85(1):140-156. [doi: 10.1080/03637751.2017.1342043]
37. Guest G, Namey E, McKenna K. How many focus groups are enough? Building an evidence base for nonprobability sample sizes. Field methods 2016 Apr 28;29(1):3-22. [doi: 10.1177/1525822X16639015]
38. Guest G, Bunce A, Johnson L. How Many Interviews Are Enough?: An experiment with data saturation and variability. Field methods 2006 Feb 01;18(1):59-82. [doi: 10.1177/1525822X05279903]
39. Corbin JM, Strauss A. Grounded theory research: Procedures, canons, and evaluative criteria. Qual Sociol 1990 Mar;13:3-21. [doi: 10.1007/BF00988593]
40. Namey E, Guest G, McKenna K, Chen M. Evaluating bang for the buck. American Journal of Evaluation 2016 Apr 28;37(3):425-440. [doi: 10.1177/1098214016630406]
41. DeCuir-Gunby JT, Marshall PL, McCulloch AW. Developing and using a codebook for the analysis of interview data: An example from a professional development research project. Field methods 2010 Dec 27;23(2):136-155. [doi: 10.1177/1525822X10388468]
42. Brown BW, Walker MB. The random utility hypothesis and inference in demand systems. Econometrica 1989 Jul;57(4):815-829. [doi: 10.2307/1913773]
43. Lancsar E, Savage E. Deriving welfare measures from discrete choice experiments: inconsistency between current methods and random utility and welfare theory. Health Econ 2004 Sep;13(9):901-907. [doi: 10.1002/hec.870] [Medline: 15362181]
44. Hunink MGM, Weinstein MC, Wittenberg E, Drummond MF, Pliskin JS, Wong JB, et al. Decision Making in Health and Medicine: Integrating Evidence and Values. Cambridge, United Kingdom: Cambridge University Press; 2014.
45. Akkazieva B, Gulacsi L, Brandtmuller A, Péntek M, Bridges JFP. Patients' preferences for healthcare system reforms in Hungary: a conjoint analysis. Appl Health Econ Health Policy 2006;5(3):189-198. [doi: 10.2165/00148365-200605030-00005] [Medline: 17132033]

46. Aristides M, Chen J, Schulz M, Williamson E, Clarke S, Grant K. Conjoint analysis of a new Chemotherapy: willingness to pay and preference for the features of raltitrexed versus standard therapy in advanced Colorectal Cancer. Pharmacoeconomics 2002;20(11):775-784. [doi: 10.2165/00019053-200220110-00006] [Medline: 12201796]
47. Bhargava JS, Bhan-Bhargava A, Foss AJE, King AJ. Views of glaucoma patients on provision of follow-up care; an assessment of patient preferences by conjoint analysis. Br J Ophthalmol 2008 Dec;92(12):1601-1605. [doi: 10.1136/bjo.2008.140483] [Medline: 18664502]
48. Bishai D, Brice R, Girod I, Saleh A, Ehreth J. Conjoint analysis of French and German parents' willingness to pay for meningococcal vaccine. Pharmacoeconomics 2007;25(2):143-154. [doi: 10.2165/00019053-200725020-00006] [Medline: 17249856]
49. Costa MLV, de Cássia Braga Ribeiro K, Machado MAC, Costa ACLV, Montagnini AL. Prognostic score in gastric cancer: the importance of a conjoint analysis of clinical, pathologic, and therapeutic factors. Ann Surg Oncol 2006 Jun;13(6):843-850. [doi: 10.1245/ASO.2006.05.040] [Medline: 16614885]
50. Cunningham CE, Deal K, Rimas H, Chen Y, Buchanan DH, Sdao-Jarvie K. Providing information to parents of children with mental health problems: a discrete choice conjoint analysis of professional preferences. J Abnorm Child Psychol 2009 Nov;37(8):1089-1102. [doi: 10.1007/s10802-009-9338-9] [Medline: 19629676]
51. Fisher K, Orkin F, Frazer C. Utilizing conjoint analysis to explicate health care decision making by emergency department nurses: a feasibility study. Appl Nurs Res 2010 Feb;23(1):30-35. [doi: 10.1016/j.apnr.2008.03.004] [Medline: 20122508]
52. Ryan M, Farrar S. Using conjoint analysis to elicit preferences for health care. BMJ 2000 Jun 03;320(7248):1530-1533 [FREE Full text] [doi: 10.1136/bmj.320.7248.1530] [Medline: 10834905]
53. Galea JT, Kinsler JJ, Salazar X, Lee SJ, Giron M, Sayles JN, et al. Acceptability of pre-exposure prophylaxis as an HIV prevention strategy: barriers and facilitators to pre-exposure prophylaxis uptake among at-risk Peruvian populations. Int J STD AIDS 2011 May;22(5):256-262 [FREE Full text] [doi: 10.1258/ijsa.2009.009255] [Medline: 21571973]
54. Beusterien KM, Dziekan K, Flood E, Harding G, Jordan JC. Understanding patient preferences for HIV medications using adaptive conjoint analysis: feasibility assessment. Value Health 2005;8(4):453-461 [FREE Full text] [doi: 10.1111/j.1524-4733.2005.00036.x] [Medline: 16091022]
55. Stone VE, Jordan J, Tolson J, Miller R, Pilon T. Perspectives on adherence and simplicity for HIV-infected patients on antiretroviral therapy: self-report of the relative importance of multiple attributes of highly active antiretroviral therapy (HAART) regimens in predicting adherence. J Acquir Immune Defic Syndr 2004 Jul 01;36(3):808-816. [doi: 10.1097/00126334-200407010-00007] [Medline: 15213564]
56. Newman PA, Duan N, Lee SJ, Rudy ET, Seiden DS, Kakinami L, et al. HIV vaccine acceptability among communities at risk: the impact of vaccine characteristics. Vaccine 2006 Mar 15;24(12):2094-2101 [FREE Full text] [doi: 10.1016/j.vaccine.2005.11.013] [Medline: 16332402]
57. El-Sadr WM, Donnell D, Beauchamp G, Hall HI, Torian LV, Zingman B, HPTN 065 Study Team. Financial incentives for linkage to care and viral suppression among HIV-positive patients: A randomized clinical trial (HPTN 065). JAMA Intern Med 2017 Aug 01;177(8):1083-1092 [FREE Full text] [doi: 10.1001/jamainternmed.2017.2158] [Medline: 28628702]
58. Finch J. The vignette technique in survey research. Sociology 1987 Feb 01;21(1):105-114. [doi: 10.1177/0038038587021001008]
59. Gourlay A, Mshana G, Birdthistle I, Bulugu G, Zaba B, Urassa M. Using vignettes in qualitative research to explore barriers and facilitating factors to the uptake of prevention of mother-to-child transmission services in rural Tanzania: a critical analysis. BMC Med Res Methodol 2014 Feb 11;14:21 [FREE Full text] [doi: 10.1186/1471-2288-14-21] [Medline: 24512206]
60. Jenkins N, Bloor M, Fischer J, Berney L, Neale J. Putting it in context: the use of vignettes in qualitative interviewing. Qual Res 2010 Apr 12;10(2):175-198. [doi: 10.1177/1468794109356737]
61. McCulloch CE, Searle SR, Neuhaus JM. Generalized, Linear, and Mixed Models, 2nd edition. Hoboken, New Jersey: Wiley Interscience; 2008.

Abbreviations

CJA: conjoint analysis
IRB: institutional review board
SAB: stakeholder advisory board

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Protocol

National Disability Insurance Scheme and Lived Experience of People Presenting to the Emergency Department: Protocol for a Mixed Methods Study

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Abstract

Background: Currently, within Australia, 3.6% of all emergency department (ED) presentations are mental health–related. Information about the context of the person presenting to the ED (beyond immediate needs), including their psychosocial disability (PSD) National Disability Insurance Scheme (NDIS) plan, is reported as incomplete and fragmented. There are missed opportunities for early support and care continuity that could potentially inform ED practitioners to revise current practices.

Objective: The aims of this study are: (1) to obtain original data from the lived experience voice of those with the PSD NDIS plan and their experience when presenting to an ED, (2) to gather information from NDIS service providers to reveal communication pathways between the ED and NDIS services, and (3) to gain knowledge from ED clinicians around processes for improving continuity of care and consumer experience.

Methods: This inductive, mixed methods phenomenological study will involve data collection analyzed sequentially, with each stage informing future stages of the research. Interviews will focus on the lived experience voice exploring concerns that have led to an ED presentation, alongside an analysis of associated clinical and administrative documentation and communications. Focus groups with NDIS support workers and support coordinators will provide phenomenological data around the experience from their perspective. National quantitative surveys among those with a PSD NDIS plan and emergency services clinicians will provide insight into current practices within community care and ED presentations. The research project design includes a lived experience advisory group who are assisting with the design of the interview and focus group schedules and national surveys, as well as in shaping the interpretation of qualitative information. All transcripts will be subject to thematic analysis to understand individuals' meaning-making of these complex and particular phenomena. The research team includes a lived experience researcher and a lived experience carer (PhD candidate).

Results: This study is funded by MIND Australia as a PhD industry scholarship, which commenced in April 2020. A systematic review as a preresearch activity has been completed and is currently under review. The Human Research Ethics Committee of the University of South Australia has approved this project. An advisory group has been selected, and interview, focus group, and survey schedules are currently being codesigned. Recruitment will commence in November 2021. It is envisaged that data collection will be completed by June 2022.

Conclusions: Understanding the lived experience of the precare, during care, and postcare stages of ED presentations from the perspective of those with a PSD NDIS plan will inform the research team around current practices and provide information about improvement for pathways of care for consumers and carers, while also informing health policy.

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KEYWORDS

lived experience; National Disability Insurance Scheme; emergency department; psychosocial disability; communication pathways

Introduction

In 2018-2019, there were 8.4 million presentations to public hospital emergency departments (EDs) in Australia, with an average of 23,000 people visiting the ED every day [1,2]. Of these, 303,340 (3.6%) presentations to the EDs in Australia were related to concerns around mental health [2]. In South Australia, there were 519,607 total presentations at EDs [1], with 23,739 (4.5%) of peoples' presentations classified due to mental health–related distress which represents a 1% increase compared with the national average [2]. People with mental health presentations to the ED can have many challenges cooccurring that have led to an acute crisis. These can include health issues such as diabetes [3]; mental health comorbidity; and/or the complexity of a psychosocial disability (PSD) such as housing instability [4-7], relationship breakdown, substance use [8], disconnection with support networks, or difficulties navigating access across multiple services [9]. Those living with a PSD are among the most disadvantaged in the community [10], as highlighted in the World Health Organization QualityRights report: "Ironically, some of the worst human rights violations and discrimination experienced by people with mental disabilities, intellectual disabilities and substance abuse problems are in health-care settings" [11].

People experiencing mental health crisis periodically have the longest wait times in the ED and, at times, leave before care is completed [12]. Alternatively, consumers can present to the ED repeatedly over several days [13]. South Australia has the longest delay in the country for those presenting to the ED with mental health concerns (16.5 hours compared to the national average of 11.5 hours) [12]. Another element of complexity is that those presenting to EDs may be discharged without follow-up care arranged [14,15]. Postdischarge from clinical care represents a time of greater risk of dying by suicide [16,17], reflecting critical concerns about the quality of support and care being offered [18]. Generally, continuity of care recognizes that consumers have relational continuity with providers who are trusted, provide personalized responses, and have shared understanding of the person's goals [19].

Lack of psychiatric beds in hospitals can also be a cause for delayed care. In 1998, there were 2943 psychiatric beds in hospitals within Australia, and this number was reduced to 2186 in 2017 [20]. The Organisation for Economic Cooperation and Development reports that the average per country for psychiatric beds is 71 per 100,000 individuals, whereas Australia has only 41 psychiatric beds per 100,000 [21] and South Australia has even less at 30 per 100,000 [9]. As the numbers of psychiatric beds are reducing and consumers are being increasingly discharged from the ED to home (to be supported by community services), the aim of this study is to discover how strategies used for implementing communication pathways contribute to continuity of care and improved experience.

In reviewing the evidence of strengthening discharge communication pathways from the ED to enhance continuity of care, this work can help to improve connection with community mental health services and person-centered, or -led outcomes [22,23]. This research project will obtain data from three sources via three research collection methods and then synthesize and triangulate the data.

Methods

Aims

The purpose of this inductive exploratory research study is to discover, describe, and interpret the perspectives of various population groups regarding ED mental health care. Within the context of ongoing disability reform (actively pursued in Australia since the early 1970s), the construction of the National Disability Insurance Scheme (NDIS) was created and called for a "coordinated national approach to improving the delivery of disability services" [24]. The NDIS has been in existence for 8 years with the initial pilot beginning in 2013 [25]. PSD was soon added to the NDIS, with streamlined access for people with a PSD implemented in April 2019 [5,6]. A primary focus of this study will be to understand and clarify the preferred communication pathways between the NDIS, ED, and consumers with a PSD NDIS plan. To inform health policy, this study will discover and interpret the meaning individuals make of their experiences, with an interpretive, mainly qualitative, approach to understanding the life world and meaning-making of participants with lived experience, their carers, NDIS providers, and ED clinicians. To inform the study, a systematic review has been completed by the research team, which has been submitted to a journal and is currently under review, addressing the following research question: What evaluated strategies are used for enhancing clinical outcomes with communication pathways for continuity of care between the emergency department and mental health community support services for people with mental health concerns or who are in suicidal crisis? (see Multimedia Appendix 1 for a description of the search strategy).

Research Questions

This study focuses on the following emerging research questions based on reporting; gaps in the literature; concerns about the use of isolation and restraint; reports of current practices within

the ED; along with consultations with people with lived experience, MIND Australia staff, the research team, and others in the sector:

1. How do those with lived experience, carers, and families experience service integration and coordination across emergency care and their NDIS providers? Are there concerns and preferences that 1. NDIS providers should be alert to prior to clients presenting to the ED? Can awareness of these concerns and preferences be a catalyst to prevent an ED presentation?
2. What are the barriers to accessing therapeutic treatment within the ED through the health/disability/mental health interface (NDIS services and EDs) and how can these be transcended for improved person-centered care and recovery?
3. How do emergency care clinicians connect with the network of NDIS providers in terms of coordination of information; support; and involvement in assessment, treatment planning, and transfer of care? What works well? What does not work well? What could be done better?

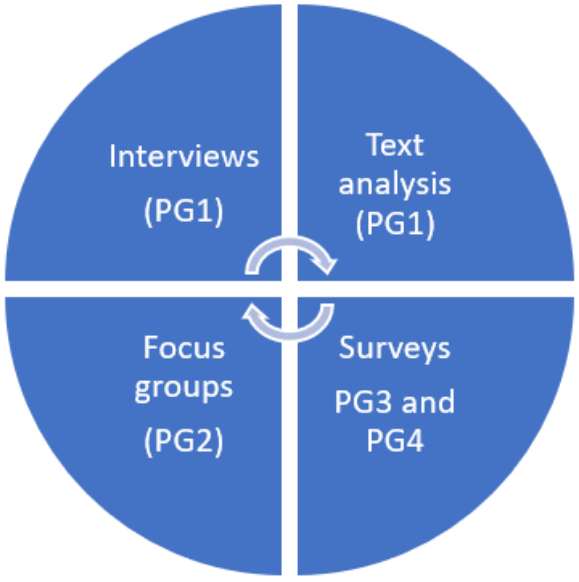
Study Design

The study is focused on exploring and interpreting (1) the lived experience of those with a PSD NDIS plan along with an analysis of clinical documentation (participant group 1); (2) the experience of NDIS support coordinator/workers working with people who have a PSD NDIS plan and how they interact with the ED, including communication pathways (participant group 2); (3) the national experience of those with a PSD NDIS plan who present at an ED (participant group 3); and (4) the experience of clinicians in the ED working with people who have a PSD NDIS plan, and how they interact with the NDIS, including communication pathways (participant group 4) (see Figure 1).

Data collection will first aim to elicit the lived experience voice of those with a PSD NDIS plan and carers using semistructured one-to-one interviews (participant group 1). In addition, documents (clinician letters, guides, NDIS plans) and other artifacts (eg, electronic messaging) provided to the person requiring care and/or their carer will also be reviewed to evaluate clinician communication [26]. The phenomenological understanding will continue with NDIS support workers and support coordinators, who will also be recruited to participate in focus groups to explore the current understanding and practice of this population group (participant group 2). Finally, the study will collect national data and understanding from those with a PSD NDIS plan and ED clinicians (participant groups 3 and 4) via an online quantitative survey (see Multimedia Appendix 2).

This exploratory study will enable the discovery of paradoxes and contradictions [27] between three population groups with four different research approaches (interviews, analysis of medical correspondence, focus groups, and quantitative surveys) to compare and contrast themes [28]. An interpretive qualitative approach is considered appropriate for the first two population groups to provide data with rich depth. Primarily, lived experience perspectives, including both consumer and carer perspectives will be generated via interviews and NDIS support workers/coordinators (participant group 2) with focus groups. National quantitative online surveys will be offered to those with a PSD NDIS plan and clinicians working in EDs to give them the flexibility to participate in their own time. The different approaches to the research questions will enable triangulation of data via a convergence of sight lines to bring depth to the analysis.

Figure 1. Exploratory research design. PG: participant group.



Trauma-Informed Approach

This research will be guided by trauma-informed practice principles [29], as many people living with a mental health diagnosis are likely to have experienced significant trauma at some point in their lives, most often during childhood. This will include seeking to avoid retraumatization of participants by focusing on their knowledge about service improvement rather than requiring them to disclose a narrative history of an unpleasant experience in the ED. Participants will be provided with a safe environment (physical or digital) and will be encouraged to bring a support person if that is something they would like to do. To engender trust, the participants will be empowered to cease the interview at any time and to not disclose anything that will cause them distress [30].

The principles behind the 5th National Mental Health and Suicide Prevention Plan [31] and the South Australian Mental Health Strategic Plan [32] clearly underpin the need for the lived experience voice to drive change. This study will align with that principle and be active in incorporating the voices of those with lived experience (ie, those with a PSD, the advisory group, and carers) alongside the mental health workforce. By engaging with a lived experience advisory group, the research team will incorporate their specific expertise to design the interview and focus group schedules and the survey questions.

Recruitment

Recruitment strategies will be developed in consultation with the advisory group.

Those with lived experience and carers (participant group 1, approximately n=20: lived experience, n=14, carers, n=7; participant group 2, n<20; participant groups 3 and 4, n>50) will be recruited for one-to-one audio-recorded interviews. Potential participants will be given information and opportunity to ask further questions from the research team and will be asked to discuss being involved in the research with their partner, carer, clinician, or friend. Table 1 summarizes the characteristics of each group and the inclusion/exclusion criteria.

Table 1. Characteristics and inclusion/exclusion criteria for each participant group.

Participant group	Sample and sample size	Inclusion criteria	Exclusion criteria
1	>20 (lived experience: n=14; carers: n=7)	Aged >18 years; have lived experience and a psychosocial disability NDIS[a] plan; not in acute care at the time of the interview; presented to the ED[b] while on a psychosocial disability NDIS plan within the last 2 years; or a carer who will have presented to the ED with a person who has a psychosocial disability NDIS plan	Anyone that is unable to give informed consent; anyone that does not have a psychosocial disability NDIS plan; anyone that has not presented to the ED
2	>20 NDIS support workers	Aged >18 years; NDIS support workers and support coordinators with experience of intervention with people who have presented to the ED	Anyone who is not an NDIS support coordinator or support worker
3	>50 individuals on a psychosocial disability NDIS plan	Same as participant group 1	Same as participant group 1
4	>50 clinicians (including doctors, nurses, psychiatrists, social workers)	Aged >18 years; clinicians (including doctors, nurses, psychiatrists, social workers) who have attended to those presenting at the ED with a psychosocial disability in the last 2 years	Clinicians (including doctors, nurses, psychiatrists, social workers) who have not worked in the ED within the last 2 years

[a]NDIS: National Disability Insurance Scheme.

[b]ED: emergency department.

Data Analysis

Audio recordings from interviews and focus group (participant groups 1 and 2) will be transcribed and thematically analyzed [28] using NVivo software. Themes will be coded and generated by two members of the research team. Quantitative data (participant groups 3 and 4) will be collated and analyzed using SPSS software.

Results

The results of this study will provide insight for strengthening discharge communication pathways between EDs and community mental health services so that these reflect person-centered and person-led care outcomes [22,23]. Meetings have commenced with the advisory group to codesign interview and focus group schedules, along with codesigning the survey questions. Recruitment for participant group 1 will commence imminently. It is envisaged that data collection for participant groups 1 and 2 will be finalized by February 2022. Data collection for the surveys of participant groups 3 and 4 will be completed by mid-2022. This study was approved by the Human Research Ethics Committee of the University of South Australia (application ID 203626) on April 10, 2021.

Discussion

Strengths and Limitations

A strength of this study is the inclusion of a lived experienced researcher and a lived experienced carer researcher (PhD candidate) on the research team. The involvement of a lived experience advisory group for interview, focus group, and survey schedule design is another strength of this project. The

advisory group will be invited to contribute and be named as authors to the academic papers that will be generated through this research. This will acknowledge their contribution to the design of interview, focus group, and survey questions, and generation of themes from the data. Another strength is that participant groups 1 and 3 are participants with lived experience.

Limitations include that the codesign focuses on authentically shared power but is restricted to the context of a PhD training journey. As this project is a PhD scholarship, true codesign with a lived experience advisory group cannot occur due to the nature of the project and that the PhD candidate is required to demonstrate research skills rather than others doing the work. Nevertheless, aspects of codesign will be included through consultation with a lived experienced advisory group.

Practical Significance

The NDIS has been in operation for 8 years. Although PSD was included in the initial architecture of the NDIS [33], many of the fundamental design features of the scheme were developed without reference to the needs of this population [34-37]. This research project will be the first of its kind in the Australian context to provide data from the lived experience voice from those with a PSD NDIS plan from the perspective of presenting to the ED in a crisis. The results of this project will inform ED clinicians and NDIS service providers of clearer needs of this population group, along with guiding pathways for better continuity of care.

Conclusion

This mixed methods study will triangulate the data from interviews among those with lived experience, clinical communications, focus groups with NDIS support workers, and national quantitative surveys among people with a PSD NDIS plan and ED clinicians. This inductive exploratory research study—with an interpretive, qualitative approach—will discover, explore, and describe the lived experience of those with a PSD NDIS plan when presenting to the ED, in retrospect, primarily from the voices of those with lived experience [37].

System encounters, system experiences, and system-wide processes between the hybrid environment of the ED and NDIS services will be explored with the goal of describing this experience and identifying better communication pathways between the various services to enable those with lived experience to have improved voice and influence health policy.

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Authors' Contributions

HM is primarily responsible for the study concept, design, recruitment, and data collection/analysis. HM drafted the manuscript. ML, LH, and NP contribute to study design and reviewed/added intellectual content to the manuscript. All authors approved the final protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy for the systematic review (submitted, under review).
[DOCX File , 16 KB - resprot_v10i11e33268_app1.docx]

Multimedia Appendix 2
Phases of research, population groups, and interventions.
[PNG File , 27 KB - resprot_v10i11e33268_app2.png]

Multimedia Appendix 3
Peer-review report 1 by Clinical & Health Sciences - University of South Australia.
[PDF File (Adobe PDF File), 397 KB - resprot_v10i11e33268_app3.pdf]

Multimedia Appendix 4
Peer-review report 2 by Clinical & Health Sciences - University of South Australia.
[DOCX File , 52 KB - resprot_v10i11e33268_app4.docx]

References

1. Emergency department care 2017–18: Australian hospital statistics, Health services series no. 89. Cat. no. HSE 216. Australian Institute of Health and Welfare. Canberra: Australian Government; 2018. URL: https://www.aihw.gov.au/getmedia/9ca4c770-3c3b-42fe-b071-3d758711c23a/aihw-hse-216.pdf.aspx [accessed 2021-10-08]

2. Emergency department care. Australian Institute of Health and Welfare. Canberra: Australian Government; 2019. URL: https://www.aihw.gov.au/reports-data/myhospitals/sectors/emergency-department-care#more-data [accessed 2021-10-08]
3. National Health Survey: Mental Health and co-existing physical health conditions, Australia, 2014-15. Australian Bureau of Statistics. 2015. URL: https://www.abs.gov.au/ausstats/abs@.nsf/mf/4329.0.00.004 [accessed 2021-10-08]
4. Kaplan D, McGrath D. Optimising support for psychosocial disability within the NDIS: Literature review. Mental Health Australia. URL: https://mhaustralia.org/sites/default/files/docs/optimising_psychosocial_supports_-_literature_review.pdf [accessed 2021-10-08]
5. Attachment A: Key data on psychosocial disability and the NDIS - 31 March 2017. National Disability Insurance Agency. 2017 Mar 31. URL: https://www.cesphn.org.au/documents/ndis/2108-key-data-on-ndis-and-psychosocial-disability/file [accessed 2021-10-08]
6. Annual report. National Disability Insurance Scheme. 2017. URL: https://www.ndis.gov.au/about-us/publications/annual-report/annual-report-2018-19 [accessed 2021-10-08]
7. Keeping body and mind together improving the physical health and life expectancy of people with serious mental illness. Royal Australian & New Zealand College of Psychiatrists. 2015. URL: https://www.ranzcp.org/files/resources/reports/keeping-body-and-mind-together.aspx [accessed 2021-10-08]
8. Hielscher E, Diminic S, Kealton J, Harris M, Lee YY, Whiteford H. Hours of care and caring tasks performed by Australian carers of adults with mental illness: results from an online survey. Community Ment Health J 2019 Feb;55(2):279-295. [doi: 10.1007/s10597-018-0244-x] [Medline: 29476284]
9. Duggan M, Harris B, Chislett WK, Calder R. Nowhere else to go: Why Australia's health system results in people with mental illness getting 'stuck' in emergency departments. Australasian College for Emergency Medicine. Melbourne: Mitchell Institute Commissioned report, Victoria University; 2020. URL: https://acem.org.au/getmedia/5ad5d20e-778c-4a2e-b76a-a7283799f60c/Nowhere-else-to-go-report_final_September-2020 [accessed 2021-10-08]
10. National Mental Health Consumer & Carer Forum. 2011. URL: https://nmhccf.org.au/sites/default/files/docs/nmhccf_psychosocial_disability_booklet_web_version_27oct11.pdf [accessed 2021-10-08]
11. WHO QualityRights tool kit to assess and improve quality and human rights in mental health and social care facilities. World Health Organization. 2012 Feb 03. URL: https://www.who.int/publications/i/item/who-qualityrights-tool-kit [accessed 2021-10-08]
12. The long wait: An analysis of mental health presentations to Australian emergency departments, ACEM, West Melbourne, Victoria. Australasian College for Emergency Medicine. 2018. URL: https://acem.org.au/getmedia/60763b10-1bf5-4fbc-a7e2-9fd58620d2cf/ACEM_report_41018 [accessed 2021-10-08]
13. Access to state-managed adult mental health services. Office of the Auditor General for Western Australia, Perth. 2019. URL: https://audit.wa.gov.au/wp-content/uploads/2019/08/Access-to-State-Managed-Adult-Mental-Health-Services.pdf [accessed 2021-10-08]
14. Dayman I. Shackle restraint during mental health treatment in SA Health system leads woman to speak out. ABC News. 2020 Sep 06. URL: https://www.abc.net.au/news/2020-09-06/shackle-restraint-during-mental-health-treatment-in-sa-health/12630918 [accessed 2021-10-08]
15. Magarey J. Netted, drugged, locked away: the damning face of child mental health in SA. INDAILY. 2019 Sep 23. URL: https://indaily.com.au/news/2019/09/23/netted-drugged-locked-away-the-damning-face-of-child-mental-health-in-sa/ [accessed 2021-10-08]
16. Chung D, Hadzi-Pavlovic D, Wang M, Swaraj S, Olfson M, Large M. Meta-analysis of suicide rates in the first week and the first month after psychiatric hospitalisation. BMJ Open 2019 Mar 23;9(3):e023883 [FREE Full text] [doi: 10.1136/bmjopen-2018-023883] [Medline: 30904843]
17. Forte A, Buscajoni A, Fiorillo A, Pompili M, Baldessarini RJ. Suicidal risk following hospital discharge: a review. Harv Rev Psychiatry 2019;27(4):209-216. [doi: 10.1097/HRP.0000000000000222] [Medline: 31274577]
18. Morris P. The Australian mental health crisis: a system failure in need of treatment. Australas Psychiatry 2006 Sep;14(3):332-333. [doi: 10.1080/j.1440-1665.2006.02300_1.x] [Medline: 16923051]
19. Wierdsma A, Mulder C, de Vries S, Sytema S. Reconstructing continuity of care in mental health services: a multilevel conceptual framework. J Health Serv Res Policy 2009 Jan;14(1):52-57. [doi: 10.1258/jhsrp.2008.008039] [Medline: 19103917]
20. Hospital resources 2016–17: Australian hospital statistics. Health services series no. 86. Cat. no. HSE 205. Australian Institute of Health and Welfare. Canberra: Australian Government; 2018. URL: https://www.aihw.gov.au/getmedia/c5fd554a-3356-474a-808a-5aab43d24708/aihw-hse-205.pdf.aspx?inline=true [accessed 2021-10-08]
21. OECD Hospital beds 2015-2019. Organisation for Economic Cooperation and Development. 2020. URL: https://data.oecd.org/healtheqt/hospital-beds.htm [accessed 2021-10-08]
22. Curran J, Gallant A, Zemek R, Newton A, Jabbour M, Chorney J, et al. Discharge communication practices in pediatric emergency care: a systematic review and narrative synthesis. Syst Rev 2019 Apr 03;8(1):83 [FREE Full text] [doi: 10.1186/s13643-019-0995-7] [Medline: 30944038]

23. Newnham H, Barker A, Ritchie E, Hitchcock K, Gibbs H, Holton S. Discharge communication practices and healthcare provider and patient preferences, satisfaction and comprehension: A systematic review. Int J Qual Health Care 2017 Oct 01;29(6):752-768. [doi: 10.1093/intqhc/mzx121] [Medline: 29025093]
24. The National Disability Insurance Scheme: a chronology. Parliament of Australia. 2018 Jul 13. URL: https://www.aph.gov.au/About_Parliament/Parliamentary_Departments/Parliamentary_Library/pubs/rp/rp1819/Chronologies/NDIS [accessed 2021-10-12]
25. Williams TM, Smith GP. Can the National Disability Insurance Scheme work for mental health? Aust N Z J Psychiatry 2014 May;48(5):391-394. [doi: 10.1177/0004867414530007] [Medline: 24671233]
26. Durbin J, Barnsley J, Finlayson B, Jaakkimainen L, Lin E, Berta W, et al. Quality of communication between primary health care and mental health care: an examination of referral and discharge letters. J Behav Health Serv Res 2012 Oct;39(4):445-461. [doi: 10.1007/s11414-012-9288-9] [Medline: 22855384]
27. Schoonenboom J, Johnson RB. How to construct a mixed methods research design. Kolner Z Soz Sozpsychol 2017;69(Suppl 2):107-131 [FREE Full text] [doi: 10.1007/s11577-017-0454-1] [Medline: 28989188]
28. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
29. SAMHSA's concept of trauma guidance for a trauma-informed approach. Substance Abuse Mental Health Services Administration. 2014. URL: https://ncsacw.samhsa.gov/userfiles/files/SAMHSA_Trauma.pdf [accessed 2021-10-08]
30. Carrotte E, Blanchard M. Understanding how to best respond to the needs of Australians living with personality disorders. SANE Australia. 2018. URL: https://www.sane.org/images/NMHC_SANE_PD_Report.pdf [accessed 2021-10-08]
31. 5th National Mental Health and Suicide Prevention Plan. Department of Health National Mental Health Strategy. Canberra: Australian Government; 2017. URL: https://www.mentalhealthcommission.gov.au/getmedia/0209d27b-1873-4245-b6e5-49e770084b81/Monitoring/Fifth-National-Mental-Health-and-Suicide-Prevention-Plan.pdf [accessed 2021-10-08]
32. South Australian Mental Health Strategic Plan 2017-2022. South Australian Mental Health Commission. 2017. URL: https://samentalhealthcommission.com.au/wp-content/uploads/SA-Mental-Health-Strategic-Plan-2017%E2%80%932022.pdf [accessed 2021-10-08]
33. Disability care and support: Productivity Commission inquiry report. Commonwealth of Australia. Canberra: Australian Government; 2011. URL: http://www.tdsa.org.au/wp-content/uploads/2015/11/Prod-Comm-NDIS-Report-2011.pdf [accessed 2021-10-08]
34. Barclay L, Callaway L, Pope K. Perspectives of individuals receiving occupational therapy services through the National Disability Insurance Scheme: Implications for occupational therapy educators. Aust Occup Ther J 2020 Feb;67(1):39-48. [doi: 10.1111/1440-1630.12620] [Medline: 31659756]
35. Hamilton D, Hancock N, Scanlan JN, Banfield M. The National Disability Insurance Scheme and people with severe and persistent mental illness/psychosocial disability: A review, analysis and synthesis of published literature. Aust N Z J Psychiatry 2020 Dec;54(12):1162-1172. [doi: 10.1177/0004867420967747] [Medline: 33111539]
36. National Disability Insurance Scheme: Psychosocial disability pathway. Mental Health Australia. 2018. URL: https://mhaustralia.org/sites/default/files/images/ndis_psychosocial_pathway_consultation_project_-_final_report_-_may_2018.pdf [accessed 2021-10-08]
37. National statement on ethical conduct in human research 2007 (Updated 2018). National Health and Medical Research Council. Canberra: Commonwealth of Australia; 2018. URL: https://www.nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2007-updated-2018 [accessed 2021-10-08]

Abbreviations

ED: emergency department
NDIS: National Disability Insurance Scheme
PSD: psychosocial disability

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Protocol

Psychosocial and Behavioral Effects of the COVID-19 Pandemic in the Indian Population: Protocol for a Cross-sectional Study

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Abstract

Background: During the year 2020, the COVID-19 pandemic spread from China to the rest of the world, which prompted the world to implement a widespread mandated quarantine or social isolation. The impending uncertainty of the pandemic must have resulted in a variety of widespread mental health maladies. There has been documentation in the literature about a lot of these in small populations of the world but limited studies have been conducted in India, leading to limited evidence in the literature.

Objective: The main objective of our study is to investigate the mental health effects that the COVID-19 pandemic has had on the general population in India both quantitatively and qualitatively. These results will help contribute to reducing the knowledge gap that is recognized in the literature, which is the result of the unprecedented and novel nature of the pandemic.

Methods: We designed and validated our own questionnaire and used the method of circulating the questionnaire via WhatsApp (Facebook Inc). WhatsApp is a social media app that is very popularly used in India; hence, it turned out to be an effective medium for gathering pilot data. We analyzed the pilot data and used them to validate the questionnaire. This was done with the expertise of our mentor, Nilima Shah, MD (psychiatry). We gathered pilot data on 545 subjects and used the results to determine the changes that were needed for the questionnaire while simultaneously validating the questionnaire.

Results: The study protocol was approved in September 2020 by the institutional review board at Vadilal Sarabhai General Hospital, Ahmedabad, Gujarat, India.

Conclusions: The following preliminary assumptions can be made about the study based on the pilot data: the majority of the survey respondents were male (289/545, 53%), most of them were educated and employed as health care workers (199/545, 36.5%). The majority of the responders were self-employed (185/545, 33.9%), single (297/545, 54.5%), and stayed with their families (427/541, 79%) for the lockdown, which helped them psychologically. Findings that are specific to mental health have been elaborated upon in the manuscript. It is evident from the data collected in previous literature that the pandemic has had significant detrimental effects on the mental health of a vast proportion of the Indian population.

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KEYWORDS

COVID-19; mental health; India; lockdown; isolation; social isolation; behavior; psychology; psychosocial effects

Introduction

Background

From March 2020 to June 2020, most of the world underwent social isolation, mandated quarantine, or lockdown to prevent the excessive spread of and further casualties from COVID-19. Such isolation has caused a dramatic change in routine livelihoods. Although the isolation was essential to containing the disease's spread, we argue that this drastic change in daily life must have led to several psychological issues that are mainly the result of the uncertain nature of the disease; hopelessness about the future; a lack of motivation due to the existential crisis posed by the disease; occupational and financial difficulties; and several novel, day-to-day struggles involving food and family [1-21].

Our preliminary review of the literature suggests that there has been a substantial increase in the incidence of mental health disturbances in people, including symptoms within the full spectrum of anxiety disorders, depression, acute stress disorder, posttraumatic stress disorder, and alcohol and substance use disorders. Numerous other studies have reported an increase in the incidence of deteriorating work performance; insomnia; and feelings of fear, apprehension, helplessness, confusion, anger, and frustration among the general population and frontline health care workers, and this has been associated with the COVID-19 lockdown [1-5,7]. There is documentation of the increased incidence of depression symptoms in young and single individuals. Stressful jobs, exposure to COVID-19 and the risk of such exposure in the workspace, and forced lockdowns during the outbreak are some of the major factors that are associated with the increased reporting of psychological disturbances [3]. The COVID-19 lockdown and the resulting psychological impact could also have resulted in multiple changes in drinking habits. We found an increase in the consumption and purchase (both in-store and web-based purchases) of alcohol, and this correlates with the increase in the duration of the lockdown. Individuals with a lower level of education and those with higher levels of perceived stress have been identified to be at the highest risk for such behavior [8]. There have also been findings of improved social support among friends and families during the lockdown and increased attention to mental health due to more time being allocated to relaxation during the lockdown [7].

Given the evidence found in literature and the unique nature of the COVID-19 pandemic, which has had unique and varied effects on the general population at the individual level and as a whole (ie, effects that are not in line with those of any particular or established clinical syndromes), we want to conduct a cross-sectional survey of the Indian population with an innovative, validated questionnaire to assess the mental health of and psychosocial changes in people who have been affected by the pandemic. Similar studies are being conducted in various other regions of the world as well [22].

There is a lack of evidence and research in the literature about the mental health of the Indian population [20]. This has resulted in a lack of awareness of the symptoms and presentations of different mental health disorders in the general public [20]. Therefore, we chose this target population to help us recognize the culture-specific and general effects that the COVID-19 lockdown and social isolation have had on their psyche. The data from this study can provide valuable and much sought-after insight into the mental status of the general public in the South Asian (Indian) population, which would be useful to mental health professionals and public health experts when making informed decisions that would eventually benefit the general public. Importantly, these interventions need to be based on the community level, since this is the population level that the pandemic has affected the most [23]. These changes need to be similarly reflected at the systemic level in order to maximize their benefit.

Statement of Purpose

Our study has qualitative and quantitative arms. The qualitative arm of this study aims to analyze the psychosocial and behavioral effects of social isolation and mandated quarantine or lockdown. This arm includes an assessment of the Indian population's awareness of and knowledge about COVID-19. The quantitative arm of the study aims to examine the extent of the association between psychosocial and behavioral effects and the various demographic factors of the target population (eg, age, sex, etc). The main purpose of our study is to determine the present mental health status of the general population and the direct effects of social isolation resulting from the COVID-19 pandemic.

Hypotheses and Aims

Hypothesis 1.1 is as follows: there are multiple adverse psychosocial and behavioral effects among remote workers, students, and students transitioning to the workforce that have arisen because of the COVID-19 pandemic lockdown.

Aim 1.1 is as follows: we aim to qualitatively analyze the psychosocial and behavioral effects among the target population via web-based survey forms and present these forms in an easily readable manner.

Hypothesis 1.2 is as follows: the multiple psychosocial and behavioral effects are associated with and vary due to the demographic factors of the target population, such as age, sex, education level, the area of education, ethnicity, the location of residence, relationships, and employment status.

Aim 1.2 is as follows: we aim to quantitatively analyze and determine the extent of these associations and their statistical significance.

Objectives

Aim 1.1 will be accomplished by collecting data via the use of a Google Forms (Google LLC) survey and by using Google Forms software to present data in the form of different kinds of charts, such as bar and pie charts. These will be included in the *Tables and Charts* section of the poststudy research article. Aim 1.2 will be accomplished by using Stata software (StataCorp LLC) to analyze the demographic variables across the data on psychosocial and behavioral effects via methods such as logistic regression and chi-square analysis. The methods used will depend on the kinds of variables being analyzed. The results of this analysis will also be included in the *Analysis* section of the poststudy research article.

Methods

Procedures

We used, and want to continue using, the snowball sampling method. We digitized our validated questionnaire via the use of Google Forms software. Afterward, we contacted everyone we knew and sent them links to the Google Forms questionnaire via different social media platforms and apps, such as WhatsApp (Facebook Inc), Facebook Messenger (Facebook Inc), SMS text messaging, and email. We made sure to divide our contacts before sending out the survey to avoid the duplicity of data, but there is a certain margin of error that is to be expected with this method of data collection. This is a limitation of our data collection method. Further, since Google Forms does not record IP addresses, there is no way of knowing who filled out the forms. There is another method that can be used; while surveying a target population, we can restrict access to Google Forms and send the questionnaire to members of a particular group. We attempted to mitigate the error of duplicity by turning on the "limit to one response" option in the Google Forms survey settings. This will require survey responders to sign in with their Gmail or Google accounts before they can respond to the survey. This can potentially compromise the blinding of the subjects; however, we can delete respondents' personal information on the Google Forms platform to protect privacy and maintain confidentiality. This will help with gathering more meaningful data. We want to continue gathering data to create a large data set with satisfactory power and the required effect size for conducting statistical analyses.

Setting and Sample

The study is ongoing, and so far, 500 adult and pediatric individuals (age group: range 15-70 years) have responded to the questionnaire. We used a cross-sectional study design that involved the use of the snowball sampling method. We distributed a questionnaire to known friends, family members, and colleagues and asked them to pass it on to their acquaintances. Due to the worldwide pandemic and the need to reduce the amount of physical interactions with human subjects, we developed a web-based questionnaire by using Google Forms. To date, the preliminary data of 500 subjects have been collected. These data were collected over a period of 40 days (since October 6, 2020). We want to gather more data once and if the institutional review board grants their approval.

Inclusion and Exclusion Criteria

The inclusion criteria are as follows: respondents aged >15 years (as approved by the institutional review board) and people who filled out the entire survey. The exclusion criteria are as follows: respondents aged ≤15 years and people who did not fill out the entire survey.

Survey Development

The questionnaire was formed with the help of Google Forms software. The questions are based on the templates of the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (*DSM-5*) questionnaire for depression and anxiety; the Patient Health Questionnaire-9; and the Primary Care Evaluation of Mental Disorders diagnostic questionnaire. We used the ideas that formed the basis of the questions in these questionnaires to address our specific research questions and avoid gathering unnecessary data. This method of using ideas from standard forms has been used previously and has been proven to be effective in answering the desired research questions [6-9]. We did not want to use standard scales as the answer format because they are usually harder to interpret and can make the response process difficult. This is why we used simplified versions of answer options in our questionnaire.

Questions 1 to 4 have been used to collect basic demographic information, such as race, age, and the area of residence. Associations between particular demographic factors and psychosocial symptoms have previously been demonstrated in the literature, so we want to take these factors into consideration in the final data analysis as well [10].

Questions 5 to 7 have been used to collect information regarding qualifications, the field of work, and employment status. The rationale behind these questions is that due to recent unforeseen conditions, many people have lost their jobs or have been rendered unemployed before they could start new jobs. This has directly and indirectly affected their mental health, as there has been an increase in the incidence of mental health disorders, including anxiety and depression, resulting from feelings such as the loss of control, hopelessness, the hyperawareness of economic losses [11,12].

Questions 6 to 8 pertain to whom respondents spent the lockdown period with and their social interactions with relatives, friends, and other people. These questions enable us to better understand how these important interpersonal relationships impact respondents' mental well-being [13].

With questions 9 to 14, we have tried to capture data on the changing sleep and eating habits, physical activities, and hobbies of individuals. These factors are generally reflective of the mental status of individuals, as evidenced in literature and by the *DSM-5* questionnaire [14,16,17].

Questions 22 to 24 ask about whether individuals or any loved ones are infected with SARS-CoV-2 and the availability of adequate testing and treatment options in their vicinity. The

knowledge of infections occurring anywhere near a person may cause a state of paranoia, worry, and anxiety [2].

Questions 28 to 29 are about substance abuse during the lockdown periods. There have been numerous studies that indicate how social isolation affects the already present habits of individuals and results in the development of newer habits of substance abuse as a maladaptive method of coping [4,8,16]. The rest of the questions—questions 16 to 21, 25 to 27, and 30—are about self-reported psychomotor symptoms of depression and anxiety from the *DSM-5* criteria [16,17].

We validated the questionnaire with the help of available pilot data. We first established face validity via consultation with Indian experts in the field. Afterward, we cleaned the collected data by using principal component analysis and calculated the Cronbach α to establish the internal consistency of the questionnaire. These methods have been used numerous times before to establish the validity of an innovative questionnaire [18]. A statistician assisted us with these techniques.

Data Analysis

We will be using Stata software to calculate power and effect size and to analyze the trends in mental disorder symptoms, sleeping and eating habits, physical activity, remote and in-person social interactions, and the mental state of sampled individuals during the period of social isolation. We will be using a mixed methods analysis in the study, that is, the data will be analyzed both qualitatively and quantitatively. The data will be used for the qualitative portion of the analysis, and they will be converted into scores and used as continuous, ordinal, or categorical variables for the quantitative analysis.

Methods such as univariate and multivariate linear and logistic regression and chi-square analysis will be used. Subjects are expected to indirectly benefit from this study due to the general feeling of being rewarded for being able to help with research and for being able to advance the fields of social science and medicine. They are also likely to become more self-aware as they reflect upon their habits to answer some of the questions. There are no anticipated risks to the subjects other than the risk of confidentiality breaches for those from whom birthdates were collected. We have taken appropriate measures to mitigate this risk, as shown in the *Confidentiality* section. Respondents were not and will not be compensated in any way.

Materials and Devices

The collection of the data was performed by using a survey instrument. After the data are collected, the generated spreadsheet will be analyzed by using Stata software.

Confidentiality

No personally identifiable information (eg, the names of respondents, the address of houses, and any other contact information) was or will be collected through the use of a survey instrument. Birthdates were collected from some of the initial respondents, but these will be used exclusively to determine the participants' ages. The birthdates will be destroyed thereafter.

Consent

The terms of consent were explained to participants in the *Description* section of the survey. A large portion of the respondents belong to health care and allied fields (199/545, 36.5%); most of them are doctors and residents. Therefore, they already possess adequate knowledge about the purposes of the information collected for a research study. The rest of the respondents (346/545, 63.5%) were informed at the time of approach, and any pertaining questions were answered. Since filling out the form is optional and voluntary, consent is implied when a completed form is submitted. The exact paragraph that is presented in the form is shown in the *Questionnaire* section.

Data Collection

The Google Forms software collects data automatically from the web-based survey instrument and converts responses from each corresponding question into a chart, table, or graph according to the most suitable method for pictorial representation. The software also generates a spreadsheet that contains all of the individual elements of information collected from a single survey (ie, in individual cells under columns and within rows). Individual entries from each survey form for further data analysis via varied methods are also available in this software.

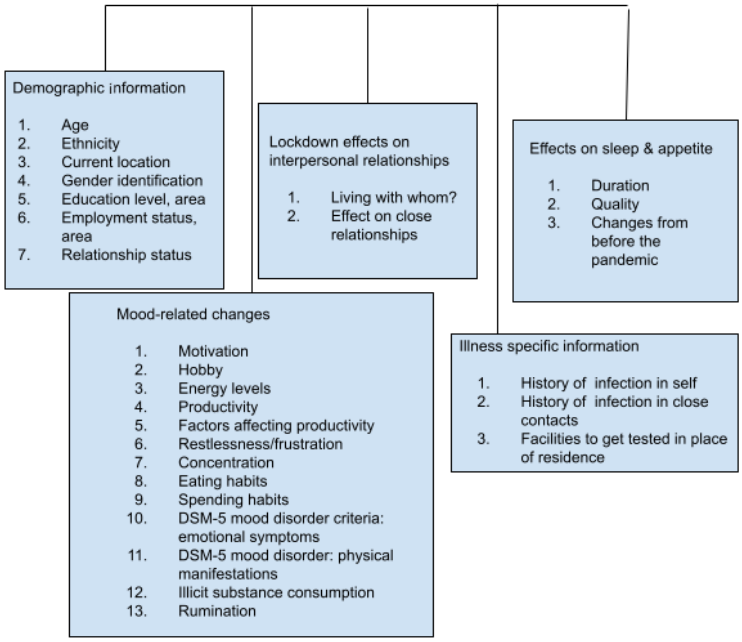
Questionnaire

The paragraph used for explaining consent is stated verbatim, as follows:

> *Title: Psychosocial and behavioral effects of Lockdown*
>
> *Paragraph for consent: This form is for a research study to assess the psychosocial and behavioral effects of remote workers, students, and students in the transition to working due to graduation in the summer of 2020; in the lockdown or self-mandated quarantine due to COVID- 19 pandemic. It should take about 15-20 mins to fill out. We greatly appreciate you taking out the time to fill out this form and contributing to society and the field of science.*
>
> *IMPORTANT: Your name is not required as a part of the survey and all the information you fill out will remain strictly confidential.*

In Figure 1, the layout of the actual questionnaire is explained with the use of a simplified flowchart.

Figure 1. Questionnaire layout. *DSM-5*: *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*.



Results

This study protocol was approved by the institutional review board at Vadilal Sarabhai General Hospital, Ahmedabad, Gujarat, India, on September 11, 2020. This study has received no monetary support. The collection of pilot data was started on June 10, 2020, and finished on September 15, 2020. The data of 550 participants were used for the preliminary data analysis and validation of the questionnaire. The data have been analyzed in depth with the use of Stata software, and we intend on publishing the data and the results of deeper statistical analyses once this protocol has been approved for publication.

Discussion

A number of preliminary conclusions can be drawn by merely looking at the results data available. An important one is that 33.8% (184/545) of the total study population reported having high levels of sleep disturbances. Sleep disturbances have been linked to a decreased need for sleep resulting from less activity and increased amounts of psychological disturbances, such as anxiety and depression. Recent evidence from other studies in the literature has suggested that numerous psychological problems occur among the general public, health care workers, and patients with COVID-19 and has emphasized poor sleep quality, which is the most common psychological morbidity that has been observed during the COVID-19 pandemic [24]. We found that feelings of anxiety and agitation (183/545, 33.6%), restlessness (159/545, 29.2%), hopelessness and helplessness (122/545, 22.4%), and not being in control of anything (138/545, 25.3%) and difficulties with concentrating (194/545, 35.6%), etc, were reported by a high proportion of respondents. Irritability (169/545, 31%), the state of being easily fatigued (107/545, 19.6%), low or depressed mood (143/545, 26.2%), a lack of interest or diminished interest (114/545, 20.9%), the slowing down of thought processes (135/545, 24.8%), and excessive worry over physical appearance (145/545, 26.6%) were among the other psychological problems. Headaches (119/545, 21.8%), muscle tension (46/545, 8.4%), and heavy legs (58/545, 10.6%) and arms (20/545, 3.7%) were the least commonly reported psychological comorbidities.

Numerous other surveys have reported that a majority of households in India do not have access to high-quality foods such as vegetables and dairy products. An overwhelming majority of Bangladeshi people in low-income groups have reported that the pandemic has affected their livelihoods and have recorded high stress scores in addition to other negative psychosocial outcomes resulting from the worries regarding their livelihoods. Low socioeconomic classes have lower rates of financial literacy and lesser savings due to having the highest reliance on daily income [25].

COVID-19–related fear, moderate to severe depressive symptoms, and moderate to severe anxiety symptoms have been reported in other surveys and documented in the literature. The incidence of psychological disturbances has been reported and seen to be significantly higher in women. Respondents under the age of 30 years have reported lower levels of fear and depressive symptoms and have shown the least amount of social responsibility. Based on GLM, having a significant other with COVID-19, being on psychiatric medication, exhibiting safety and checking behaviors, and complying with guidelines are associated with higher levels of COVID-19–related fear. A linear regression analysis revealed that gender, age, and depressive and anxiety symptoms affect levels of COVID-19–related fear [26].

The results from our survey and all of the other evidence in the literature are proof that we need to direct our attention and health care resources toward the mental health of the population. Improving mental health can potentially to lead to increased motivation, willpower, and mental strength, which are some of the factors that can result in increased productivity and an overall better quality of life among the general population. Since our survey results are self-reported, they are limited by the lack

of objectivity in the survey's measures. However, the quality of life and psychological well-being of a person are personal issues that can vary from person to person. More detailed studies that are specifically tailored to an individual's and target population's mental well-being are required. Such studies would tremendously help with understanding the human psyche and aid researchers with making contributions to scientific literature.

Conflicts of Interest

None declared.

References

1. Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. Lancet 2020 Mar 14;395(10227):912-920 [FREE Full text] [doi: 10.1016/S0140-6736(20)30460-8] [Medline: 32112714]
2. Serafini G, Parmigiani B, Amerio A, Aguglia A, Sher L, Amore M. The psychological impact of COVID-19 on the mental health in the general population. QJM 2020 Jun 22;113(8):531-537 [FREE Full text] [doi: 10.1093/qjmed/hcaa201] [Medline: 32569360]
3. Liu X, Kakade M, Fuller CJ, Fan B, Fang Y, Kong J, et al. Depression after exposure to stressful events: lessons learned from the severe acute respiratory syndrome epidemic. Compr Psychiatry 2012 Jan;53(1):15-23 [FREE Full text] [doi: 10.1016/j.comppsych.2011.02.003] [Medline: 21489421]
4. Wu P, Liu X, Fang Y, Fan B, Fuller CJ, Guan Z, et al. Alcohol abuse/dependence symptoms among hospital employees exposed to a SARS outbreak. Alcohol Alcohol 2008;43(6):706-712 [FREE Full text] [doi: 10.1093/alcalc/agn073] [Medline: 18790829]
5. Pfefferbaum B, North CS. Mental Health and the Covid-19 Pandemic. N Engl J Med 2020 Aug 06;383(6):510-512. [doi: 10.1056/NEJMp2008017] [Medline: 32283003]
6. Giallonardo V, Sampogna G, Del Vecchio V, Luciano M, Albert U, Carmassi C, et al. The impact of quarantine and physical distancing following COVID-19 on mental health: Study protocol of a multicentric italian population trial. Front Psychiatry 2020 Jun 05;11:533 [FREE Full text] [doi: 10.3389/fpsyt.2020.00533] [Medline: 32581895]
7. Zhang Y, Ma ZF. Impact of the COVID-19 pandemic on mental health and quality of life among local residents in Liaoning Province, China: A cross-sectional study. Int J Environ Res Public Health 2020 Mar 31;17(7):2381 [FREE Full text] [doi: 10.3390/ijerph17072381] [Medline: 32244498]
8. Koopmann A, Georgiadou E, Kiefer F, Hillemacher T. Did the general population in Germany drink more alcohol during the COVID-19 pandemic lockdown? Alcohol Alcohol 2020 Oct 20;55(6):698-699 [FREE Full text] [doi: 10.1093/alcalc/agaa058] [Medline: 32556079]
9. Wang C, Pan R, Wan X, Tan Y, Xu L, Ho CS, et al. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. Int J Environ Res Public Health 2020 Mar 06;17(5):1729 [FREE Full text] [doi: 10.3390/ijerph17051729] [Medline: 32155789]
10. Shi L, Lu ZA, Que JY, Huang XL, Liu L, Ran MS, et al. Prevalence of and risk factors associated with mental health symptoms among the general population in China during the coronavirus disease 2019 pandemic. JAMA Netw Open 2020 Jul 01;3(7):e2014053 [FREE Full text] [doi: 10.1001/jamanetworkopen.2020.14053] [Medline: 32609353]
11. The Hindu Data Team. Data | An estimated 12.2 crore Indians lost their jobs during the coronavirus lockdown in April: CMIE. The Hindu. 2020 May 07. URL: https://www.thehindu.com/data/data-over-12-crore-indians-lost-their-jobs-during-the-coronavirus-lockdown-in-april/article31520715.ece [accessed 2021-09-15]
12. Morath E. How many U.S. workers have lost jobs during coronavirus pandemic? There are several ways to count. The Wall Street Journal. 2020 Jun 03. URL: https://www.wsj.com/articles/how-many-u-s-workers-have-lost-jobs-during-coronavirus-pandemic-there-are-several-ways-to-count-11591176601 [accessed 2021-09-15]
13. Kawohl W, Nordt C. COVID-19, unemployment, and suicide. Lancet Psychiatry 2020 May;7(5):389-390 [FREE Full text] [doi: 10.1016/S2215-0366(20)30141-3] [Medline: 32353269]
14. Markowitz J. Virtual treatment and social distancing. Lancet Psychiatry 2020 May;7(5):388-389 [FREE Full text] [doi: 10.1016/S2215-0366(20)30140-1] [Medline: 32353268]
15. Schnettler B, Miranda H, Lobos G, Orellana L, Sepúlveda J, Denegri M, et al. Eating habits and subjective well-being. A typology of students in Chilean state universities. Appetite 2015 Jun;89:203-214. [doi: 10.1016/j.appet.2015.02.008] [Medline: 25675858]
16. Rodriguez LM, Litt DM, Stewart SH. Drinking to cope with the pandemic: The unique associations of COVID-19-related perceived threat and psychological distress to drinking behaviors in American men and women. Addict Behav 2020 Nov;110:106532 [FREE Full text] [doi: 10.1016/j.addbeh.2020.106532] [Medline: 32652385]

17. Vahia VN. Diagnostic and statistical manual of mental disorders 5: A quick glance. Indian J Psychiatry 2013 Jul;55(3):220-223 [FREE Full text] [doi: 10.4103/0019-5545.117131] [Medline: 24082241]
18. Online assessment measures. American Psychiatric Association. URL: https://www.psychiatry.org/psychiatrists/practice/dsm/educational-resources/assessment-measures [accessed 2021-09-15]
19. Boateng GO, Neilands TB, Frongillo EA, Melgar-Quiñonez HR, Young SL. Best practices for developing and validating scales for health, social, and behavioral research: A primer. Front Public Health 2018 Jun 11;6:149 [FREE Full text] [doi: 10.3389/fpubh.2018.00149] [Medline: 29942800]
20. Pradeep BS, Gururaj G, Varghese M, Benegal V, Rao GN, Sukumar GM, et al. National Mental Health Survey of India, 2016 - Rationale, design and methods. PLoS One 2018 Oct 25;13(10):e0205096. [doi: 10.1371/journal.pone.0205096] [Medline: 30359382]
21. Mental health in the times of COVID-19 pandemic: guidance for general medical and specialised mental health care settings. Institute of Mental Health & Neuro Sciences. 2020 Apr. URL: https://www.mohfw.gov.in/pdf/COVID19Final2020ForOnline9July2020.pdf [accessed 2021-09-15]
22. Survey tool and guidance: rapid, simple, flexible behavioural insights on COVID-19. World Health Organization: Regional Office for Europe. 2020 Jul 29. URL: https://apps.who.int/iris/bitstream/handle/10665/333549/WHO-EURO-2020-696-40431-54222-eng.pdf?sequence=1&isAllowed=y [accessed 2021-09-15]
23. Amerio A, Bianchi D, Santi F, Costantini L, Odone A, Signorelli C, et al. Covid-19 pandemic impact on mental health: a web-based cross-sectional survey on a sample of Italian general practitioners. Acta Biomed 2020 May 11;91(2):83-88 [FREE Full text] [doi: 10.23750/abm.v91i2.9619] [Medline: 32420931]
24. Morris ME, Aguilera A. Mobile, social, and wearable computing and the evolution of psychological practice. Prof Psychol Res Pr 2012 Dec;43(6):622-626 [FREE Full text] [doi: 10.1037/a0029041] [Medline: 25587207]
25. Krishnamoorthy Y, Nagarajan R, Surendran G, Sakthivel M. Impact of COVID-19 on psychological status of general population. IntechOpen. URL: https://www.intechopen.com/online-first/76705 [accessed 2021-09-15]
26. Parlapani E, Holeva V, Voitsidis P, Blekas A, Gliatas I, Porfyri GN, et al. Psychological and behavioral responses to the COVID-19 pandemic in Greece. Front Psychiatry 2020 Aug 19;11:821 [FREE Full text] [doi: 10.3389/fpsyt.2020.00821] [Medline: 32973575]

Abbreviations

DSM-5*: *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

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Protocol

Home Treatment for Acute Mental Health Care: Protocol for the Financial Outputs, Risks, Efficacy, Satisfaction Index and Gatekeeping of Home Treatment (FORESIGHT) Study

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Abstract

Background: Crisis Resolution and Home Treatment (CRHT) teams represent a community-based mental health service offering a valid alternative to hospitalization. CRHT teams have been widely implemented in various mental health systems worldwide, and their goal is to provide care for people with severe acute mental disorders who would be considered for admission to acute psychiatric wards. The evaluation of several home-treatment experiences shows promising results; however, it remains unclear which specific elements and characteristics of CRHT are more effective and acceptable.

Objective: This study aims to assess the acceptability, effectiveness, and cost-effectiveness of a new CRHT intervention in Ticino, Southern Switzerland.

Methods: This study includes an interventional, nonrandomized, quasi-experimental study combined with a qualitative study and an economic evaluation to be conducted over a 48-month period. The quasi-experimental evaluation involves two groups: patients in the northern area of the region who were offered the CRHT service (ie, intervention group) and patients in the southern area of the region who received care as usual (ie, control group). Individual interviews will be conducted with patients receiving the home treatment intervention and their family members. CRHT members will also be asked to participate in a focus group. The economic evaluation will include a cost-effectiveness analysis.

Results: The project is funded by the Swiss National Science Foundation as part of the National Research Program NRP74 for a period of 48 months starting from January 2017. As of October 2021, data for the nonrandomized, quasi-experimental study and the qualitative study have been collected, and the results are expected to be published by the end of the year. Data are currently being collected for the economic evaluation.

Conclusions: Compared to other Swiss CRHT experiences, the CRHT intervention in Ticino represents a unique case, as the introduction of the service is backed by the closing of one of its acute wards. The proposed study will address several areas where there are evidence gaps or contradictory findings relating to the home treatment of acute mental crisis. Findings from this study will allow local services to improve their effectiveness in a challenging domain of public health and contribute to improving access to more effective care for people with severe mental disorders.

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KEYWORDS

acute mental healthcare; home treatment; crisis resolution; home visits; mental health; home care; crisis; home; community-based; mental health services; economic; risk; risks; efficacy; public health; accessibility

Introduction

Over the last three decades, mental health care in many Western societies has been characterized by a strong emphasis on the sociopsychiatric approach [1]. This has contributed to a radical process of deinstitutionalization (ie, the decline in the number of beds) and transinstitutionalization (ie, an increase in the number of mental health beds in general hospitals and nursing homes) through the establishment of patient- and community-focused mental health care services [2-4]. This shift represents a move away from a system in which patients' needs were determined and met by health systems toward a "nothing about me without me" system, in which patients' self-determination, as well as service users' and carers' experience of care are considered fundamental for the success of the service provided. Crisis Resolution and Home Treatment (CRHT) teams are one of several types of community-based mental health services offering valid alternatives to hospitalization [1]. CRHT teams take care of people with severe acute mental disorders that would be considered for admission to acute psychiatric wards. Their main tasks include assessing people during a mental health crisis, providing intensive support, and developing a treatment plan to deliver ad hoc services in the patient's home, on a daily basis, until the crisis is resolved or until the patient is stabilized and can be transferred to community services or private psychiatrists for further long-term care. The interventions of CRHT teams are therefore restricted to acute crises and should not exceed the length of an otherwise indicated hospital stay (typically no longer than 1 month).

The evaluation of home-treatment experiences shows promising results. Since the 1960s, several studies, including randomized controlled trials (RCTs) [5-15] and nonrandomized comparative studies [16-19], have explored the feasibility of managing psychiatric crises at home rather than in hospitals. The extensive literature reviews conducted by Johnson [1], Joy [20], and Burns [21] highlight that: (1) all the studies investigating outcomes from precursors of CRHT demonstrated a reduction in admission rates when home care was available; (2) findings on symptom severity and social outcomes have been more heterogeneous, although they generally favored the home-treatment group in cases where significant differences were reported; (3) improvements in community-based mental health teams may lead to greater benefits for patients; and (4) some concerns and uncertainties exist about the validity of the evidence owing to some marked differences between the groups recruited in most studies, in terms of gender, diagnosis, and housing. Further observational studies also demonstrated a reduction in readmission rates and a decline in bed occupancy following the introduction of CRHT [22,23]. Other studies suggested an overall impact of CRHT in reducing voluntary admissions, whereas evidence of the impact of CRHT on compulsory admissions is still limited and requires further investigation [24,25]. Overall, the inclusion of a psychiatrist within the CRHT team and the provision of 24-hour service appeared to be beneficial; however, it remains unclear which specific elements and characteristics of CRHT are more effective and acceptable, and whether they are equally effective across patient groups [26]. The cost-effectiveness of home treatment compared to inpatient services has never been formally investigated. Informed decisions by policymakers and relevant stakeholders are currently hampered by the paucity of studies on relevant aspects of the CRHT, which is probably also explained by the practical and ethical difficulties of conducting research in the area of mental health crisis.

In terms of acceptability among users, only a small number of studies have investigated patients' and carers' opinions in relation to CRHT services. Nolan [27] explored users' and carers' perspectives on the use of alternative services and found that most patients had positive views about being treated at home rather than in hospital, and similar outcomes were identified by Hopkins and Niemiec [28]. However, potential drawbacks of CRHT include difficulties in dealing with several health and social care professionals, discontinuity of care between CRHT and community mental health care, and a perceived excessive treatment focus on medication compliance. As for the impact of CRHT on carers, most of the limited evidence dates back to the 1980s [29] and the early 1990s [30]. A more recent survey found that up to 55 percent of carers expressed a preference for home treatment over hospital care [31]. However, the authors suggested that a longer history of repeated acute episodes and limited familiarity with innovative CRHT might have influenced their observations.

In the last 15 years, several CRHT services have been implemented and tested in Switzerland. In August 2007, for example, the Canton of Lucerne developed the first CRHT Swiss service in response to a severe shortage of psychiatric beds. Findings indicated the feasibility of the service and highlighted its acceptability by patients and families, as well as its economic

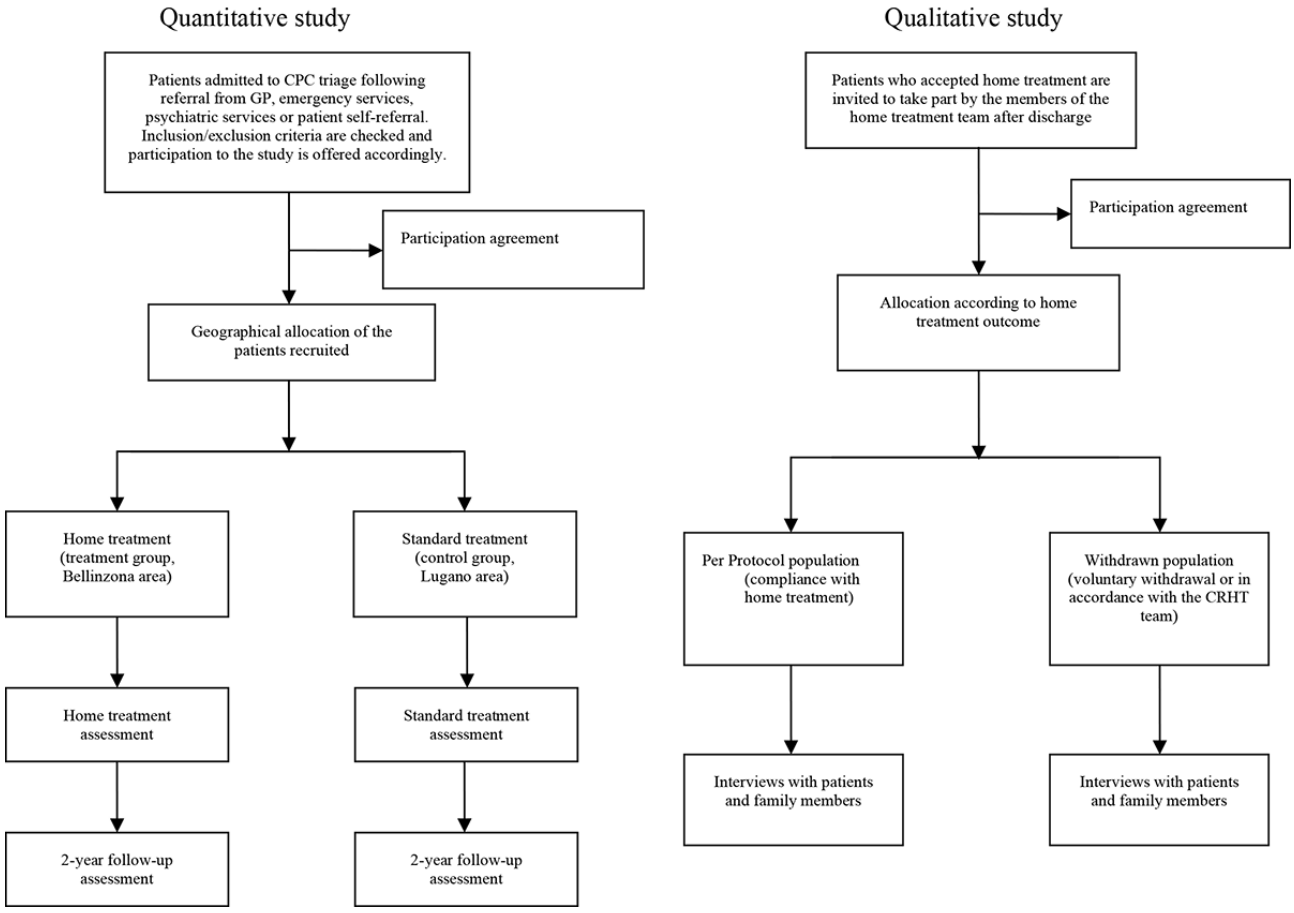
sustainability [32]. In more recent years, the Canton of Aargau, the Canton of Zürich, and the Canton of Ticino have launched their independent CRHT services [33,34]. Compared to other Swiss CRHT experiences, Ticino represents a unique case, wherein the implementation of a CRHT team is backed by the closing of one of the acute wards at the Cantonal Psychiatric Clinic (CPC), a public psychiatric hospital located in Mendrisio, Switzerland. The service design and its evaluation are rooted in the British home treatment experiences [1]. Moreover, a pilot conducted in late spring 2016 explored the feasibility of conducting a mixed methods study in order to formally evaluate the intervention [35]. This study aims to assess the clinical efficacy of CRHT in Ticino; explore its determinants of feasibility and acceptability; and evaluate the cost-effectiveness of CRHT as an alternative to hospitalization to treat acute crisis for people affected by severe mental health disorders.

Methods

Study Design

This study adopts a mixed methods approach, which includes a quasi-experimental design and a qualitative study over a 48-month period (see Figure 1). The qualitative and quantitative approaches are adopted to evaluate the CRHT service from multiple perspectives, including its cost-effectiveness. The study has been registered as an interventional, nonrandomized, quasi-experimental study (registration number ISRCTN38472626).

Figure 1. Flowchart of the study design. CPC: Cantonal Psychiatric Clinic; CRHT: Crisis Resolution and Home Treatment.



Quasi-experimental study designs allow the research team to control the treatment, but they do not include random assignment of participants [36]. In addition, quasi-experimental study designs use existing or predefined groups; thus, they are often more convenient and less disruptive than a true experimental design. In the proposed study, in particular, the recruitment process typical of an RCT would pose practical and ethical issues. From a practical perspective, the inclusion of potential patients outside the Bellinzona area, the northern area of the Canton (where the CRHT team is based) in the intervention group would significantly extend the area to be covered by the new home service. Consequently, this would pose major logistic issues that could affect the implementation of the CRHT intervention. From an ethical perspective, the random allocation process of an RCT would leave potential patients affected by acute mental disorders without the possibility to choose between a home-based treatment intervention and hospitalization. A quasi-experimental study design, on the other hand, allows the research team to demonstrate causality between the proposed intervention and a series of predefined outcomes without having to control the random assignment of participants.

Study Setting

The new intervention is being implemented in the Canton of Ticino, which has approximately 350,000 inhabitants and is located in Southern Switzerland. Acute mental health crises are usually managed by one public hospital and three private clinics. Three of these structures (ie, the public CPC with 140 beds, the

Clinica Viarnetto with 45 beds, and the Malcantonese Hospital with 26 beds) are located in the southern area of the region, whereas the private clinic of Santa Croce (with 80 beds) is located in the northern area. In addition, the regional network of psychiatric services includes four well-established community mental health teams (eg, sociopsychiatric service [SPS]) available from 9:00 AM to 5:00 PM on weekdays; a service of Psychiatry & Psychological Medicine (SPPM) available from 8:00 AM to 6:00 PM, providing acute psychiatric consultations in five different hospitals; and on-call psychiatrists from both the SPS and the SPPM teams covering psychiatric emergencies from 6:00 PM to 8:00 AM. One of the CPC wards was closed to new inpatient admissions and replaced by the newly established CRHT. Health insurance providers and the Health Department of the Canton of Ticino have agreed to finance CRHT for each patient as if they were treated in an inpatient setting.

Intervention

The CRHT team is based in Bellinzona and cares for patients aged 18 to 65 years, who would typically be admitted to the CPC on a voluntary basis. The team is available 24 hours a day, 7 days a week (on call from 10:30 PM to 7:00 AM). The new service brings together different health and social care professionals, including 3 physicians (a full-time consultant psychiatrist, a part-time psychiatrist, and a part-time senior consultant psychiatrist on call), 10 mental health nurses, 1 team manager, 1 part-time social worker on call, and 1 part-time clinical psychologist. Referrals are accepted from general practitioners, the local community mental health team, accident and emergency teams, private psychiatrists, and the CPC clinic in Mendrisio. All patients for whom immediate in-patient treatment is deemed necessary have access to the new home treatment service, with the exclusion of people affected by acute alcohol or drug intoxication, extreme agitation, or those who could represent a risk for themselves and others. As referrals may also be accepted by the CPC itself in Mendrisio, patients are considered eligible for the study only if they stayed in the CPC for less than 48 hours before being transferred to the CRHT program. Patients are typically visited at home on a daily basis for approximately 1 h, with the option for multiple visits a day (or night), if necessary. Interventions are individually tailored but include typical components of acute care, such as crisis intervention, pharmacotherapy, psychoeducation, brief psychotherapy, and social care. Key elements addressed by the CRHT include monitoring symptoms; monitoring medication and side effects; identifying and managing safety or risk issues; providing emotional, social, and psychological support; providing carer or family support; liaising with other services and professionals involved in the process of care; and planning discharge meetings and follow-ups. The patient is seen with family members or caregivers from the very beginning, if feasible. This is because the CRHT team provide patients, family members, and carers with elements of psychoeducation on mental health crises along with ways to prevent future relapses and reduce mental illness stigma. In addition, the team promotes an active collaboration with the local SPS, general practitioners, private psychiatrists, and carers to support the long-term needs of those patients.

Quasi-Experimental Study

Overview

The first part of the study evaluates the clinical efficacy of CRHT in Southern Switzerland. In particular, patients aged 18 to 65 years living in two areas in Ticino (Bellinzona e Valli and Lugano) diagnosed with acute mental illness and requiring hospital admission to the CPC were considered for inclusion. Patients at high risk of suicide or self-harm, and those with alcohol or drug problems were excluded from the study. Compulsory admissions were also excluded from the study. Patients in the Bellinzona e Valli area were offered the CRHT service and formed the intervention group; those in the Lugano area formed the control group and received care as usual (ie, hospitalization). Preliminary statistical analysis based on observational data drawn from the CPC database indicates that there are no significant differences in some important health indicators (eg, Brief Symptom Checklist [BSCL] and Health of the Nation Outcome Scales [HoNOS]) between patients living in these two areas. This increases the comparability between the two groups and reduces confounding effects [37]. The study design can, therefore, be considered as a natural experiment based on geography. To calculate the minimal sample size for the study, we used the mean and SD values of the HoNOS scale scores for the experimental and control groups reported in Johnson's study [15]. To ensure a statistical power of 80%, at the 5% significance level for a 2-tailed hypothesis test, the minimal sample size equals 142. The recruitment period was of 15 months, and every recruited patient was followed for a period of 24 months after discharge.

Quantitative data were collected by the CRHT health care professionals as part of their standard operating procedures for the storage of clinical information, in line with the CPC's administrative and clinical demands. A team comprising a CPC data manager and researchers from the University of Applied Sciences and Arts of Southern Switzerland (project partner in charge of the data analysis) met on a regular basis in order to monitor the quality of the data collected. The CRHT team checked the eligibility of all patients from both areas of the Canton, according to the abovementioned inclusion criteria. The willingness of patients from Lugano (the northern area) to accept the CRHT was a prerequisite for the intention-to-treat (ITT) analysis, although this theoretical acceptance did not imply any actual assignment to treatment.

Outcome Measures

The primary outcome measures of the study are the number of inpatient days; total days in treatment and use of other mental health services; direct costs (treatment and follow-up); and HoNOS and BSCL scores. The secondary outcome measures of the study are patients' satisfaction (PoC-18 questionnaire); relatives' satisfaction (PoC-18 questionnaire); occurrence of serious incidents involving deliberate self-harm and violence toward others; satisfaction of the CRHT; and number of days patients were on sick leave and absent from work. Information regarding important heterogeneity factors, such as gender, age, level of education, employment status, unhealthy lifestyle, and the patient's clinical and social history, including diagnosis and previous service use, are also recorded.

Data Analysis

By adopting an ITT approach, the study analyzes all patients who are enrolled regardless of deviations (ie, drop out, protocol deviation, withdrawals, and noncompliance) that may occur after assignment to the treatment and control groups. ITT provides a more reliable estimate of treatment effect, minimizes type-1 errors, and preserves sample size. Univariate tests are used to assess differences between control and treatment groups for all patients' characteristics, as well as for clinical and nonclinical outcomes. A univariate comparison of questionnaire responders and nonresponders will also be conducted. Following the assumption of Conditional Geographic Treatment Ignorability, we estimate the effects of CRHT on the outcome measures considered by means of generalized linear models and matching techniques, in order to control for some important pretreatment covariates (eg, sociodemographic, clinical, and social variables), with the aim of making treatment and control groups as comparable as possible and adjusting for potential confounders [37-39].

Qualitative Study

The recruitment phase of the qualitative study started once the observational period of the quantitative study was concluded, in order to avoid potential bias. In particular, the qualitative study aims to investigate the acceptability of the intervention among patients and their carers, as well as among health care professionals of the CRHT team. Further elements to be explored included the interactions between the CRHT team and patients, the role of family members involved by the CRHT team, and the way health care workers collaborated in this new professional context. Data were collected through individual semistructured interviews with a purposeful sampling of patients and their family members and through focus groups with the members of the CRHT team. Two categories of patients were considered for inclusion: (1) those who have accepted the CRHT and have been compliant with it (*per-protocol population*) and (2) those who have accepted the CRHT but have subsequently withdrawn from it (*withdrawn population*). Patients from these two groups had a personal experience with the home treatment service. A comparison between their perspectives is anticipated to provide highlights on the experience of each group and potentially reveals the conditions for successful home treatment. The maximum variation sampling strategy was used in order to maximize the variability of respondents' experiences [40]. The sample was thus diversified in terms of sex (men or women), age (young or old), family situation (living with family members or not), and psychiatric history (first hospitalization or not), as we anticipated these four characteristics may influence patients' experience. In line with the pilot study previously conducted [35], we aimed to recruit about 20 dyads (patients and family members) from the *per-protocol population* and about 7 people from the *withdrawn population*. CRHT members were asked to participate in a focus group to explore several aspects, including the challenges of providing such intervention, how the members of the team collaborate within the team, and with the psychiatrist services in Ticino, as well as the forms of collaborations within the team and with the patients and their families. Focus groups were conducted in the premises of the CRHT team by a moderator and an assistant moderator.

Interviews and focus groups were conducted by a researcher not involved in the home treatment team. Data collection and analysis for the interviews were conducted simultaneously, until data saturation was achieved. For this reason, participants were progressively recruited and interviewed based on the themes that emerge from the provisional analysis. All the interviews and the focus groups were audio-recorded, transcribed, and anonymized.

Economic Evaluation

The last part of the study, for which the data collection is still ongoing, explores the cost-effectiveness of the CRHT intervention implemented. The economic evaluation follows the approach illustrated by McCrone [41]. Direct and indirect costs are obtained for both the treatment and follow-up phases (see Table 1). Treatment costs are provided by the CPC, whereas the follow-up costs are provided by the patients' health insurance companies. Differences in the health care costs between the two treatments (CRHT vs hospitalization) are assessed using bootstrapped clustered regression analysis. Cost-effectiveness of home treatment are evaluated using cost-effectiveness acceptability curves (CEACs). CEACs involve the treatment and follow-up periods, and these are based on the differences between effectiveness measures and total costs. For the treatment period, the effectiveness measures will include the reduction in the HoNOS and BSCL scores at the end of the treatment, whereas for the follow-up period, the effectiveness measures will include the total number of days without treatment and/or other service utilization and the total number of non-inpatient days registered during the follow-up phase.

Table 1. Direct and indirect costs for the intervention and control groups.

Cost type	Intervention group (CRHT[a])	Control group (hospitalization)
Direct costs		
Treatment phase	Sum of direct medical and nonmedical costs.	Total bed cost per day × total number of inpatient days
	Direct medical costs include the same variable cost categories as for hospitalized patients (therapies, medication, staff salaries of carers, etc); direct nonmedical costs differ and are mostly attributable to staff travel costs.	The total bed cost per day is split into fixed and variable costs. Variable costs include direct medical (therapies, medication, staff salaries of carers, etc) and nonmedical costs (food, accommodation, etc). The fixed cost per bed and day will be calculated by dividing the total fixed cost of the service by the number of inpatient days.
Follow-up phase	Direct costs in the follow-up phase correspond to direct medical costs, including the costs of medical consultations, medical emergencies, hospitalizations, pharmaceutical therapies, etc	Same costs for the intervention group
Indirect costs		
Treatment and follow-up phases	Indirect costs correspond to the costs of lost production. During both phases, the number of days of absence from work will be recorded on the basis of medical certificates issued. The cost of a day of absence from work will be valued using a regional age- and gender-specific average salary.	Same costs for the intervention group

[a]CRHT: Crisis Resolution and Home Treatment.

Collaboration

This FORESIGHT (Financial Outputs, Risks, Efficacy, Satisfaction Index and Gate-keeping of Home Treatment in Ticino) study is a joint project of the Organizzazione Sociopsichiatrica Cantonale, the Department of Business Economics, Health and Social Care of the University of Applied Sciences and Arts of Southern Switzerland, and Fondazione Pro Mente Sana. A steering committee that encompasses all important actors (ie, the main applicant, 3 coapplicants, and project partner) will facilitate a continuous interaction between the CRHT team and the researcher team. During the data collection phase, regular meetings will be held in order to monitor the progress of the project.

Ethics Approval and Consent to Participate

The project is funded by the Swiss National Science Foundation as part of the National Research Program NRP74 (grant 407440_167375). The funding body had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript. The project is approved by the regional Ethics Committee (reference 2017-00247) and is registered as an interventional, nonrandomized, quasi-experimental study (registration ISRCTN38472626). Oral and written information was provided to all patients, and written consent was obtained from all participants.

Results

The project is funded by the Swiss National Science Foundation as part of the National Research Program NRP74 for a period of 48 months starting from January 2017. As of February 2021, data for the nonrandomized, quasi-experimental study have been collected, and the results are expected to be published by the end of the year. Data are currently being collected and/or analyzed for the qualitative study and economic evaluation. Due to some recruitment issues, the COVID-19 pandemic, and the ensuing substantially limited access to potential participants as well as restrictions for meetings and interviews, it was decided, in accordance with the funding agency, to extend the project until the end of December 2021. The updated schedule of the project is presented in a table in Multimedia Appendix 1.

Discussion

Principal Findings

This paper describes the protocol for a mixed methods study designed to assess the clinical efficacy, acceptability, and cost-effectiveness of a new home treatment intervention for people affected by acute psychiatric crises. Compared to other Swiss CRHT experiences, the CRHT service in Ticino represents a unique case, as the introduction of the service is backed by the closing of one of its acute wards. Therefore, this home treatment experience has the specific characteristic of being addressed to all patients, with an acute psychiatric crisis living in the northern area of Ticino and eligible for treatment at home, rather than a selected subgroup of patients.

Crisis care for service users, where support is provided during a crisis either in their home or in a community setting, is found by several reviews to provide a package of support that is worthwhile, acceptable, and less expensive than standard care [26,42-44]. In particular, crisis care has the potential to avoid repeated admissions to hospital and improve the mental state of services users more than standard care among this group. To increase the chances of a successful implementation, the CRHT intervention has been planned and designed together with local health professionals and the support of the relevant stakeholders in the Canton.

To our knowledge, this is the first study to implement and evaluate a CRHT intervention in Southern Switzerland. The choice of conducting a mixed methods study, which involves

a quasi-experimental design, a qualitative study, and a cost-effectiveness analysis, is supported by the idea of evaluating the CRHT intervention comprehensively and from different perspectives thanks to the input of a multidisciplinary team. In addition to gathering preliminary data on the efficacy of this program for improving health-related outcomes among the target group, the proposed study also gathers valuable data on program engagement and experiences in the program among the target group and their carers. This is important given that only a small number of studies have investigated patients' and carers' experiences in relation to CRHT services. Conducting interviews with participants (potentially including those who drop out of the program) will allow the researchers to gain insight into how people approach the service and live the home visits conducted by the CRHT team. The proposed study will integrate a cost-effectiveness analysis to determine the incremental cost-effect of the program compared to treatment as usual. This will deliver a preliminary understanding of whether the program provides value for money compared with hospitalization.

Given this is the first experience of home treatment in Southern Switzerland, it is anticipated that the findings from this study will potentially have an extensive impact at the local level. In particular, these findings will inform the refinement and extended implementation of CRHT intervention in other areas of the Canton, as well as the development of ad hoc educational interventions to train health care professionals, including nurses and doctors, on crisis interventions and home treatment services. In addition, thanks to the multitude of data collected, the research team will be able to draw further recommendation on CRHT service in terms of clinical efficacy, as well as patients and providers' acceptability and cost-effectiveness compared to the standard inpatient treatment.

Conclusions

The FORESIGHT study aims to address several topics related to the home treatment of acute mental crisis for which there is no evidence or consistent findings, specifically, whether the CRHT service provided in Ticino is clinically effective, the determinants of its feasibility and acceptability, and the satisfaction of those that receive and those that provide the service. This study also has the potential to extend our current theoretical understanding of the mechanisms of action underlying home treatment interventions for people affected by an acute psychiatric crisis. Finally, the study will identify important results in relation to the CRHT service delivery and its cost-effectiveness as an alternative to hospitalization for crisis resolution. Establishing the feasibility and effectiveness of the CRHT in Ticino could provide a scalable solution for improving the mental health and quality of life of people with mental disorders.

Authors' Contributions

ZM conceived the original idea. SL wrote the manuscript with support from ES and MCZ. LC holds the scientific responsibility of the protocol; RF holds the clinical responsibility of the project. All authors were involved in planning the study, and they have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Project plan: 5-year timeline.
[PDF File (Adobe PDF File), 264 KB - resprot_v10i11e28191_app1.pdf]

References

1. Johnson S, Needle J, Bindman J, Thornicroft G. Crisis Resolution and Home Treatment in Mental Health. Cambridge: Cambridge University Press; 2008.
2. Thornicroft GM, Tansella M. Balancing community-basedand hospital-based mental health care. World Psychiatry 2002 Jun;1(2):84-90 [FREE Full text] [Medline: 16946858]
3. Thornicroft G, Tansella M. Components of a modern mental health service: a pragmatic balance of community and hospital care: overview of systematic evidence. Br J Psychiatry 2004 Oct;185:283-290. [doi: 10.1192/bjp.185.4.283] [Medline: 15458987]
4. Gilburt H, Peck E, Ashton R, Edwards N, Naylor C. Service transformation: lessons from mental health. London: The King's Foundation; 2014.
5. Pasamanick B, Scarpitti FR, Lefton M, Dinitz S, Wernert JJ, McPheeters H. Home versus hospital care for schizophrenics. JAMA 1964 Jan 18;187(3):177-181. [doi: 10.1001/jama.1964.03060160005001]
6. Langsley D, Machotka P, Flomenhaft K. Avoiding mental hospital admission: a follow-up study. Am J Psychiatry 1971 Apr;127(10):1391-1394. [doi: 10.1176/ajp.127.10.1391] [Medline: 5549932]
7. Polak P, Jones M. The psychiatric nonhospital: a model for change. Community Ment Health J 1973;9(2):123-132. [doi: 10.1007/BF01411088] [Medline: 4196980]
8. Fenton FR, Tessier L, Struening EL. A comparative trial of home and hospital psychiatric care. One-year follow-up. Arch Gen Psychiatry 1979 Sep;36(10):1073-1079. [doi: 10.1001/archpsyc.1979.01780100043003] [Medline: 475542]

9. Stein LI, Test MA. Alternative to mental hospital treatment. I. Conceptual model, treatment program, and clinical evaluation. Arch Gen Psychiatry 1980 Apr;37(4):392-397. [doi: 10.1001/archpsyc.1980.01780170034003] [Medline: 7362425]
10. Hoult J, Reynolds I, Charbonneau-Powis M, Coles P, Briggs J. A controlled study of psychiatric hospital versus community treatment - the effect on relatives. Aust N Z J Psychiatry 1981 Dec;15(4):323-328. [doi: 10.3109/00048678109159455] [Medline: 6951573]
11. Pai S, Kapur RL. Evaluation of home care treatment for schizophrenic patients. Acta Psychiatr Scand 1983 Feb;67(2):80-88. [doi: 10.1111/j.1600-0447.1983.tb06726.x] [Medline: 6846041]
12. Merson S, Tyrer P, Lack S, Birkett P, Lynch S, Onyett S, et al. Early intervention in psychiatric emergencies: a controlled clinical trial. The Lancet 1992 May;339(8805):1311-1314. [doi: 10.1016/0140-6736(92)91959-c]
13. Marks IM, Connolly J, Muijen M, Audini B, McNamee G, Lawrence RE. Home-based versus hospital-based care for people with serious mental illness. Br J Psychiatry 1994 Aug;165(2):179-194. [doi: 10.1192/bjp.165.2.179] [Medline: 7953031]
14. Knapp MRJ, Marks IM, Wolstenholme J, Beecham JK, Astin J, Audini B, et al. Home-based versus hospital-based care for serious mental illness. Controlled cost-effectiveness study over four years. Br J Psychiatry 1998 Jun;172:506-512. [doi: 10.1192/bjp.172.6.506] [Medline: 9828991]
15. Johnson S, Nolan F, Pilling S, Sandor A, Hoult J, McKenzie N, et al. Randomised controlled trial of acute mental health care by a crisis resolution team: the north Islington crisis study. BMJ 2005 Aug 15;331(7517):599. [doi: 10.1136/bmj.38519.678148.8f]
16. Sainsbury P, Grad J. Evaluating the community psychiatric service in Chichester. Aims and methods of research. Milbank Mem Fund Q 1966 Jan;44(1):Suppl:231-Suppl:242. [Medline: 5907659]
17. Dean C, Phillips J, Gadd EM, Joseph M, England S. Comparison of community based service with hospital based service for people with acute, severe psychiatric illness. BMJ 1993 Aug 21;307(6902):473-476 [FREE Full text] [doi: 10.1136/bmj.307.6902.473] [Medline: 8400929]
18. Minghella E, Ford R, Freeman T, Hoult J, McGlynn P, O'Halloran P. Open all hours. 24-hour response for people with mental health emergencies. London: The Sainsbury Centre for Mental Health; 1998.
19. Johnson S, Nolan F, Hoult J, White IR, Bebbington P, Sandor A, et al. Outcomes of crises before and after introduction of a crisis resolution team. Br J Psychiatry 2005 Jul;187:68-75. [doi: 10.1192/bjp.187.1.68] [Medline: 15994574]
20. Joy C, Adams C, Rice K. Crisis intervention for people with severe mental illnesses. Cochrane Database Syst Rev 2000(2):CD001087. [doi: 10.1002/14651858.CD001087] [Medline: 10796414]
21. Burns T, Knapp M, Catty J, Healey A, Henderson J, Watt H, et al. Home treatment for mental health problems: a systematic review. Health Technol Assess 2001;5(15):1-139 [FREE Full text] [doi: 10.3310/hta5150] [Medline: 11532236]
22. Glover G, Arts G, Babu KS. Crisis resolution/home treatment teams and psychiatric admission rates in England. Br J Psychiatry 2006 Nov;189:441-445. [doi: 10.1192/bjp.bp.105.020362] [Medline: 17077435]
23. Keown P, Tacchi M, Niemiec S, Hughes J. Changes to mental healthcare for working age adults: impact of a crisis team and an assertive outreach team. Psychiatr Bull 2018 Jan 02;31(8):288-292. [doi: 10.1192/pb.bp.106.012054]
24. Dunn L. Mental Health Act assessments: does a community treatment team make a difference? Int J Soc Psychiatry 2001;47(2):1-19. [doi: 10.1177/002076400104700201] [Medline: 11434407]
25. Dunn LM. Mental Health Act assessments: Does a home treatment team make a difference? In: Brimblecombe N, editor. Acute Mental Health Care in the Community: Intensive Home Treatment. London: Wiley; 2001.
26. Wheeler C, Lloyd-Evans B, Churchard A, Fitzgerald C, Fullarton K, Mosse L, et al. Implementation of the Crisis Resolution Team model in adult mental health settings: a systematic review. BMC Psychiatry 2015 Apr 08;15:74 [FREE Full text] [doi: 10.1186/s12888-015-0441-x] [Medline: 25879674]
27. Nolan F. Which patients like crisis teams and what do they like about them? 2005 Presented at: The Sainsbury Centre for Mental Health Conference on Crisis Resolution Teams; September 8, 2005; York.
28. Hopkins C, Niemiec S. Mental health crisis at home: service user perspectives on what helps and what hinders. J Psychiatr Ment Health Nurs 2007 May;14(3):310-318. [doi: 10.1111/j.1365-2850.2007.01083.x] [Medline: 17430455]
29. Hoult J, Reynolds I, Charbonneau-Powis M, Weekes P, Briggs J. Psychiatric hospital versus community treatment: the results of a randomised trial. Aust N Z J Psychiatry 1983 Jun;17(2):160-167. [doi: 10.3109/00048678309160000] [Medline: 6578788]
30. Reynolds I, Jones J, Berry D, Hoult J. A crisis team for the mentally ill: the effect on patients, relatives and admissions. Med J Aust 1990 Jun 18;152(12):646-652. [doi: 10.5694/j.1326-5377.1990.tb125421.x] [Medline: 2377101]
31. Fulford M, Farhall J. Hospital versus home care for the acutely mentally ill? Preferences of caregivers who have experienced both forms of service. Aust N Z J Psychiatry 2001 Oct;35(5):619-625. [doi: 10.1080/0004867010060510] [Medline: 11551277]
32. Kraan K. Integrated home treatment in acute episodes of mental illness. Results from a Pilot Project in Lucerne. 2012 Presented at: European Congress Social Psychiatry; July 4-6, 2012; Geneva.
33. Stulz N, Wyder L, Maeck L, Hilpert M, Lerzer H, Zander E, et al. Home treatment for acute mental healthcare: randomised controlled trial. Br J Psychiatry 2020 Jun;216(6):323-330. [doi: 10.1192/bjp.2019.31] [Medline: 30864532]
34. Rossa S. La cura del paziente con sintomatologia psichiatrica acuta al domicilio. Thesis submitted in the Master of Advanced Studies in economia e management sanitario e sociosanitario 2004:115.

35. Caiata-Zufferey M, Lisi A. Home treatment per acuzie psichiatriche in Ticino. Report in Italian. Rapporto di ricerca 2016:45.
36. Walker W. The strengths and weaknesses of research designs involving quantitative measures. J Res Nurs 2016 Aug 18;10(5):571-582. [doi: 10.1177/136140960501000505]
37. Keele L, Titiunik R. Natural experiments based on geography. PSRM 2015 Apr 08;4(1):65-95. [doi: 10.1017/psrm.2015.4]
38. McKee M, Britton A, Black N, McPherson K, Sanderson C, Bain C. Methods in health services research. Interpreting the evidence: choosing between randomised and non-randomised studies. BMJ 1999 Jul 31;319(7205):312-315 [FREE Full text] [doi: 10.1136/bmj.319.7205.312] [Medline: 10426754]
39. MacLehose R, Reeves B, Harvey I, Sheldon T, Russell I, Black A. A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies. Health Technol Assess 2000;4(34):1-154 [FREE Full text] [Medline: 11134917]
40. Patton M. Qualitative research and evaluation methods. Thousand Oaks: Sage; 1990.
41. McCrone P, Knapp M, Proudfoot J, Ryden C, Cavanagh K, Shapiro D, et al. Cost-effectiveness of computerised cognitive-behavioural therapy for anxiety and depression in primary care: randomised controlled trial. Br J Psychiatry 2004 Jul;185:55-62. [doi: 10.1192/bjp.185.1.55] [Medline: 15231556]
42. Murphy S, Irving C, Adams C, Waqar M. Crisis intervention for people with severe mental illnesses. Cochrane Database Syst Rev 2015 Dec 03(12):CD001087 [FREE Full text] [doi: 10.1002/14651858.CD001087.pub5] [Medline: 26633650]
43. Malone D, Newron-Howes G, Simmonds S, Marriot S, Tyrer P. Community mental health teams (CMHTs) for people with severe mental illnesses and disordered personality. Cochrane Database Syst Rev 2007 Jul 18(3):CD000270 [FREE Full text] [doi: 10.1002/14651858.CD000270.pub2] [Medline: 17636625]
44. Catty J, Burns T, Knapp M, Watt H, Wright C, Henderson J, et al. Home treatment for mental health problems: a systematic review. Psychol Med 2002 Apr;32(3):383-401. [doi: 10.1017/s0033291702005299] [Medline: 11989985]

Abbreviations

BSCL: Brief Symptom Checklist
CEAC: Cost-Effectiveness Acceptability Curve
CPC: Cantonal Psychiatric Clinic
CRHT: Crisis Resolution and Home Treatment
HoNOS: Health of the Nation Outcome Scales
ITT: intention to treat
RCT: randomized controlled trial
SPPM: Service of Psychiatry and Psychological Medicine
SPS: sociopsychiatric service

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Protocol

Longitudinal Neurocognitive and Pulmonological Profile of Long COVID-19: Protocol for the COVIMMUNE-Clin Study

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Abstract

Background: There is a dearth of information about “brain fog,” characterized by concentration, word-finding, or memory problems, which has been listed in the new World Health Organization provisional classification “U09.9 Post-COVID-19 Condition.” Moreover, the extent to which these symptoms may be associated with neurological, pulmonary, or psychiatric difficulties is unclear.

Objective: This ongoing cohort study aims to carefully assess neurocognitive function in the context of the neurological, psychiatric, and pulmonary sequelae of SARS-CoV-2 infection among patients with asymptomatic/mild and severe cases of COVID-19 after remission, including actively recruited healthy controls.

Methods: A total of 150 participants will be included in this pilot study. The cohort will comprise patients who tested positive for SARS-CoV-2 infection with either an asymptomatic course or a mild course defined as no symptoms except for olfactory and taste dysfunction (n=50), patients who tested positive for SARS-CoV-2 infection with a severe disease course (n=50), and a healthy control group (n=50) with similar age and sex distribution based on frequency matching. A comprehensive neuropsychological assessment will be performed comprising nuanced aspects of complex attention, including language, executive function, verbal and visual learning, and memory. Psychiatric, personality, social and lifestyle factors, sleep, and fatigue will be evaluated. Brain magnetic resonance imaging, neurological and physical assessment, and pulmonological and lung function examinations (including body plethysmography, diffusion capacity, clinical assessments, and questionnaires) will also be performed. Three visits are planned with comprehensive testing at the baseline and 12-month visits, along with brief neurological and neuropsychological examinations at the 6-month assessment. Blood-based biomarkers of neurodegeneration will be quantified at baseline and 12-month follow-up.

Results: At the time of submission, the study had begun recruitment through telephone and in-person screenings. The first patient was enrolled in the study at the beginning of April 2021. Interim data analysis of baseline information is expected to be complete by December 2021 and study completion is expected at the end of December 2022. Preliminary group comparisons indicate worse word list learning, short- and long-delayed verbal recall, and verbal recognition in both patient cohorts compared

with those of the healthy control group, adjusted for age and sex. Initial volumetric comparisons show smaller grey matter, frontal, and temporal brain volumes in both patient groups compared with those of healthy controls. These results are quite robust but are neither final nor placed in the needed context intended at study completion.

Conclusions: To the best of our knowledge, this is the first study to include objective and comprehensive longitudinal analyses of neurocognitive sequelae of COVID-19 in an extreme group comparison stratified by disease severity with healthy controls actively recruited during the pandemic. Results from this study will contribute to the nascent literature on the prolonged effects of COVID-19 on neurocognitive performance via our coassessment of neuroradiological, neurological, pulmonary, psychiatric, and lifestyle factors.

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KEYWORDS

SARS-CoV-2; COVID-19; postacute COVID-19 syndrome; cognition; neuropsychology; lung; magnetic resonance imaging

Introduction

Background

Prolonged symptoms among patients after resolution of initial SARS-CoV-2 infection are becoming increasingly salient. In addition to long-term respiratory problems and chronic fatigue, patients may also have trouble with concentration and memory as well as psychiatric or neurological complications [1]. These may also occur after an asymptomatic course of the infection; hence, the effect of disease severity remains unclear. One of the most common self-reported symptoms among patients is “brain fog,” which is also denoted as “mental fog” or “clouding of consciousness” [2]. These terms refer to a reduction in alertness and awareness of the environment, an inability to concentrate, and confusion, and can have many causes. Although the term “brain fog” offers an intuitive shorthand for this experience, it is not an official medical diagnosis with clear definitions. In addition, the reported frequency of this experience varies widely depending on the study. These symptoms may ensue myriad other disorders and dysfunctions, including organ dysfunctions, psychological burdens, and disorders such as sleep disturbance and chronic fatigue. Objective data of cognitive performance after acute SARS-CoV-2 infection is, so far, scarce.

An online patient-led survey of COVID-19 patients (N=3762, 78% women, 1.7% nonbinary) sponsored by University College London yielded self-reported fatigue, postexertional malaise, and cognitive dysfunction more than 6 months after initial COVID-19 infection as the most prevalent symptoms from a diverse range of other outcomes [2]. Specifically, subjectively experienced brain fog/cognitive dysfunction was reported by 55.5% of participants and memory problems were self-reported by 50.5% of participants. However, among the small subset of those who reported long-term cognitive or memory difficulties who also had a brain scan, only 13.1% (52/397) revealed neuroradiological correlates.

Such diverse symptoms are proposed to belong to a syndrome now denoted variously as “Long Covid” [3], “persistent post-COVID syndrome” [4], or “post-acute sequelae of SARS-CoV-2 infection” [5], and affected patients have been described as “COVID-19 long haulers” [6]. Although COVID-19 symptoms can now be provisionally classified using the emergency code “U09.9 Post-COVID-19 Condition” from Chapter 22 of the International Classification of Diseases as of January 1, 2021, there are currently no specifications or consensus definitions other than an assumed postpriori connection to acute infection. Such manifestations in COVID-19 patients warrant careful study in an objective, quantifiable, and nuanced manner in the context of possible confounding or contributing factors.

To our knowledge, objective reports of cognitive outcomes are still quite limited. A North American University of Washington study assessed subjective symptoms using an electronic follow-up questionnaire 3-9 months after the onset of SARS-CoV-2 infection. This sample included 177 recovered COVID-19 patients presenting at a specialized clinic (mean age 48.0, SD 15.2 years; 57% women) and a small number of healthy participants (mean age 50.8, SD 15.8 years; n=21, 52% women) [1]. The number of inpatients (16/177, 9.0%) was quite small compared to outpatients (150/177, 84.7%). In addition, 11 (6.2%) patients with asymptomatic courses during the acute infection phase who never presented at the hospital were included in the cohort. The most commonly reported symptoms post-COVID-19 (assessed via self-report) were fatigue and loss of smell in approximately 14% of patients. Brain fog was present in a mere 2.3% of the sample. Around a third of patients reported worse health-related quality of life and approximately 8% reported difficulty with regard to daily activities, most commonly household chores. Persistent symptoms occurred more frequently in those over 64 years of age (13/30, 43%) compared with patients under 65 years of age (42/147, 29.6%). The age structure of the total cohort included comparatively few older patients (30/177, 16.9% of the total cohort), who are commonly known to have more severe courses of COVID-19 and may be at higher risk of later complications [1].

In contrast to these findings, another North American study performed at the Northwestern Memorial Hospital, Chicago, Illinois, analyzed 50 COVID-19 laboratory-positive and 50 COVID-19 laboratory-negative acute cases [2]. All patients were seen at a specialized neurological COVID-19 outpatient clinic between May 13 and November 11, 2020. Both groups

had met the characteristic clinical manifestations of COVID-19 and had neurological complications attributed to a suspected SARS-CoV-2 infection for up to 6 weeks, such as headache, numbness, tingling, and fatigue. No demographic differences were found, with an overall average age of 43.2 (SD 11.3) years, and 70% were women. The laboratory-positive patients were examined on average 4.72 (SD 1.83) months after symptom onset, which was approximately 1 month earlier than the laboratory-negative group at an average of 5.82 (SD 1.56) months. Self-reports were used to assess neurological, cognitive, and quality of life symptoms via a computer-based televisit. Across groups, patients reported equal amounts of fatigue (85%) and brain fog (81%), along with depression or anxiety (47%), which were the most frequent symptoms. Cognitive function was assessed in person in a subset of 36 patients using the National Institutes of HealthToolbox v2.1 instrument. Interestingly, the groups did not differ on any measure of executive function, attention, working memory, or processing speed in this study, which may rather reflect the health status of the comparison group (who may indeed have had undetected SARS-CoV-2 infections despite laboratory testing). When positive SARS-CoV-2 patients were compared to matched US normative data, they performed significantly worse on tests of attention and working memory by more than half a standard deviation.

A Zhejiang University School of Medicine in Hangzhou study of a small group of COVID-19 patients (mean age 47, SD 10.54 years; n=29, 3% women) and controls (mean age 42.48, SD 6.94 years; n=29, 59% women) showed discreet difficulties in three parameters of sustained attention in a self-administered, iPad-based online test battery [3]. The tests are part of the MATRICS Consensus Cognitive Battery validated for the Chinese population [4]. The neuropsychological data appear to have been collected in the early postinfection period (ie, 2-3 weeks after infection). It was not reported how many of the cohort were hospitalized or rather seen in an outpatient setting nor how severe the initial course of COVID-19 had been.

Further, an Italian study of 38 patients (mean age 53.45, SD 12.64 years; 29% women) assessed patients hospitalized in Milan between February and April 2020 for complications of SARS-CoV-2 infection [5]. Neuropsychological testing was performed at 4.43 (SD 1.22) months after discharge using the Brief Repeatable Battery of Neuropsychological Tests used in multiple sclerosis research [6]. Patients were screened beforehand with the Montreal Cognitive Assessment (MoCA; cutoff>18.28 points) to exclude those with dementia or cognitive decline. Slowed cognitive processing speed was identified in over 40% of patients; delayed verbal recall impairment was found in 26%, with an overlap in these deficits in 21% of the cohort. More than 60% of all patients performed below the normal cutoff score on at least one cognitive parameter. The average verbal and spatial memory scores were more than half a standard deviation below the norm mean. The average cognitive speed score for COVID-19 patients was more than one standard deviation below the mean of the Italian norm population [6]. Measures of verbal recall were worse for older patients over 55 years (n=20) compared to younger patients with moderate effect sizes, as calculated by us. Importantly, a subanalysis of 33 (87%) subjects of this cohort was selected based on the presence or absence of acute respiratory distress syndrome (ARDS). Those with ARDS (n=12) during hospitalization were compared to those without ARDS (n=21). Despite these small samples, remarkably worse performance for those with ARDS compared to those without were found (based on our effect size calculations derived from data reported in the article: verbal long-term storage (Cohen d=1.05), delayed verbal recall (Cohen d=0.97), and a challenging variant of a test of speed-dependent sustained attention and working memory task (Cohen d=2.63).

In addition to respiratory difficulties, which may be linked to outcomes such as fatigue or brain fog in a very direct manner, neurological complications of COVID-19 themselves may confer a higher risk of incurring cognitive difficulties in both the short and long term [7,8]. Various types of neurological damage and disease may follow COVID-19 with such diverse manifestations as chemosensory disorders, muscular damage, encephalopathy, delirium, coma, meningitis, encephalitis, cerebrovascular diseases, and peripheral and central neuroimmunological disorders [7,8]. Neurological damage has been hypothesized to belong to four types: (1) neurological consequences of pulmonary disease and associated systemic disease (systemic inflammatory response syndrome, sepsis); (2) direct invasion of the virus into the central nervous system (CNS); (3) those caused by postinfectious, immune-mediated complications, including Guillain-Barré syndrome or acute disseminated encephalomyelitis; and (4) peripheral organ dysfunction or failure [1,3]. Indeed, neurological complications of COVID-19 may derive from an amalgam of these four types [8].

Further, psychological distress and psychiatric disorders may directly relate to worse long-term cognitive performance among COVID-19 patients; however, it is known that the general population also presents higher rates of psychiatric burden since the start of the pandemic. Therefore, there is a need to take public health aspects of the COVID-19 pandemic into account in understanding the specific effects of SARS-CoV-2 infection, which requires active recruitment of control groups since the start of the pandemic.

A recent retrospective analysis gives indications of newly diagnosed neurological and psychiatric disease within the first 180 days after SARS-CoV-2 infection (mean age 46, SD 19.7 years; N=236,379, 55.6% women, 0.04% other), which are directly relevant to the phenomenon of “brain fog” and cognition [9]. This cohort comprised mostly nonhospitalized patients (80.4%; mean age 43.3, SD 19.0 years) and around 20% hospitalized patients (mean age 57, SD 18.7 years). Just under 4% were at the intensive care unit (ICU) (mean age 59.1, SD 17.3 years) and around 3% had encephalopathy (mean age 66.7, SD 17.0 years). In total, 33.62% (95% CI 33.17-34.07) of COVID-19 patients had one neurological or psychiatric symptom, with less than half that number being initial presentations (12.84%, 95% CI 12.36-13.33) after infection. Using a propensity-score matching approach, separate COVID-19 cohorts were compared to cohorts with influenza or other respiratory tract infections (RTIs). In the matched comparison of COVID-19 patients (mean age 39.7, SD 18.4

years; n=105,579, 58.6% women) to a sample of influenza patients (mean age 38.6, SD 19.7 years; n=105,579, 57.6% women), a higher hazard ratio (HR) was found for COVID-19 patients for the incidence of any of 14 neurological or psychiatric outcomes (1.78, 95% CI 1.68-1.89). When compared to the matched RTI cohort (mean age 46.0, SD 20.4 years; n=236,038, 56.3% women), the COVID-19 cohort (mean age 45.9, SD 19.7 years; n=236,038, 55.7% women) displayed a significantly higher HR for any first outcome (1.32, 95% CI 1.27-1.36) [9]. Thus, COVID-19 was associated with a higher risk for neurological and psychiatric outcomes compared to rates found in patients with influenza or other respiratory diseases *prior* to the pandemic.

Turning to the relevance of assessing post-COVID-19 sequelae for the world population, other viruses that have run their course, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) are valuable sources of information [10]. Specifically, Ellul et al [10] reported CNS diseases among 0.04% of SARS and 0.20% of MERS case counts. The authors extrapolated from the then-current worldwide minimum COVID-19 case count in July 2020 that 1800-9600 patients worldwide were likely to suffer from CNS symptoms. The case count has increased to almost 198 million (as of August 2, 2021) [11], which yields an estimate of anywhere between 79,000 and close to 400,000 patients worldwide who may currently have verifiable CNS symptoms (Table 1).

Table 1. Extrapolations of rates of central nervous system (CNS) complications from COVID-19 according to current case counts using estimates from Ellul et al [10] based on severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) for selected regions and countries.

Disease	CNS complication base rate (%) [10]	Extrapolated CNS complications from COVID-19, n					
		World[a]	Europe[b]	Germany[a]	United States[a]	India[a]	Brazil[a]
SARS	0.04	79,335	1511	13,774	14,001	12,678	7975
MERS	0.20	396,673	7557	68,872	70,007	63,392	39,877

[a]Based on the COVID-19 web-based dashboard from Johns Hopkins Coronavirus Resource Center accessed August 2, 2021 [11].

[b]Based on the COVID-19 situation update for the European Union/European Economic Area, as of July 30, 2021 [12].

Although epidemiological models of COVID-19 spread show the difficulty of knowing how it will continue (eg, drops due to vaccinations, potential for herd immunity) or what mutations may portend, it is worthwhile to consider hypothetical future population saturation rates and their consequences [13]. Based on the last reported world population estimates from the United Nations of just over 7.7 billion people [14], and extrapolating the base rates of CNS complication in SARS and MERS from Ellul et al [10], we calculated the dimensions of potential CNS damage for the World, Europe, Germany, the United States, India, and Brazil, which are listed for the purpose of illustration in Table 2 (this listing is neither exhaustive nor necessarily reflective of future outcomes in any given region or country). A saturation rate of 30% of the world population by the time the pandemic subsides could lead to between 93 million to around half a billion CNS symptom sufferers worldwide. A 70% saturation rate by the end of the pandemic could lead to between around 220 million to almost 1.1 billion CNS symptom sufferers worldwide. These estimates do not take into account the symptoms that are harder to objectify but are often reported by patients after COVID-19, such as fatigue, “brain fog,” or concentration or memory problems. These estimates also do not account for neuropsychiatric disorders.

Table 2. Extrapolations of central nervous system (CNS) complications from COVID-19 based on hypothetical saturation rates of the world population by the end of the pandemic according to base rate estimates using severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) data [10].

Population	Population size (millions), n[a]	CNS complications based on hypothetical saturation rates, n	
		30% saturation	70% saturation
Global	7794.80		
SARS (0.04%)		93,537,600	218,254,400
MERS (0.20%)		467,688,000	1,091,272,000
Europe	747.636		
SARS (0.04%)		8,971,632	20,933,808
MERS (0.20%)		44,858,160	104,669,040
Germany	83.7839		
SARS (0.04%)		1,005,406	2,345,949
MERS (0.20%)		5,027,034	11,729,746
United States	331.00		
SARS (0.04%)		39,720,000	92,680,000
MERS (0.20%)		198,600,000	463,400,000
India	1380.00		
SARS (0.04%)		16,560,000	38,640,000
MERS (0.20%)		82,800,000	193,200,000
Brazil	1380.00		
SARS (0.04%)		2,550,720	5,951,680
MERS (0.20%)		12,753,600	29,758,400

[a]Population mid-2020 estimates from the United Nations [14].

In contrast to these comparatively conservative estimates, Taquet et al [9] found a much higher base rate of neurological sequelae of 2.1% following SARS-CoV-2 infections, which may indicate upward of 4,165,061 cases of neurological sequelae (CNS and peripheral nervous system [PNS]) worldwide, with around 70,000 in Germany and 750,000 in Europe alone (see Table 3). This indicates the much higher rates of outcomes extrapolated to several countries and regions for purposes of illustration (the list is not exhaustive). A more detailed breakdown of CNS versus PNS rates is not possible to extract from the reported data due to multiple comorbidities in the sample population.

Table 3. Extrapolations based on the latest case counts using the base rates from Taquet et al [9] of first presentation of neurological and neuropsychiatric outcomes after SARS-CoV-2 infection for select regions/countries.[a]

Neurological and psychiatric outcomes	Base rates (%) [9]	Case counts, n					
		World[b] (N=198,336,258)	Germany[b] (N=3,778,277)	Europe[c] (N=34,435,890)	United States[b] (N=35,003,546)	India[b] (N=31,695,958)	Brazil[b] (N=19,938,358)
Neurological	2.10	4,165,061	79,344	723,154	735,074	665,615	418,706
Any psychiatric disorder (mood, anxiety, psychotic)	8.63	17,116,419	326,065	2,971,817	3,020,806	2,735,361	1,720,680
Substance misuse	1.92	3,808,056	72,543	661,169	672,068	608,562	382,816
Insomnia	2.53	5,017,907	95,590	871,228	885,590	801,908	504,440
Any first outcome	12.84	25,466,376	485,131	4,421,568	4,494,455	4,069,761	2,560,085

[a]This table is for illustrative purposes only and is neither exhaustive nor necessarily reflective of the future outcomes in any given country or region.

[b]From the COVID-19 web-based dashboard of Johns Hopkins Coronavirus Resource Center accessed August 2, 2021 [11].

[c]Based on the COVID-19 situation update for the European Union/European Economic Area as of July 30, 2021 [12].

Turning to possible mechanisms of neurological damage that may lead to cognitive problems, two lines of research should be highlighted. One is direct infiltration into the brain, possibly via angiotensin converting enzyme-2 (ACE2) receptors, and

another is more indirectly due to acute systemic inflammation. It is known that SARS-CoV-2 viral cells specifically bind to ACE2 receptors, which are expressed in brain structures such as the olfactory bulb, hypothalamus, and limbic system [15]. However, to date, there is still no certainty about how or to what extent SARS-CoV-2 cells may enter the brain directly. Human autopsy studies show little to no direct infiltration of the brain [16,17], although a strong and widespread systemic inflammatory response is apparent [18].

A post-COVID-19 condition may, in fact, reflect more general phenomena that have been documented in the wake of several severe inflammatory diseases and syndromes. Based on our own work among sepsis patients [19], we contend that the hippocampus may be one of the earliest and most affected structures of the brain during chronic or acute inflammatory states due to its particular vulnerability to neuroinflammatory events. Various animal models of acute systemic inflammation show cognitive impairment (especially learning and memory) as well as CNS dysfunction (especially in the hippocampus) after resolution of the initial inflammatory response [20-23]. This may be due to intimate structural connections between the limbic system, which undergirds both the emotional response and several cognitive abilities, and the hypothalamus, which has a central role in the immune-brain connection [24].

As seen among other inflammatory conditions such as sepsis and after major surgery or respiratory conditions such as pneumonia and ARDS, long-term consequences can negatively affect a person's life in many aspects [25-29]. Several areas of daily activities, including employment, education, housework, and hobbies, can be difficult or impossible years after the initial inflammatory syndrome has been resolved. The psychiatric burden (eg, anxiety, depression, posttraumatic stress disorder) is also known to increase after hospitalization for severe illnesses, which shows associations with cognitive disorders [30,31].

Accordingly, a systematic and thorough study of cognitive ability in the context of neurological and pulmonological complications, activities of daily living, psychiatric health, fatigue, sleep, and other key psychological factors is needed to understand the nature of COVID-19 sequelae. It is therefore pertinent to first examine cognitive abilities among symptomatic and mildly symptomatic/asymptomatic patients to characterize the nature of impairment and its associations with the severity of acute infection. Second, multiple known potentially contributing factors such as CNS or respiratory damage need to be examined. Third, the increased psychiatric burden of the general population and of COVID-19 patients should be addressed, as well as general changes during the pandemic, which requires recruitment of a prospective healthy control cohort. This is the intention of the pilot study, "Long-term Consequences of COVID-19 for Pulmonary and Neurocognitive Disorders (COVIMMUNE-Clin)," outlined herein.

The current understanding of the long-term cognitive sequelae of COVID-19 is limited. Certainly, it remains unclear whether cognitive trajectories are stable, fluctuate, or generally improve or worsen over the long term. There is an urgent need to clarify the extent to which cognitive changes are due to individual or collective experiences or to biological changes from SARS-CoV-2 infection.

Objectives

We will compare the neurocognitive function and pulmonary sequelae of SARS-CoV-2 infection among patients with asymptomatic/mild and severe cases of COVID-19 after remission of infection as well as in comparison to those of actively recruited healthy controls.

Methods

Research Consortium

This is one of three subprojects within a three-pronged research consortium entitled "COVIMMUNE-Studies on immune system function and disease progression of COVID-19." An investigator at the University Hospital Bonn leads each subproject. The goals of the consortium are to understand the interplay of genetic, epigenetic, and environmental factors that influence innate and adaptive immune responses to SARS-CoV-2, and their links to the broad clinical spectrum of COVID-19 and the associated long-term lung and CNS pathologies.

Ethical Considerations

This study is being conducted according to the World Medical Association Declaration of Helsinki; the Regulation (EU) No 536/2014 of the European Parliament and of the Council of April 16, 2014, on clinical trials on medicinal products for human use; as well as local ethical research guidelines and research guidelines of University Hospital Bonn (Regulations for ensuring good scientific practice) and the European General Data Protection Regulation (EU) 2016/679 [32-34]. The study protocol was thoroughly reviewed for German data protection compliance by the local data protection officer prior to submission for ethical approval. The study protocol was reviewed by the local Internal Review Board (Medical Ethics Review Board of the University of Bonn Medical Center, ID 511/20) and final approval was obtained on March 10, 2021.

This study is registered at the German Clinical Trials Registry (primary registry trial identifier: DRKS00023806; registration date: March 16, 2021, cross-referenced at the World Health Organization International Clinical Trials Registry Platform).

This pilot study is being conducted exclusively by trained and qualified medical investigators, psychologists, and study nurses who have current Good Clinical Practices certifications.

All participants are informed both in writing (participant information) and verbally by (medical) study investigators regarding all important aspects of the study, including risks and benefits to the individual participant. Participants have sufficient time to process this information and ask any questions prior to providing consent. Each participant gives written consent before taking part in any study-specific procedure. As part of the informed consent process, participants are made aware of the rationale for the study; scope of the study; benefits and risks of study participation; storage and use of data, including data protection measures within the study; data protection rights; the right to withdraw consent at any time; and the right to access their own study data.

Study Design

This is a monocentric longitudinal prospective cohort study at the University Hospital of Bonn. Assessments will be conducted at three time points (baseline, 6 months, and 12 months) for all participant groups.

Study Population

A total of 150 participants between the ages of 25 to 75 years will be included in the study. Inclusion and exclusion criteria for the study are presented in Textbox 1. The first cohort (Cohort I) will comprise patients after a SARS-CoV-2 infection with either an asymptomatic course (n=50) or, at most, those who had symptoms of olfactory or taste dysfunction (anosmia, ageusia) only; all other symptoms lead to exclusion from this arm. The second cohort (Cohort II) will include patients after SARS-CoV-2 infection with a severely affected course (n=50), defined as having been admitted to hospital (any ward type) for at least 24 hours due to SARS-CoV-2 infection at any time during the course of the disease. The third cohort (Cohort III) is a healthy control group (n=50) with a similar age and sex distribution to those of the other cohorts, based on frequency matching. For the healthy control arm, a SARS-CoV-2 rapid antibody test will be administered at screening to exclude recent or active infection. We anticipate that the antibody test will reflect those who have developed SARS-CoV-2 antibodies due to SARS-CoV-2 vaccination and this will not exclude them from participation. Further, to exclude those with verbal episodic memory abnormalities before inclusion in the healthy control group, the Hopkins Verbal Learning Test will be administered as a screening method [35]. The exclusion criterion will be long-delayed verbal recall of less than –1.0 SD below the age-specific reference norm value. Additional inclusion criteria for the healthy control group are denial of memory concerns and no known history or current diagnosis of psychiatric or neurological illness.

Textbox 1. Summary of inclusion and exclusion criteria.

General inclusion criteria

- written informed consent
- aged 25 to 75 years
- able and willing to participate throughout the study
- fluent German language abilities

Cohort-specific inclusion criteria

Cohort I: Asymptomatic course of COVID-19 (SARS-CoV-2–positive) or mild course (ie, no symptoms other than anosmia and/or ageusia)

Cohort II: severely affected course of COVID-19 (SARS-CoV-2–positive) (ie, requiring hospital stay)

Cohort III: Healthy controls will only be included in the study if they also meet all of the following criteria:

- must perform >–1.0 SD on the Hopkins Verbal Learning Test
- no substance abuse
- no known history of or current diagnosed psychiatric illness
- negative SARS-CoV-2 rapid antibody test at baseline

General exclusion criteria

- inability to give informed consent
- any condition that clearly interferes with participation in the study
- any condition that interferes with the clinical or neuropsychological study procedures
- sensory impairment that prevents or significantly interferes with neuropsychological testing
- contraindication for magnetic resonance imaging
- severe or unstable medical condition
- current major depressive episode
- psychotic disorder, bipolar disorder, substance abuse at present or in the past
- known neurodegenerative disorder (Alzheimer disease, Parkinson disease, frontotemporal dementia, Huntington disease, amyotrophic lateral sclerosis)
- vascular dementia, history of stroke
- history of malignant disease

Recruitment Strategy

Two patient cohorts are being recruited directly via letter. The first cohort derives from the German COVID-19 Case Cluster Study (Heinsberg Study). This study cohort comprises several patients severely affected by COVID-19 who are likely to be at increased risk of subsequent cognitive decline, as well as a large number of mild or asymptomatic cases. Second, SARS-CoV-2–positive patients that have been treated since February 2020 at the University of Bonn Medical Center will be identified by the patient record system or by our COVID-19 outpatient unit, and will then be contacted by letter. In addition, as needed, we will recruit participants for all groups of the study via advertisement on our website, popular social media platforms, and in newspapers. These diverse recruitment methods will indicate an email address for potential participants to contact directly. Those expressing interest in participation will be contacted by our study team via telephone and will undergo a brief telephone screening with the help of a standardized guideline for identifying potential participants.

All participants will be informed and give consent prior to any study-specific procedure.

Study Procedures

The three groups will be enrolled in a sequential manner to ensure a similar structure with regard to age and sex. The individual assessments will vary from visit to visit. All assessments will take place on one study day. The following will be assessed or carried out for all participants after providing written informed consent and review of the inclusion and exclusion criteria: demographics, medical/surgical history, medical/disease status, neurological examination, blood chemistry, neuropsychological examination, magnetic resonance imaging (MRI), lung function assessment, and (for the healthy controls only) a SARS-CoV-2 rapid antibody test.

Neurocognitive Examination

The neurocognitive assessment will include comprehensive, standardized, and validated neuropsychological tests, questionnaires, and scales to assess pandemic-related changes on lifestyle, psychological health, sleep, psychiatric symptom burden, and basic and instrumental activities of daily living. Trained, qualified personnel will conduct the neuropsychological assessments at the Department of Neurodegenerative Diseases and Geriatric Psychiatry.

Part of the neuropsychological assessment will be a specially selected, comprehensive computerized assessment with the Vienna Test System (Wiener Testsystem Version 8.15, Schuhfried, Mödling). This will comprise normed, standardized tests for the following domains: complex attention; verbal learning and memory; visual-spatial learning and memory; semantic verbal abilities; and psychological scales for depression, anxiety, and somatic illness.

The primary endpoint of this study is an episodic memory measure due to the posited vulnerability of the hippocampus to effects of systemic inflammation and loss of integrity of the blood-brain barrier in neurovascular and neurodegenerative diseases [36-38]. Since the immune response to SARS-CoV-2 infection itself could increase the risk of developing a cognitive disorder such as mild cognitive impairment or dementia, we chose to include the types of tests commonly used in the diagnostic workup at memory clinics as well as an extensive battery of computerized attentional, executive function tasks.

In addition, we will ask a series of self-report questions regarding changes in memory and general cognitive ability compared to before onset of the acute phase of COVID-19 using a modified version of the Everyday Cognition-12 questionnaire [39]. For healthy controls, we will ask the same questions with the reference point being before the beginning of the pandemic. This is an effort to compensate for the fact that we cannot exclude those with cognitive difficulties prior to SARS-CoV-2 infection in Cohorts I and II.

Other scales used include instrumental activities of daily living, a COVID-19-specific scale of basic activities of daily living (Post-COVID-19 Functional Scale-German) [40], health-related quality of life, and a short screening scale for posttraumatic stress disorder. Owing to established associations between cognitive decline and neuroticism [41], scales will be implemented to assess personality along the dimension neuroticism-extraversion [42]. Further, important lifestyle factors will be explored, including leisure activities and satisfaction with one's financial situation, perceived loneliness and social isolation, perceived changes in responsibilities at work and at home, and maintenance of intellectual and daily activities [43-46].

Lastly, loss of smelling ability has been connected to systemic inflammation and neurodegenerative disease as well as SARS-CoV-2 infection [47]. Hence, olfaction will be assessed by the Sniffin' Sticks Test of Smelling Ability (Screening 12 Test, Burghart Messtechnik GmbH) based on the "Odor-Curves-On-Paper" Method [48]. This method enables safe and hygienic testing conditions and has been validated in earlier studies [49].

Neurological and Physical Assessment

As part of the initial medical workup, medical doctors will assess the medical history and current medications. Concomitant medication, procedures, and medical diagnoses will be documented at each follow-up. In addition, orienting tests of visual, auditory, and olfactory function will be performed. Body weight and height will be measured at the first visit, and heart rate as well as blood pressure will be measured at the first and last visits. At each visit, a neurological examination will be performed. This examination includes analysis of mental status, cranial nerves, motor system, reflexes, sensory system, coordination, and gait assessment.

Blood Samples

The amount of blood taken at each individual blood draw (baseline and 12-month follow-up) is approximately 18 milliliters. Samples will be drawn by a certified nurse or a medical doctor who is a member of entrusted study personnel for patients and healthy control subjects. Each blood sample includes serum and ethylenediaminetetraacetic acid (EDTA)-plasma, which will be divided into 200-microliter

aliquots immediately after sampling and stored at –80°C until biomarker assessment.

Biomarker Panel

Analysis of blood biomarkers of neurodegeneration will be performed by SIMOA Quanterix assays using fully automated HD-X platforms. Samples will be run in duplicates with a maximum accepted coefficient of variation of 20%. Our design includes sufficient backup material to repeat measures in case of technical failures, if necessary. The biomarker panel includes neurofilament light chain and neuron-specific enolase (NSE). Samples will be analyzed once after conclusion of the baseline recruitment to address analytes with potentially limited long-term storage stability such as NSE [50]. Different sampling methods that might impact the results of blood-based neurodegeneration markers are still under investigation and recommendations might change during the study [51,52]. Our design includes sufficient amounts of both serum and EDTA-plasma to adapt to new findings on preanalytics at the time of analysis and to choose the optimal sample type for each analyte.

SARS-CoV-2 Rapid Antibody Test

The Acro 2019-nCoV IgG/IgM Rapid Test (Hangzhou Alltest Biotech Co, Ltd, China) is a reliable and rapid chromatographic immunoassay for the qualitative detection of SARS-CoV-2 immunoglobulin (Ig)G and IgM antibodies in human whole blood, serum, and plasma samples. A certified nurse or a medical doctor who is a member of entrusted study personnel will draw the whole blood sample. The SARS-CoV-2 rapid antibody test will be administered at screening and at the 12-month visit only for the healthy control arm of the study.

Pulmonological and Lung Function Examinations

The pulmonological and lung function examinations will take place at the Department of Internal Medicine (Pneumology) and include forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), Tiffeneau index (FEV1/FVC), and diffusion capacity for carbon monoxide by the single-breath method. Clinical pulmonological and lung function assessments will include assessment of dyspnea, cough, fatigue, dizziness, chest pain, anxiety, a lung function test, body plethysmography, a 6-minute walking distance test, quality of life questionnaires, and a shortness of breath questionnaire.

MRI Assessments

At baseline and at 12 months, subjects will undergo MRI according to a standardized clinical protocol at the Department of Neuroradiology on a clinical 3.0 Tesla magnet (Achieva, Philips Healthcare, Best, the Netherlands). Sequences will comprise 3D magnetization-prepared rapid acquisition with gradient echo, fluid attenuated inversion recovery, diffusion, susceptibility weighted imaging, T2-weighted image, and diffusion tensor imaging. Volumetric analysis will be conducted at the Department of Neuroradiology. The acquired MRI datasets will be visually and semiquantitatively assessed by an experienced radiological examiner. In addition, postprocessing of the MRI datasets will be performed using CE-certified artificial intelligence–based software (mdbrain, Mediaire GmbH, Heidelberg, Germany), which allows for automated quantitative analyses of the brain and determines volumes of different brain areas in milliliters as well as age- and sex-adjusted percentiles of a (manufacturer-dependent) normative collective.

Data Analysis

Statistical Analysis

Demographic background, clinical, and biomarker variables will be analyzed in both patient populations and in healthy controls. Additional analyses will be performed for cognitive and neurological data, lung function, MRI, psychiatric burden, and the activities of daily living and health-related quality of life scales. Quantitative variables will be presented in summary statistics of number of patients, mean (SD), and median (range) by appropriate group and time point. Qualitative variables will be described using the frequency count of the events, and the number and percentage of responding patients. The primary and secondary endpoints will be analyzed in an exploratory manner utilizing mixed models and correlational analysis. Statistical analysis will be performed using IBM SPSS Statistics Version 25, 64-Bit Version (IBM Corp, 2017).

Preliminary data based on the Auditory Word List Test reported here were analyzed via multivariate analysis of variance and pairwise effect sizes were calculated based on Hedges *g*, which allows for effect size calculation with different group sizes.

Sample Size Calculation

A power analysis was performed on the basis of the primary endpoint: long-delayed verbal recall from the word list recall task of the Vienna Testing System's Auditory Verbal Learning Test [53]. This parameter was chosen due to the close association of long-delayed recall and hippocampal integrity [54], as well as the hypothesized vulnerability of hippocampal function to complications following COVID-19. In earlier studies, a medium-size difference was observed between healthy controls and patients with dementia [53]. Given the current state of knowledge of the study population, we also feel confident in assuming a medium-sized effect for our study. An a priori analysis of sample size was performed based on a medium effect size (f=0.28), a type 1 error probability of 5%, power of 80%, and 3 groups. The outcome parameters yielded a required total sample size of 126 and an estimated actual power of 80%. This resulted in a group size of 42 per arm of the study, which we increased to 50 per arm to account for potential losses to follow-up. To deal with possible SARS-CoV-2 infection of healthy volunteers during the course of the study, 20 more healthy control participants will be recruited for a total of 70 healthy controls.

Results

Schedule

Funding for this subproject was granted to the principal investigator (MTH) at the Department of Neurodegenerative Diseases and Geriatric Psychiatry and the coprincipal investigator (DS) at the Department of Internal Medicine II, Cardiology, Pneumology and Angiology at the University of Bonn Medical Center in Bonn, Germany. This subproject aims at fully characterizing and contextualizing neurocognitive

performance after SARS-CoV-2 infection within the cohorts studied.

At the time of submission, the study had begun recruitment with the first enrollment on April 8, 2021. As of July 2, 2021, 50 participants (aged 26-70 years, 60% women) have been enrolled into the study. An interim data analysis of baseline information is expected to be completed in December 2021. Study completion is anticipated at the end of December 2022 and final results are anticipated to be published after the first quarter of 2023.

Verbal Learning and Memory

Preliminary multivariate data analysis of neurocognitive data collected through July 2, 2021, showed statistically significant differences. Group differences between healthy controls (n=28, 67.9% women; mean age 41.18, SD 11.60 years), patients with asymptomatic/mild COVID-19 (n=9, 44.4% women; mean age 46.22, SD 12.06 years), and patients with a severe COVID-19 course (n=13, 53.8% women; mean age 48.62, SD 12.04 years) were found in several parameters: word list learning, verbal recall short-delayed and verbal recall long-delayed, and verbal recognition. These comparisons are preliminary in nature and the current group sizes are not yet sufficient for such analyses.

Hedges *g* effect sizes were calculated to reveal sample size–corrected differences due to unequal group sizes. Healthy controls outperformed both the asymptomatic/mild and severe patient cohorts in verbal learning and memory parameters with performance in the age-adjusted norms. Large effect sizes were found for healthy controls for wordlist learning, short- and long-delayed recall, and recognition when compared with those of the asymptomatic/mild group. Similarly, when comparing the healthy controls to the severe patient cohort, moderate effect sizes were found for long-delayed verbal recall and recognition. Interestingly, there was a small effect size for wordlist learning and short-delayed verbal recall. Long-delayed verbal recall and recognition showed moderate effect sizes between the asymptomatic/mild and severe patient cohorts, with the former performing worse. These effects are expected to become more robust once the target sample size has been enrolled.

Neuroimaging

Preliminary interim results of baseline neuroradiological MRI examinations of a total of 54 study participants, evaluated by an experienced neuroradiologist, showed no semiquantitative differences in presence, number, and location of medullary lesions and intraparenchymal microbleeds among the different study groups, consisting of healthy control subjects and asymptomatic/mild and severe patients. By contrast, automated measurements of brain tissue volumes or age- and sex-adjusted percentiles tentatively suggest statistically significant group differences in decreased frontal and temporal grey matter brain volumes of patients with severe COVID-19 compared with those of healthy subjects and asymptomatic patients. In addition, patients with severe COVID-19 had statistically significant decreases in measured volume mesiotemporally on both sides compared with that of patients who had an asymptomatic disease course.

Discussion

Preliminary Findings

Cognitive Impairment

Since this is an ongoing study, only preliminary findings could be reported, which included (tentatively) worse performance of COVID-19 patients compared to actively recruited healthy controls on measures of episodic verbal memory (long-delayed verbal recall and verbal recognition) as well as decreased brain volumes in specific brain areas of patients with severe COVID-19 compared with those of healthy subjects and asymptomatic patients.

In line with these findings, short-term lower cognitive performance based on cognitive screening tests such as the MoCA or Mini Mental Status Examination have been reported in the short term (up to 1 month) after acute infection among those with severe COVID-19 courses, ICU stay, and ARDS (n=12) [55], as well as among patients at a COVID-19 rehabilitation unit (n=87) [56]. Further, another larger study (n=135) utilizing the MoCA screening found cognitive impairment, defined as scores below 26 out of 30 possible points, in 23% of their cohort (29%, 30%, and 3% in patients with severe, moderate, and mild COVID - 19, respectively) [57] at a rehabilitation clinic after discharge. In contrast, a point prevalence study at 4 weeks after acute COVID-19, which used the modified Telephone Instrument for Cognitive Status, found no change in cognition in a cohort of 71 patients [58].

In the moderate term (3-5 months) following acute COVID-19, a few small studies indicated some cognitive impairments; however, almost none of these studies used objective episodic memory tasks for assessment. For example, in a small cohort of COVID-19–recovered patients (n=29) studied 3 months after acute infection, cognitive changes were found in a comprehensive test battery, which included memory tasks; however, only a subset of cognitive parameters were reported and none of these included the memory tasks. Compared to actively recruited healthy controls, a few parameters of continuous attention were meaningfully lowered for patients following acute COVID-19 [3].

Our findings are supported by a few small, medium-term studies, which have also found some cognitive impairments after SARS-CoV-2 infection. At 4 months after infection, self-reported cognitive impairment was found in 20.7% (86/416) of a large cohort, including approximately half intensive and half nonintensive hospitalized patients, interviewed by telephone [59]. In a subset of the same study, 17.5% (73/416) reported subjective memory difficulties [59]. This study included a mixture of objective and questionnaire-based assessments of cognitive difficulties, warranting further, careful, objective study. Our study is also in line with a comparable, yet much smaller cohort (n=29) based on an objective cognitive screening (Screen for Cognitive Impairment in Psychiatry Danish Version, SCIP-D), in which at least some cognitive impairment was detected in 19 (65%) patients [60].

Based on a comprehensive neuropsychological test battery (Brief Repeatable Battery of Neuropsychological Tests), further

evidence for cognitive impairment was found at 5 months after discharge in a small (n=38) nonintensive sample of patients hospitalized for complications of SARS-CoV-2 infection [5]. Slower processing speed was reported for 42.1% (16/38) of patients, worse delayed verbal recall was found for 26.3% (10/38) of patients, and worse delayed visuospatial recall was reported for 18.4% (7/38) of patients [5].

In contrast, a very large epidemiological study that included individuals who recovered from COVID-19 and concurrently obtained controls utilized a remote-based intelligence assessment, including short-term verbal memory and verbal as well as spatial working memory, but neither long-term verbal recall nor verbal recognition was assessed [61]. They reported no significant group difference in spatial working memory, although this was at the threshold level and was a main effect for visual attention. The timeframe of remote testing was around 3-4 months after hospital discharge. Importantly, this study hinted at a "dose" effect of SARS-CoV-2 infection on cognitive ability based on a stratification of symptoms and type of care needed (from best to worst cognitive performance: symptomatic patients with versus those without respiratory symptoms, those with respiratory symptoms and no home assistance versus those with medical home assistance, those hospitalized with no ventilation versus those with a ventilator) [61].

Taken altogether, the extant evidence is quite mixed and requires systematic and objective examination over the long term (ie, 12 months and more). This study will be the first such attempt.

Neuroradiological Findings

Previous MRI studies were mainly based on retrospective hospital data and focused on acute clinical imaging of COVID-19, describing the increased occurrence of (postinfectious) encephalitis [62], acute demyelinating/necrotic hemorrhagic encephalomyelitis–like signal changes [63,64], cerebrovascular disease [65], and Guillain-Barre syndrome [66]. The lack of difference among study groups according to the presence, number, and location of medullary lesions or intraparenchymal microbleeds may be a result of the small number of those included in the preliminary analysis, as recruitment is ongoing. According to the rates of, for example, intracranial hemorrhage, ischemic stroke, or encephalitis up to 6 months after SARS-CoV-2 infection based on Taquet et al [9], we anticipate very few of such manifest cases in this study.

The identification of abnormalities in different brain regions could help clinicians understand the potential neurological sequelae and psychological effects of COVID-19. Quantitative neuroimaging in this study indicated that patients with asymptomatic and severe-type COVID-19 without clinically prescribed specific neurological manifestations or obvious lesions on conventional MRI may still show changes in brain microstructure. Compared with healthy controls and the asymptomatic-type COVID-19, global brain microstructural changes were detected in both the gray and white matter in the severe disease course group. A decrease in cortical thickness and changes in white matter microstructure were more profound and extensive in the severe than in the asymptomatic group, particularly in the frontal and temporal systems bilaterally, but without clear side predisposition in our preliminary cohort. The observed decreased frontal and temporal grey matter brain volumes of patients with severe COVID-19 compared with those of healthy subjects and asymptomatic patients is consistent with other reports of grey matter brain volume loss, even among COVID-19 remitted patients and those with asymptomatic courses [67].

Thus, brain integrity appears to be potentially susceptible to either COVID-19–induced neurotoxicity (ie, direct viral encephalitis) or systemic inflammation induced by the immune response [62], although the exact etiology of the observed changes is still uncertain at this point. However, only few MRI studies with volumetric brain analysis of patients who recovered from COVID-19 are available to date. Moreover, these studies provide inconsistent data, showing that there has been either a decrease in cortical thickness and subcortical volume, particularly in the left frontal and limbic system [68], or an increase in cortical thickness of the olfactory cortices and temporomesial regions, particularly the hippocampal region [69], following COVID-19. Further research is therefore urgently needed to improve understanding of the distribution pattern of potentially COVID-19–induced brain microstructural damage.

Strengths and Weaknesses

This study is being performed to address the dearth of information regarding long-term cognitive performance among patients who recovered from COVID-19. To date, no studies have employed such comprehensive neurocognitive testing in conjunction with lung function, neurological function, and neuroradiological examinations, and with actively recruited healthy control subjects. Hence, this study is a first step at filling several gaps in our knowledge on the severity of COVID-19 courses and these factors. The first key question to be answered is whether there is any evidence of cognitive impairment over the long term. Another question is whether cognitive performance appears to depend on intact lung capacity or pulmonological health, since these serve the oxygenation of the brain. Our experience with patients so far indicates few lung function difficulties over the long term for a majority of patients. A further question is whether and what changes in brain integrity and volume may undergird reductions in cognitive performance. In addition, several questions regarding olfactory ability in the long term will be addressed by this study: the association of subjective versus objective assessment of smelling ability, associations with cognitive performance, and with emotional well-being.

Next, we assess a series of lifestyle, psychiatric, and psychological health factors that directly or indirectly negatively affect cognitive health. A great strength of this study is that we compare patients to actively recruited healthy control participants who also underwent pandemic conditions so as to ecologically control for potential general negative effects of the pandemic on all of our assessments.

There are several strengths to this study design, which have been thoroughly addressed in the Introduction. To the best of our knowledge, this is the first study to collect cognitive, pulmonary, lung function, neuroimaging, and further psychiatric, personality, and lifestyle data as part of a multidisciplinary,

long prospective cohort study. Despite the current large number of publications, only some have focused on cognitive outcomes. Most of these did so only superficially, and none of these reported long-term outcomes (12 months or more). Specifically, the detailed cognitive assessment in this study will deliver comprehensive and objective data that are currently scarce. The results of this exploratory pilot study will deliver important information about the clinical presentation of cognitive symptoms following acute COVID-19 in a broad context and compare them to actively recruited healthy controls who also endured long-term pandemic conditions, which may also affect cognition. Despite being a pilot study, there will be adequate statistical power with a sample size of 150 participants.

There are also several design weaknesses to this pilot study. One is the difficulty in representing all affected age groups. It is known that age groups are affected differently by COVID-19 with respect to the infection rate, mortality, and likely also the extent of prolonged symptoms. Although the age range of those enrolled into the study so far is 26-70 years, participants are on average of middle age for all cohorts. This may reflect the magnitude of symptoms or of concerns among middle-aged patients. We are trying to keep the same age and sex distribution across groups as closely as we can during enrollment. In addition, age will be taken into account in several different ways for data analysis, including transforming the raw scores to age- and sex-normed standard values.

A further potential problem is the heterogeneity in the severe arm of the study. We include those who were in hospital overnight and released the next day as well as those who had longer hospital stays or even intensive care stays. We are aware of the scores of confounding factors this represents, such as organ failure or dysfunction, ventilation, and extracorporeal oxygenation, among others. The intake interview addresses any diagnoses such as organ failure. We will describe the type of hospital stay for the severe arms and will create separate calculations of parameters with and without intensive care patients, since these represent a special group. It is beyond the scope of this study to take individual or specialized treatments at the ICU into account.

The question of what role chronic fatigue syndrome (CFS) plays in cognitive difficulties is central to our study. Diagnoses of CFS at any time prior to or during the study will be taken into account. In addition, several items in our study directly address symptoms of chronic fatigue and sleep disorder, which will be used in comparison of the cognitive and pulmonary data.

It is also unclear whether our findings represent true change among the COVID-19 cohort postinfection given that it is impossible to have a pre-COVID-19 baseline. Likewise, it is not possible to exclude COVID-19 patients with memory problems. We do, however, ask a series of self-report questions regarding changes in memory and general cognitive ability since the acute phase of COVID-19, which includes questions regarding everyday attention, memory, and executive function. For healthy controls, we ask the same questions with relation to the start of the pandemic. This will enable a comparison of subjective perception across groups.

Lastly, participants may become infected (or reinfected) with SARS-CoV-2 during the course of the study. We are not able to conduct polymerase chain reaction testing to assess the current COVID-19 status at the assessment points in this study due to a lack of financing and personnel. We are dealing with this in two ways: one is the blood drop–based antibody testing of the healthy group at baseline and at the 12-month visit to exclude infection within the last few weeks or months (IgG and IgM antibodies), although this is not a perfect method. Second, we ask all participants about current and past (re)infection status at each study visit. Since COVID-19 testing is ubiquitous, we rely on our participants answering this truthfully and to the best of their knowledge.

Future Research

Future research of cognitive performance after SARS-CoV-2 infection should include stratifications based on age, infection severity, duration since initial infection, organ dysfunction (eg, lung, heart), and perhaps according to required treatments. Age is known to be a key risk factor for cognitive impairment in other syndromes and disease states (such as dementias). Yet, younger patients who acquire cognitive impairment after SARS-CoV-2 infection do so during their most productive years of life. The immediate and mid-term cognitive performance troughs after intensive care are also well-known phenomena [70]. Hence, stratifying according to acute SARS-CoV-2 infection severity (ie, number and type of symptoms, requirement of ventilation, organ dysfunctions, in-home care versus hospitalization versus intensive care) would help to clarify those most at risk of developing cognitive problems. Further, stratifications based on the SARS-CoV-2 strain and number of SARS-CoV-2 *reinfections* in light of mutations such as the B.1.617.2 (Delta) variant [71], which may infect even fully vaccinated patients but may be less lethal, would be important for understanding the impact of SARS-CoV-2 infection on cognition.

In addition, cognitive studies require carefully selected, objective measures based on specialized knowledge of functional cognitive modules and cognitive science to identify the specific neuropsychological functions that are affected. Lastly, myriad factors known to be associated with cognitive ability need to be systematically assessed in addition to cognition to identify their independent contributions and possible interactions. These suggestions for future research will be important for identifying at-risk groups, indications for neuropsychological testing services after SARS-CoV-2 infection, rehabilitation or therapy to those with manifest cognitive impairments, and possibly for targeting neuroprotective therapies during the acute stage of SARS-CoV-2 infection.

Conclusions

After having thoroughly reviewed the existing literature, to the best of our knowledge, this is the first study to include objective and comprehensive longitudinal analyses of neurocognitive sequelae of COVID-19 in an extreme group comparison of asymptomatic/mild versus severe SARS-CoV-2 infection and actively recruited healthy controls within a broad context of other, pertinent variables. This study will contextualize

neurocognitive performance via coassessment of neurological, pulmonary, and a series of psychiatric and lifestyle factors.

The preliminary results of on average poorer verbal learning and verbal memory, along with reduced grey matter and frontal and temporal brain volumes briefly reported herein are quite robust. These findings may change as they are by no means final. Our cognitive and neuroradiological findings also require careful analysis together with other assessments of pulmonary and lung function, neurological, and psychological and lifestyle factors at study completion.

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Authors' Contributions

Concept and design: MTH, CNW, DS, AR, PT; drafting of the manuscript: CNW, MW, LB, RG, FB, SB, CS; critical revision of the manuscript for important intellectual content: all authors.

Conflicts of Interest

None declared.

References

1. Logue JK, Franko NM, McCulloch DJ, McDonald D, Magedson A, Wolf CR, et al. Sequelae in adults at 6 months after COVID-19 infection. JAMA Netw Open 2021 Feb 01;4(2):e210830 [FREE Full text] [doi: 10.1001/jamanetworkopen.2021.0830] [Medline: 33606031]
2. Graham EL, Clark JR, Orban ZS, Lim PH, Szymanski AL, Taylor C, et al. Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 "long haulers". Ann Clin Transl Neurol 2021 May;8(5):1073-1085. [doi: 10.1002/acn3.51350] [Medline: 33755344]
3. Zhou H, Lu S, Chen J, Wei N, Wang D, Lyu H, et al. The landscape of cognitive function in recovered COVID-19 patients. J Psychiatr Res 2020 Oct;129:98-102 [FREE Full text] [doi: 10.1016/j.jpsychires.2020.06.022] [Medline: 32912598]
4. Shi C, Kang L, Yao S, Ma Y, Li T, Liang Y, et al. The MATRICS Consensus Cognitive Battery (MCCB): Co-norming and standardization in China. Schizophr Res 2015 Dec;169(1-3):109-115 [FREE Full text] [doi: 10.1016/j.schres.2015.09.003] [Medline: 26441005]
5. Ferrucci R, Dini M, Groppo E, Rosci C, Reitano MR, Bai F, et al. Long-lasting cognitive abnormalities after COVID-19. Brain Sci 2021 Feb 13;11(2):235 [FREE Full text] [doi: 10.3390/brainsci11020235] [Medline: 33668456]
6. Amato MP, Portaccio E, Goretti B, Zipoli V, Ricchiuti L, De Caro MF, et al. The Rao's Brief Repeatable Battery and Stroop Test: normative values with age, education and gender corrections in an Italian population. Mult Scler 2006 Dec;12(6):787-793. [doi: 10.1177/1352458506070933] [Medline: 17263008]
7. Pezzini A, Padovani A. Lifting the mask on neurological manifestations of COVID-19. Nat Rev Neurol 2020 Nov;16(11):636-644 [FREE Full text] [doi: 10.1038/s41582-020-0398-3] [Medline: 32839585]
8. Heneka MT, Golenbock D, Latz E, Morgan D, Brown R. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. Alzheimers Res Ther 2020 Jun 04;12(1):69 [FREE Full text] [doi: 10.1186/s13195-020-00640-3] [Medline: 32498691]
9. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry 2021 May;8(5):416-427 [FREE Full text] [doi: 10.1016/S2215-0366(21)00084-5] [Medline: 33836148]
10. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. Lancet Neurol 2020 Sep;19(9):767-783 [FREE Full text] [doi: 10.1016/S1474-4422(20)30221-0] [Medline: 32622375]
11. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis 2020 May;20(5):533-534 [FREE Full text] [doi: 10.1016/S1473-3099(20)30120-1] [Medline: 32087114]
12. COVID-19 SUFTE, as O, 2021 I. COVID-19 situation update for the EU/EEA, as of 18 October 2021. European Center for Disease Control. URL: https://www.ecdc.europa.eu/en/cases-2019-ncov-eueea [accessed 2021-30-07]
13. Tsori Y, Granek R. Epidemiological model for the inhomogeneous spatial spreading of COVID-19 and other diseases. PLoS One 2021;16(2):e0246056 [FREE Full text] [doi: 10.1371/journal.pone.0246056] [Medline: 33606684]
14. Statistical Yearbook 2020, Sixty-third Issue. UN-iLibrary. URL: https://www.un-ilibrary.org/content/books/9789210050784 [accessed 2021-05-10]

15. Chen R, Wang K, Yu J, Howard D, French L, Chen Z, et al. The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in the human and mouse brains. Front Neurol 2020;11:573095. [doi: 10.3389/fneur.2020.573095] [Medline: 33551947]
16. Matschke J, Lütgehetmann M, Hagel C, Sperhake JP, Schröder AS, Edler C, et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. Lancet Neurol 2020 Nov;19(11):919-929 [FREE Full text] [doi: 10.1016/S1474-4422(20)30308-2] [Medline: 33031735]
17. Liu J, Tan B, Wu S, Gui Y, Suo J, Li Y. Evidence of central nervous system infection and neuroinvasive routes, as well as neurological involvement, in the lethality of SARS-CoV-2 infection. J Med Virol 2021 Mar;93(3):1304-1313 [FREE Full text] [doi: 10.1002/jmv.26570] [Medline: 33002209]
18. Schurink B, Roos E, Radonic T, Barbe E, Bouman CSC, de Boer HH, et al. Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study. Lancet Microbe 2020 Nov;1(7):e290-e299 [FREE Full text] [doi: 10.1016/S2666-5247(20)30144-0] [Medline: 33015653]
19. Widmann CN, Heneka MT. Long-term cerebral consequences of sepsis. Lancet Neurol 2014 Jun;13(6):630-636. [doi: 10.1016/S1474-4422(14)70017-1] [Medline: 24849863]
20. Semmler A, Frisch C, Debeir T, Ramanathan M, Okulla T, Klockgether T, et al. Long-term cognitive impairment, neuronal loss and reduced cortical cholinergic innervation after recovery from sepsis in a rodent model. Exp Neurol 2007 Apr;204(2):733-740. [doi: 10.1016/j.expneurol.2007.01.003] [Medline: 17306796]
21. Bowyer JF, Sarkar S, Burks SM, Hess JN, Tolani S, O'Callaghan JP, et al. Microglial activation and responses to vasculature that result from an acute LPS exposure. Neurotoxicology 2020 Mar;77:181-192 [FREE Full text] [doi: 10.1016/j.neuro.2020.01.014] [Medline: 32014511]
22. Hellstrom IC, Danik M, Luheshi GN, Williams S. Chronic LPS exposure produces changes in intrinsic membrane properties and a sustained IL-beta-dependent increase in GABAergic inhibition in hippocampal CA1 pyramidal neurons. Hippocampus 2005;15(5):656-664. [doi: 10.1002/hipo.20086] [Medline: 15889405]
23. Deng X, Ai W, Lei D, Luo X, Yan X, Li Z. Lipopolysaccharide induces paired immunoglobulin-like receptor B (PirB) expression, synaptic alteration, and learning-memory deficit in rats. Neuroscience 2012 May 03;209:161-170. [doi: 10.1016/j.neuroscience.2012.02.022] [Medline: 22395112]
24. Hiramoto RN, Rogers CF, Demissie S, Hsueh CM, Hiramoto NS, Lorden JF, et al. Psychoneuroendocrine immunology: site of recognition, learning and memory in the immune system and the brain. Int J Neurosci 1997 Dec;92(3-4):259-285. [doi: 10.3109/00207459708986405] [Medline: 9522270]
25. Iwashyna TJ. Trajectories of recovery and dysfunction after acute illness, with implications for clinical trial design. Am J Respir Crit Care Med 2012 Aug 15;186(4):302-304 [FREE Full text] [doi: 10.1164/rccm.201206-1138ED] [Medline: 22896591]
26. Lage C, González-Suárez A, Alcalde-Hierro MP, Sampedro-González MI, Villanueva-Eguaras Á, Sánchez-Crespo MR, et al. Major surgery affects memory in individuals with cerebral amyloid-β pathology. J Alzheimers Dis 2021;79(2):863-874. [doi: 10.3233/JAD-191229] [Medline: 33361588]
27. Semmler A, Widmann CN, Okulla T, Urbach H, Kaiser M, Widman G, et al. Persistent cognitive impairment, hippocampal atrophy and EEG changes in sepsis survivors. J Neurol Neurosurg Psychiatry 2013 Jan;84(1):62-69. [doi: 10.1136/jnnp-2012-302883] [Medline: 23134661]
28. Widmann CN, Schewe JC, Heneka MT. Sepsis-associated encephalopathy versus sepsis-induced encephalopathy--authors' reply. Lancet Neurol 2014 Oct;13(10):968-969. [doi: 10.1016/S1474-4422(14)70204-2] [Medline: 25231518]
29. Widmann CN, Sinning J, Ghanem A, Brosseron F, Heneka M, Wagner M. [P2–088]: Chronic and acute systemic inflammation and long-term cognitive decline. Alzheimers Dement 2017 Jul 01;13(7S Part 13):P640-P640. [doi: 10.1016/j.jalz.2017.06.737]
30. Calsavara AJC, Nobre V, Barichello T, Teixeira AL. Post-sepsis cognitive impairment and associated risk factors: A systematic review. Aust Crit Care 2018 Jul;31(4):242-253. [doi: 10.1016/j.aucc.2017.06.001] [Medline: 28645546]
31. Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JF. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. Am J Respir Crit Care Med 2005 Feb 15;171(4):340-347. [doi: 10.1164/rccm.200406-763OC] [Medline: 15542793]
32. Amtliche Bekanntmachungen Ordnung zur Sicherung guter wissenschaftlicher Praxis an der Rheinischen Friedrich-Wilhelms-Universität Bonn. Rheinischen Friedrich-Wilhelms-Universität Bonn. 2020 Sep 21. URL: https://bonndoc.ulb.uni-bonn.de/xmlui/bitstream/handle/20.500.11811/8928/Amtl.%20Bek.%2021013.pdf?sequence=1&isAllowed=y [accessed 2020-09-02]
33. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. J Am Coll Dent 2014;81(3):14-18. [Medline: 25951678]
34. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) (Text with EEA relevance). Publication Office of the European Union. 2016. URL: http://op.europa.eu/en/publication-detail/-/publication/3e485e15-11bd-11e6-ba9a-01aa75ed71a1 [accessed 2021-08-25]
35. Benedict RH, Schretlen D, Groninger L, Brandt J. Hopkins Verbal Learning Test – Revised: normative data and analysis of inter-form and test-retest reliability. Clin Neuropsychol 2010 Aug 09;12(1):43-55. [doi: 10.1076/clin.12.1.43.1726]

36. Varatharaj A, Galea I. The blood-brain barrier in systemic inflammation. Brain Behav Immun 2017 Feb;60:1-12 [FREE Full text] [doi: 10.1016/j.bbi.2016.03.010] [Medline: 26995317]
37. Nation DA, Sweeney MD, Montagne A, Sagare AP, D'Orazio LM, Pachicano M, et al. Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. Nat Med 2019 Feb 14;25(2):270-276 [FREE Full text] [doi: 10.1038/s41591-018-0297-y] [Medline: 30643288]
38. Sweeney MD, Sagare AP, Zlokovic BV. Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. Nat Rev Neurol 2018 Mar;14(3):133-150 [FREE Full text] [doi: 10.1038/nrneurol.2017.188] [Medline: 29377008]
39. Tomaszewski Farias S, Mungas D, Harvey DJ, Simmons A, Reed BR, Decarli C. The measurement of everyday cognition: development and validation of a short form of the Everyday Cognition scales. Alzheimers Dement 2011 Nov;7(6):593-601 [FREE Full text] [doi: 10.1016/j.jalz.2011.02.007] [Medline: 22055976]
40. Siegrist P, Maercker A. Deutsche Fassung der Short Screening Scale for DSM-IV Posttraumatic Stress Disorder. Aktueller Stand der Validierung (English: German Version of the Short Screening Scale for DSM-IV Posttraumatic Stress Disorder. Current Status of Validation). Trauma Gewalt 2010 Aug;156(6):208-213 [FREE Full text]
41. Wilson RS, Arnold SE, Schneider JA, Kelly JF, Tang Y, Bennett DA. Chronic psychological distress and risk of Alzheimer's disease in old age. Neuroepidemiology 2006;27(3):143-153. [doi: 10.1159/000095761] [Medline: 16974109]
42. Gerhard U. Zeitschrift für Klinische Psychologie und Psychotherapie. Göttingen: Hogrefe; Apr 1999:145-146.
43. Hultsch DF, Hertzog C, Small BJ, Dixon RA. Use it or lose it: engaged lifestyle as a buffer of cognitive decline in aging? Psychol Aging 1999;14(2):245-263. [doi: 10.1037/0882-7974.14.2.245]
44. Plassman BL, Williams JW, Burke JR, Holsinger T, Benjamin S. Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. Ann Intern Med 2010 Aug 03;153(3):182-193 [FREE Full text] [doi: 10.7326/0003-4819-153-3-201008030-00258] [Medline: 20547887]
45. Baumgart M, Snyder H, Carrillo M, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. Alzheimers Dement 2015 Jun;11(6):718-726 [FREE Full text] [doi: 10.1016/j.jalz.2015.05.016] [Medline: 26045020]
46. Cacioppo JT, Hawkley LC. Perceived social isolation and cognition. Trends Cogn Sci 2009 Oct;13(10):447-454 [FREE Full text] [doi: 10.1016/j.tics.2009.06.005] [Medline: 19726219]
47. Li Y, Xu J, Liu Y, Zhu J, Liu N, Zeng W, et al. A distinct entorhinal cortex to hippocampal CA1 direct circuit for olfactory associative learning. Nat Neurosci 2017 Apr;20(4):559-570. [doi: 10.1038/nn.4517] [Medline: 28263300]
48. Mueller CA, Grassinger E, Naka A, Temmel AFP, Hummel T, Kobal G. A self-administered odor identification test procedure using the "Sniffin' Sticks". Chem Senses 2006 Jul;31(6):595-598. [doi: 10.1093/chemse/bjj064] [Medline: 16754696]
49. Besser G, Liu DT, Renner B, Mueller CA. Self-administered testing of odor threshold and discrimination using Sniffin' Sticks—reviving the "Odor-Curves-On-Paper" method. Chem Percept 2019 Apr 4;13(1):71-77. [doi: 10.1007/s12078-019-09263-x]
50. Ramont L, Thoannes H, Volondat A, Chastang F, Millet M, Maquart F. Effects of hemolysis and storage condition on neuron-specific enolase (NSE) in cerebrospinal fluid and serum: implications in clinical practice. Clin Chem Lab Med 2005;43(11):1215-1217. [doi: 10.1515/CCLM.2005.210] [Medline: 16232088]
51. Walter M, Wiltfang J, Vogelgsang J. Pre-analytical sampling and storage conditions of amyloid-β peptides in venous and capillary blood. J Alzheimers Dis 2020;78(2):529-535. [doi: 10.3233/JAD-200777] [Medline: 33016918]
52. O'Connell GC, Alder ML, Webel AR, Moore SM. Neuro biomarker levels measured with high-sensitivity digital ELISA differ between serum and plasma. Bioanalysis 2019 Nov;11(22):2087-2094 [FREE Full text] [doi: 10.4155/bio-2019-0213] [Medline: 31829739]
53. Jahn T, Heßler J. Handbook Cognitive Functions Dementia, Short description CRD Version 2. 2nd edition. Mödling, Jänner: Schuhfried GmbH; 2019:1-82.
54. Lekeu F, Magis D, Marique P, Delbeuck X, Bechet S, Guillaume B, et al. The California Verbal Learning Test and other standard clinical neuropsychological tests to predict conversion from mild memory impairment to dementia. J Clin Exp Neuropsychol 2010 Feb;32(2):164-173. [doi: 10.1080/13803390902889606] [Medline: 19459119]
55. Negrini F, Ferrario I, Mazziotti D, Berchicci M, Bonazzi M, de Sire A, et al. Neuropsychological features of severe hospitalized coronavirus disease 2019 patients at clinical stability and clues for postacute rehabilitation. Arch Phys Med Rehabil 2021 Jan;102(1):155-158 [FREE Full text] [doi: 10.1016/j.apmr.2020.09.376] [Medline: 32991870]
56. Alemanno F, Houdayer E, Parma A, Spina A, Del Forno A, Scatolini A, et al. COVID-19 cognitive deficits after respiratory assistance in the subacute phase: A COVID-rehabilitation unit experience. PLoS One 2021;16(2):e0246590 [FREE Full text] [doi: 10.1371/journal.pone.0246590] [Medline: 33556127]
57. Rass V, Beer R, Schiefecker AJ, Kofler M, Lindner A, Mahlknecht P, et al. Neurological outcome and quality of life 3 months after COVID-19: A prospective observational cohort study. Eur J Neurol 2021 Oct;28(10):3348-3359 [FREE Full text] [doi: 10.1111/ene.14803] [Medline: 33682276]
58. Mcloughlin BC, Miles A, Webb TE, Knopp P, Eyres C, Fabbri A, et al. Functional and cognitive outcomes after COVID-19 delirium. Eur Geriatr Med 2020 Oct;11(5):857-862 [FREE Full text] [doi: 10.1007/s41999-020-00353-8] [Medline: 32666303]

59. Writing Committee for the COMEBAC Study Group, Morin L, Savale L, Pham T, Colle R, Figueiredo S, et al. Four-month clinical status of a cohort of patients after hospitalization for COVID-19. JAMA 2021 Apr 20;325(15):1525-1534 [FREE Full text] [doi: 10.1001/jama.2021.3331] [Medline: 33729425]
60. Miskowiak KW, Johnsen S, Sattler SM, Nielsen S, Kunalan K, Rungby J, et al. Cognitive impairments four months after COVID-19 hospital discharge: pattern, severity and association with illness variables. Eur Neuropsychopharmacol 2021 May;46:39-48 [FREE Full text] [doi: 10.1016/j.euroneuro.2021.03.019] [Medline: 33823427]
61. Hampshire A, Trender W, Chamberlain SR, Jolly AE, Grant JE, Patrick F, et al. Cognitive deficits in people who have recovered from COVID-19. EClinicalMedicine 2021 Sep;39:101044 [FREE Full text] [doi: 10.1016/j.eclinm.2021.101044] [Medline: 34316551]
62. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020 Feb 15;395(10223):497-506 [FREE Full text] [doi: 10.1016/S0140-6736(20)30183-5] [Medline: 31986264]
63. Manzano GS, McEntire CRS, Martinez-Lage M, Mateen FJ, Hutto SK. Acute disseminated encephalomyelitis and acute hemorrhagic leukoencephalitis following COVID-19: systematic review and meta-synthesis. Neurol Neuroimmunol Neuroinflamm 2021 Nov;8(6):e1080 [FREE Full text] [doi: 10.1212/NXI.0000000000001080] [Medline: 34452974]
64. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: imaging features. Radiology 2020 Aug;296(2):E119-E120 [FREE Full text] [doi: 10.1148/radiol.2020201187] [Medline: 32228363]
65. Hernández-Fernández F, Sandoval Valencia H, Barbella-Aponte RA, Collado-Jiménez R, Ayo-Martín Ó, Barrena C, et al. Cerebrovascular disease in patients with COVID-19: neuroimaging, histological and clinical description. Brain 2020 Oct 01;143(10):3089-3103 [FREE Full text] [doi: 10.1093/brain/awaa239] [Medline: 32645151]
66. Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? Lancet Neurol 2020 May;19(5):383-384 [FREE Full text] [doi: 10.1016/S1474-4422(20)30109-5] [Medline: 32246917]
67. Duan K, Premi E, Pilotto A, Cristillo V, Benussi A, Libri I, et al. Alterations of frontal-temporal gray matter volume associate with clinical measures of older adults with COVID-19. Neurobiol Stress 2021 May;14:100326 [FREE Full text] [doi: 10.1016/j.ynstr.2021.100326] [Medline: 33869679]
68. Qin Y, Wu J, Chen T, Li J, Zhang G, Wu D, et al. Long-term microstructure and cerebral blood flow changes in patients recovered from COVID-19 without neurological manifestations. J Clin Invest 2021 Apr 15;131(8):e147329. [doi: 10.1172/JCI147329] [Medline: 33630760]
69. Lu Y, Li X, Geng D, Mei N, Wu PY, Huang CC, et al. Cerebral micro-structural changes in COVID-19 patients - an MRI-based 3-month follow-up study. EClinicalMedicine 2020 Aug;25:100484 [FREE Full text] [doi: 10.1016/j.eclinm.2020.100484] [Medline: 32838240]
70. Granja C, Amaro A, Dias C, Costa-Pereira A. Outcome of ICU survivors: a comprehensive review. The role of patient-reported outcome studies. Acta Anaesthesiol Scand 2012 Oct 04;56(9):1092-1103. [doi: 10.1111/j.1399-6576.2012.02686.x] [Medline: 22471617]
71. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (Delta) variant. N Engl J Med 2021 Aug 12;385(7):585-594 [FREE Full text] [doi: 10.1056/NEJMoa2108891] [Medline: 34289274]

Abbreviations

ACE2: angiotensin-converting enzyme 2
ARDS: acute respiratory distress syndrome
CFS: chronic fatigue syndrome
CNS: central nervous system
EDTA: ethylenediaminetetraacetic acid
FEV1: forced expiratory volume in 1 second
FVC: forced vital capacity
HR: hazard ratio
ICU: intensive care unit
Ig: immunoglobulin
MERS: Middle East respiratory syndrome
MoCA: Montreal Cognitive Assessment
MRI: magnetic resonance imaging
NSE: neuron-specific enolase
PNS: peripheral nervous system
RTI: respiratory tract infection
SARS: severe acute respiratory syndrome

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Protocol

Identification of Genetic Predispositions Related to Ionizing Radiation in Primary Human Skin Fibroblasts From Survivors of Childhood and Second Primary Cancer as Well as Cancer-Free Controls: Protocol for the Nested Case-Control Study KiKme

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Abstract

Background: Therapy for a first primary neoplasm (FPN) in childhood with high doses of ionizing radiation is an established risk factor for second primary neoplasms (SPN). An association between exposure to low doses and childhood cancer is also suggested; however, results are inconsistent. As only subgroups of children with FPNs develop SPNs, an interaction between radiation, genetic, and other risk factors is presumed to influence cancer development.

Objective: Therefore, the population-based, nested case-control study KiKme aims to identify differences in genetic predisposition and radiation response between childhood cancer survivors with and without SPNs as well as cancer-free controls.

Methods: We conducted a population-based, nested case-control study KiKme. Besides questionnaire information, skin biopsies and saliva samples are available. By measuring individual reactions to different exposures to radiation (eg, 0.05 and 2 Gray) in normal somatic cells of the same person, our design enables us to create several exposure scenarios for the same person simultaneously and measure several different molecular markers (eg, DNA, messenger RNA, long noncoding RNA, copy number variation).

Results: Since 2013, 101 of 247 invited SPN patients, 340 of 1729 invited FPN patients, and 150 of 246 invited cancer-free controls were recruited and matched by age and sex. Childhood cancer patients were additionally matched by tumor morphology, year of diagnosis, and age at diagnosis. Participants reported on lifestyle, socioeconomical, and anthropometric factors, as well as on medical radiation history, health, and family history of diseases (n=556). Primary human fibroblasts from skin biopsies of

the participants were cultivated (n=499) and cryopreserved (n=3886). DNA was extracted from fibroblasts (n=488) and saliva (n=510).

Conclusions: This molecular-epidemiological study is the first to combine observational epidemiological research with standardized experimental components in primary human skin fibroblasts to identify genetic predispositions related to ionizing radiation in childhood and SPNs. In the future, fibroblasts of the participants will be used for standardized irradiation experiments, which will inform analysis of the case-control study and vice versa. Differences between participants will be identified using several molecular markers. With its innovative combination of experimental and observational components, this new study will provide valuable data to forward research on radiation-related risk factors in childhood cancer and SPNs.

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fibroblast; irradiation; childhood cancer; neoplasm; second primary neoplasm; second cancer; study design; participation; feasibility; cell line

Introduction

Childhood cancer is defined as a malignant neoplasm or any neoplasm in the central nervous system occurring in children and adolescents before the age of 20 years [1]. Worldwide, the age-standardized incidence rate (world standard) is 152.8 per million person-years in those aged 0 to 19 years, is slightly higher in boys than in girls, and varies for different diagnostic groups dependent on age and region [2]. Risk factors for most childhood cancers remain largely unknown [1]. Common genetic susceptibility with low risk and rare genetic disorders with high risk explain less than 10% of the cases [3-15]. Corresponding with the current state of science, the immune system also plays an important role in the development of cancer [16], and several environmental factors [17-26], such as early infections [27] and vaccination [28], have been suggested but not established to be protective by modulating immunological pathways, in particular for childhood leukemia. In contrast, specific chemical substances such as benzene are established risk factors for the development of leukemia and antineoplastic agents (eg, DNA alkylating agents, topoisomerase II inhibitors, doxorubicin) for the development of acute myeloid leukemia and sarcomas in childhood [29]. However, these substances do not constitute the major part in the development of childhood cancer, since only a minority of children is exposed to such chemical carcinogens [30].

Exposure to high doses of ionizing radiation, either due to nuclear disasters [31] or in cancer therapies [32-35], is a rare and known environmental risk factor for acute myeloid leukemia in childhood [1] and second primary neoplasms (SPNs) [1,29,36-39,41]. Indeed gene-radiation interactions are assumed to be involved in the etiology of childhood cancer [1,42] and SPNs [43-46] as well. Besides high-dose ionizing radiation, the magnitude of the risk for first primary neoplasms (FPNs) in childhood from very low doses (≤0.05 Gray [Gy]) is still uncertain and difficult to resolve via conventional epidemiological studies [1]. Low doses of ionizing radiation are commonly used in medical diagnostics, like computed tomography examinations [47], and regarded as a risk factor in addition to the directly exposed treatment volume, where high doses of ionizing radiation are applied during radiation therapy [48]. Exposure to low doses also occurs during the staging procedure of neoplasms via computed tomography examinations and follow-up after treatment. In utero exposure to ionizing radiation during abdominal X-rays of pregnant women was consistently observed to be a risk factor for acute leukemia in many epidemiological studies conducted in the 1950s and 1960s [49-56]. Today, X-ray examinations during pregnancy are conducted using lower radiation doses [57], and recent studies were not able to identify any increased risk anymore [58]. Similarly, a recent study on cancer incidence after exposure to postnatal diagnostic X-rays did not find an increased risk for leukemia, lymphoma, central nervous system tumors, blastomas, or sarcomas [59]. However, data on the effect of low doses are still scarce and inconsistent due to missing direct biological human evidence [60,61]. Additionally, observational studies are often small and may not show proper confounder control [62-69].

To address these open questions and challenges with a more powerful approach, we designed a nested, molecular-epidemiological, case-control study that combines observational epidemiological research with standardized experimental components in primary human fibroblasts. We want to identify genetic predispositions related to the cellular response to high and low doses of ionizing radiation in SPN cases compared with FPN controls first and in childhood cancer cases compared with cancer-free controls second. This publication focuses on the description of the innovative study design and its potential use in research as well as on procedures of sampling and proportions of participation.

Methods

Aim and Study Design

The population-based, nested case-control study KiKme (German: “Krebserkrankungen im Kindesalter und molekulare Epidemiologie”; English: “Cancer in childhood and molecular-epidemiology”) was designed to analyze genetic predispositions and other molecular-biological factors associated with ionizing radiation in primary human fibroblasts from former childhood cancer patients (SPNs and FPNs) and cancer-free controls. Applying a molecular-epidemiological, case-control study design, using primary human skin fibroblasts as a model of normal human somatic tissue enables us to

measure individual changes in reaction to different radiation exposures on a cellular level and to conduct an informed search for genomic causes in fibroblasts from the same person simultaneously [70]. The combination with observational data from questionnaires and the linkage of therapy data on chemo- and radiotherapy from treating hospitals complete the study and allow us to control for known confounding factors.

Study Population

More than 70,000 former childhood cancer patients are registered in the German Childhood Cancer Registry [71]. This large cohort provides the basis for the nested case-control study KiKme. Since 1980, this registry has recorded population-based childhood cancer cases occurring in children younger than 15 years old in former Western Germany with almost complete coverage. Since 1991, cases from former Eastern Germany are recorded as well. In 2009, the age limit for recorded childhood cancer was raised from under 15 years old to under 18 years old [32]. Diagnoses of childhood cancer are validated in cooperation with treating hospitals and an open-end follow-up is conducted with an emphasis on obtaining information on SPNs [72]. The cohort in which our case-control study KiKme was nested includes children with only 1 cancer diagnosis (FPN) as well as with multiple cancer diagnoses over time (SPN). Subjects were eligible if they were diagnosed with an FPN in childhood, were at least 18 years old (as of June 2012), showed survival after cancer diagnosis for 1 year or more, and were still alive when the study was performed. Additionally, an address and an agreement for data storage in the German Childhood Cancer Registry had to be available. The inclusion criteria resulted in a maximum of 1976 available former childhood cancer patients (247 SPNs with 1729 matching FPNs). All these former childhood cancer patients were initially contacted by the German Childhood Cancer Registry in consideration with the guidelines of the Association for Pediatric Oncology and Hematology in Germany.

For the pilot study of this project, 48 former childhood cancer patients with any morphology of FPN and SPN were included. Within the main study period, only participants (n=392) with an FPN of the most common childhood cancers of the International Classification of Childhood Cancer - third edition (ICCC-3) [73] were recruited: leukemia ICCC-3 I(a), I(b), I(c), I(d); lymphoma ICCC-3 II(a), II(b), II(c); and tumors of the central nervous system ICCC-3 III(a), III(b), III(c), III(d), IV(a). Cancer sites of the second primary diagnosis had to be at a potentially radiation-related site: thyroid carcinoma ICCC-3 XI(b); skin carcinoma ICCC-3 XI(e); leukemia ICCC-3 I(a), I(b), I(d) (all causally related to radiation [41]); or malignant melanoma ICCC-3 XI(d) (potentially related to radiation [41]). The number of possible SPN cases meeting the inclusion criteria was limited by the quantity of potential SPN participants who were still alive (n=247). Potential FPN controls (n=1729) were matched by age at recruitment (maximal age range of 5 years), sex, cancer morphology (ICCC-3), year of diagnosis (maximal range of 7 calendar years), and age at diagnosis (maximal age range of 4 years) to available SPN cases using a risk set sampling approach. Taking the year of diagnosis into account enables us to control for changes in therapy procedures. To be included as a possible FPN control, no SPN diagnosis had to exist at the date of the second diagnosis of the corresponding SPN case, and the FPN control had to be alive.

In order to not only be able to compare genetic predispositions related to ionizing radiation in SPN cases and FPN controls, we also recruited cancer-free controls for each matching group in an additional hospital-based study arm in the Department of Orthopedics and Traumatology of the University Medical Center Mainz. They were matched by sex and within a maximal 10-year age range at the time of the recruitment to participating SPN cases and FPN controls. Cancer-free controls were mainly recruited from patients who were hospitalized for elective orthopedic surgery after an accident. Cancer-free controls with severe or chronic diseases (eg, cancer, Alzheimer's disease, multiple sclerosis, cardiovascular disease, diabetes) were excluded from participation due to a possible association with shared genetic predispositions and cancer development [74].

Procedures and Survey Modules

The study combines information from questionnaires and molecular-biological experiments including investigations on radiation-induced effects using primary human skin fibroblasts derived from skin biopsies of the participants. In addition, saliva samples were collected as a second, independent source for DNA. Participants who reported being infected with severe infectious diseases (eg, hepatitis or AIDS) were excluded from a skin biopsy and saliva collection to avoid any transmission in the laboratory. Also, skin biopsies were not conducted if participants suffered from other severe diseases (eg, hemophilia) to prevent them from suffering adverse health consequences.

Questionnaires

Most study participants (SPN, FPN, cancer-free control) answered a self-completed questionnaire to assess socioeconomic and anthropometric factors, as well as information on lifestyle, medical history, and health. The general questionnaire contained questions on birth characteristics, ethnic origin, anthropometric factors, education, current life circumstances, smoking, drinking, diseases, and medications, as well as medical therapies and lifelong exposure to medically applied radiation (medical radiation history) of the participant. Data on cancer therapies were validated by comparing questionnaire data with information on type and dose of medication as well as dose and number of radiotherapy fractions from therapy protocols of treating hospitals [75]. All therapy data will be used to develop an individual exposure matrix for each participant. Furthermore, there were questions on family history of severe diseases. The complex information on family history of cancer was additionally requested in a personal interview in the clinic or through a telephone interview for all participants not attending the clinic in Mainz. The interview included information about cancer type and age at diagnosis within their relatives (children, siblings, nephews and nieces, parents, grandparents, aunts, uncles, and cousins).

Saliva Collection, Processing, and Storage

Saliva collection took place using the Oragene DNA Kit (DNA Genotek Inc, Ottawa, Ontario, Canada). The participant was asked not to drink, eat, smoke, or chew chewing gum 30 minutes before collection. Five minutes before the start, the participant

rinsed his or her mouth and filled the saliva tube of the kit with saliva without air bubbles. The saliva was mixed with the DNA stabilizing fluid and immediately forwarded to the laboratory within the recruitment center. For persons participating near their residence, saliva samples were sent to the laboratory in Mainz in a provided cardboard box by standard mail. After receiving the collected samples, half of each saliva sample was lysed and incubated at 56 °C in the laboratory. After incubation, samples were mixed with ethanol, and the lysate was loaded in a NucleoSpin Blood L Column and centrifuged. After washing the silica membrane, the DNA was eluted with DNA buffer. The DNA sample was then stored at –80 °C. The remaining half of saliva from each participant was stored at –20 °C for later use.

Skin Biopsy Collection, Processing, and Storage

Skin samples were taken by punch biopsy under local anesthesia with a diameter of 3 mm at the cubital region for cancer patients and during surgery in the scar region for cancer-free controls. The resulting wounds were sewn with a single stitch. After successful extraction, biopsied skin was transferred to a vial with rich cell culture medium (Amniogrow, CytoGen GmbH, Wetzlar, Germany), stored at room temperature, and immediately taken to the laboratory or by courier service within 24 hours. Subcutaneous tissue was removed, and the biopsy was dissected in rich cell culture medium (Amniogrow, CytoGen GmbH, Wetzlar, Germany) and cultured in a humidified incubator at 37 °C with 5% CO_2 (Heracell Vios 160i, Thermo Fisher Scientific, Waltham, MA) to allow the outgrowth and expansion of fibroblasts. Culture medium (Amniogrow, CytoGen GmbH, Wetzlar, Germany) was changed every 3-4 days. Passaging of fibroblasts was done using 0.05% trypsin with 0.1% ethylenediaminetetraacetate when reaching approximately 70% confluence. After the first passage, cells were cultured in low glucose Dulbecco's minimal essential medium (Sigma-Aldrich, St. Louis, MO) containing 1% nonessential amino acids, 15% fetal bovine serum, and 1% penicillin/streptomycin (all supplements from Biochrom GmbH, Berlin Germany). Cultures were grown for 2-4 weeks to reach sufficient cell numbers for cryopreservation in liquid nitrogen or nitrogen gas.

Sampling

All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research. Approval by the Ethics Committee of the Medical Association of Rhineland-Palatinate was obtained (no. 837.262.12 (8363-F), no. 837.103.04 (4261), and no. 837.440.03 (4102)). Study participants who voluntarily gave consent for examinations, collection of samples, subsequent analysis, time-limited storage of personal data, and collected samples were included. Participants could consent to single components of the study while abstaining from others at any time. After confirmation to participate in the KiKme study, an appointment for the discussion of the informed consent was made. A date for skin biopsy, saliva sampling, and telephone or personal interview was obtained. Cases participating at the University Medical Center Mainz were offered the possibility of medical consultation. These consultations were not documented for this report. Participants were reimbursed and compensated for travel costs. To further increase participation despite potential long travel to Mainz, all cancer patients were also given the option to participate near their residence. If available, participants could name their attending dermatologist. Otherwise, the study team contacted a dermatologist near the residence of the participant. The attending dermatologists were asked to act as a cooperating partner, were trained for the study, and took the skin biopsy with the signed informed consent.

Potential cancer-free control participants were identified in the surgery schedules of the department for orthopedic surgery. They were contacted and informed about the content of the study during their stay in the hospital. Participation could be refused at any time during the procedure. To increase the study participation of cancer-free controls, the biopsy was taken from excess material during their surgical procedure.

Analysis Plan

From all participants, cultured human fibroblasts from 156 participants with the best matching results based on our criteria (52 triplets each with 1 SPN, 1 FPN, and 1 cancer-free control participant) will be selected for the radiation experiments (mean age of participants at sampling: SPN 33 years, range 20-51 years; FPN 33 years, range 21-49 years; controls 33 years, range 19-48 years; median age of participants at first neoplasm: SPN 8 years, range 0-14 years and FPN 8 years, range 1-14 years; mean calendar year of the first neoplasm: SPN 1991, range 1980-2011 and FPN 1991, range 1980-2009). During radiation experiments, cultured human fibroblasts from each of the 156 selected and carefully matched participants will be exposed to a low (eg, 0.05 Gy) as well as a high dose (2 Gy) of X-rays and will be sham-irradiated (0 Gy). The low dose of radiation will be applied to mimic an exposure scenario during medical diagnostics (eg, computed tomography), and the high dose represents an average single tumor dose applied to the target volume of conventional fractionated radiation therapy. The fibroblast of each triplet will be treated simultaneously to avoid batch effects within groups. In a preliminary analysis, we identified the time point after radiation with the highest amount of differentially expressed genes for our chosen radiation doses [76]. The identified time point will be used to analyze differences in gene expression patterns between patient groups. The high number of samples from different participants in irradiation experiments (around one-third of the participants) allows us to distinguish possible gene expression patterns with candidate genes and underlying cellular pathways between groups and to identify differences between SPN cases and FPN controls as well as differences between former childhood cancer patients (SPNs and FPNs) and cancer-free controls. To be able to compare gene expression before and after exposure to ionizing radiation, RNA from 468 dishes with cultured human fibroblasts of the irradiation experiments (156 exposed to 0.05 Gy, 156 exposed to 2 Gy, and 156 sham-irradiated; 3 dishes for each participant) will be extracted and Illumina-sequenced. RNA sequencing data will be processed and cleaned as well as normalized using the Voom method [77]. Gene expression of irradiated cells will be compared with the expression of sham-irradiated cells after the same time interval for each participant. Differentially expressed genes dependent on

radiation dose will be detected using linear models and empirical Bayesian statistics. The differential gene expression after irradiation will be computed by comparing measurements of fibroblasts from each participant with measurements after sham-irradiation (eg, counts of transcripts in cells of each individual after 0 Gy versus counts after 2 Gy). *P* values will be computed for the interaction between the effect of radiation and group and for the effect of radiation alone using the R package limma (lmFit, eBayes, makeContrasts) with *patient ID* as a block variable and the factors *patient group* and *radiation doses* [78]. The analyses will be performed without adjustment, with adjustment for age only, and with adjustment for age and gender. For the comparison between former childhood cancer patients with and without SPNs, the analyses will additionally be adjusted for age at first primary neoplasm diagnosis and for tumor subtype. Furthermore, sensitivity analyses will be performed separately for male participants and female participants with age adjustment. Differentially expressed genes will then be selected at a false discovery rate (FDR) level of 0.05 (Benjamini-Hochberg procedure). In addition, differentially expressed genes and their $\log_2$ fold change will be examined using Ingenuity Pathway Analysis (IPA; Version 1.13, QIAGEN Inc, 2018) with a right-tailed Fisher exact test examining pathway enrichment and z-score (≥|2|) indicating (in-) activation of pathways [79]. In addition, IPA will be employed to predict upstream regulators as well as downstream diseases and functions. We will choose promising marker genes to validate the RNA sequencing experiments via real-time quantitative polymerase chain reaction. Thus, RNA sequencing data intend to identify differentially expressed candidate genes, which finally enables a weighted analysis of DNA single-nucleotide variants (SNVs) in these genes and related regions by selecting the smallest *P* value from all comparisons. To filter SNVs, a gene list will be created that contains all genes that were identified as differentially expressed in the messenger RNA and long noncoding RNA analyses after Bonferroni correction (with adjustment for age and gender as well as with adjustment for age at first tumor diagnosis and for tumor type). Furthermore, the list could be supplemented with genes from the associated pathways of the Ingenuity Pathway Database and known radiation-associated genes (RadAtlas) [80] as well as genes associated with childhood cancer (International Cancer Genome Consortium [ICGC], Pediatric Cancer Genomic Data Portal [PeCan], PedcBio portal, Pediatric cancer gene database [Pedican], Xena browser) [81,82]. SNVs will be assigned to the genes if they are located in an area that includes the gene body, consisting of exons and introns, and 500 kilobases upstream and downstream of the gene body. In addition, SNVs will be assigned to the genes that were identified in the Genotype-Tissue Expression (GTEx) project [83] as expression quantitative trait loci (eQTLs) for the gene [84]. The analysis will be carried out using forest tests (RVTEST) [85,86] applying a single-variant Wald test at the SNV level. The burden test (combined multivariate and collapsing [CMC] method) [87], sequence kernel association test (SKAT) [88], and variable threshold method [89] will be used for the gene-based examination of the DNA sequencing data at RVTEST. Association studies will be performed based on the generated gene list using FDR as correction for multiple testing with a significance level of 5% and genome wide without FDR adjustment. Simulation studies assuming our sample size and different SNV effect sizes (odds ratio [OR] 1.3, 1.5, 2, 3, and 4) for genome-wide association studies resulted in the significance level selection of 5% at the gene level and 0.005% at the SNV level. In addition, a weighted analysis of SNVs will be performed genome wide by using likelihood-based boosting [85] and gene list *P* values as weights. Both tumor groups (former SPN and FPN patients) will be compared against the cancer-free controls, and, additionally, the tumor groups will be compared against each other. Results of the SNV analysis will be verified in a 2-stage procedure: First, identified genetic group differences in fibroblasts from about one-half of the participants (n=286) will be replicated in DNA sequenced from the saliva of the same participants. In the second stage, validated results will be replicated in the saliva DNA of an independent confirmation collective consisting of the remaining half of the participants (n=275). This 2-stage approach enables us to ameliorate problems of false discovery. Possible confounding or effect modification (eg, by sex, age at diagnosis of first or second primary neoplasm, type of first or second primary neoplasm, or batch effects) will be taken into account in this analysis. In addition, sensitivity analysis for other possible confounding factors like family history of cancer or received therapies will be conducted.

To identify possible risk associations with cancer treatment, participants were asked whether they had received cancer therapies. Used medications and affected body regions will be additionally inquired (n=556). For validation, self-reports will be compared with data from cancer therapies of the patients from hospitals and clinical studies [75]. By measuring sensitivity and specificity, the quality of binary variables will be analyzed. Receiver operatic characteristic curves will be used for a graphical comparison. Positive and negative predictive values will be used to analyze the validity of the questionnaire. Cohen kappa will be used to measure the concordance between the information from questionnaires and from treating hospitals. Influencing factors (eg, number of neoplasms, sex, sociodemographic factors, comorbidities, time since cancer treatment) on the dichotomous outcome variable *degree of agreement* will be analyzed using logistic regression [75]. If the questionnaire is reliable, conditional logistic regression and mixed models will be used to estimate possible risk associations with cancer therapies.

Differences in family history between childhood cancer patients with FPNs and SPNs as well as cancer-free controls could also be a confounder or effect modifier and will be investigated concerning family history of cancer, degree of family relatedness, age of diagnosis, and family history of chronic disease (n=556). Our interest here is to identify whether an increased number of cancer cases in families is associated with childhood cancer incidence. A family history of cancer was recorded as dichotomous variables for each degree of kinship, for maternal and paternal kinship, and for sex of family members in the questionnaires. The number of cases within families will be related to family size. Clustering of cancer within families will be estimated by the genealogical index of familiarity [90] and stratified by groups (SPN, FPN, cancer-free controls) to ascertain whether the average kinship among affected

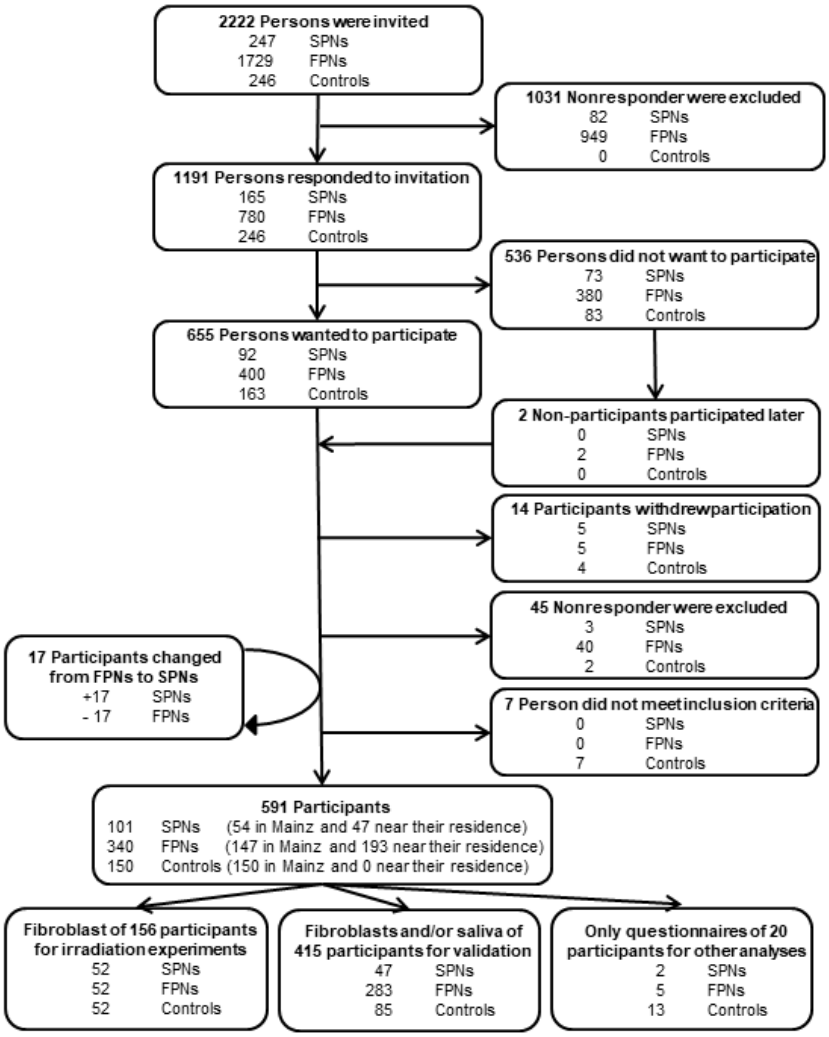
individuals in a pedigree differed from a randomly drawn control set of that pedigree. The kinship sum test [91] will be applied to identify affected individuals exhibiting a closer relationship to other affected individuals than would be expected by chance. Conditional logistic regression will be applied to investigate the association between family history of cancer and the risk of primary childhood cancer (SPN and FPN). Analyses will be adjusted for sex and age at recruitment and stratified for kinship and sex. Cox proportional hazard models will be calculated adjusted for age, sex, family history of cancer, and primary childhood tumor entity to estimate standard incidence rates for SPNs among the cohort of childhood cancer patients. Further, conditional logistic regressions will be used to explore the associations between childhood cancer (SPN and FPN) and other diseases in the family (eg, diabetes, hypertension, elevated blood cholesterol).

The available biosamples of the study will further be used to forward research on other biological markers (eg, hyper- and hypovariability of gene expression, noncoding RNA, copy number variations, epigenetic changes like methylation pattern of genes, proteins associated with double-strand breaks, chromosomal aberrations) and to investigate their possible association with radiation-related cancer development in other KiKme research projects.

Results

The recruitment started in 2013, and the result is shown in Figure 1. Originally, we invited 247 SPNs and 1729 FPNs to participate in the study, of which 92 SPNs (92/247, 37.3%) and 399 FPNs (399/1729, 23.1%) were willing to participate. During the recruiting process, some participants refused their participation while others accepted. Thus, some rematching was needed. To gain complete matching groups in the radiation experiments, we allowed 17 FPN patients that developed an SPN later in life to migrate to the SPN group. However, taking the risk set sampling approach into account, their questionnaire data could be used both as an SPN case and as an FPN control in the questionnaire-based analyses (eg, on the risk of family history of cancer). Overall, 54.4% of the participants (47 SPN and 193 FPN of 441 total participants) participated in the study near their residence in a medical practice of 1 of the 182 cooperating dermatologists.

Figure 1. Enrollment of participants (SPNs, FPNs, and controls) in the population-based, nested case-control study KiKme. FPN: first primary neoplasm; SPN: second primary neoplasm.



A total of 591 former childhood cancer patients and cancer-free controls aged 19 to 53 years (mean age 32 years, 51% women and 49% men) participated in the study (Table 1). The age distribution of participants with SPNs compared with FPNs was very similar (χ^2 test: P=.28), whereas participating cancer-free controls were slightly younger than participants with childhood cancer (χ^2 test: P<.001). Similar differences were found for nonparticipating childhood cancer survivors and nonparticipating cancer-free controls (χ^2 test nonparticipants with SPNs versus FPNs: P=.11; χ^2 test nonparticipating cancer-free controls versus nonparticipating childhood cancer survivors: P<.001). Further characteristics of participants and nonparticipants like age at diagnosis and tumor morphology are summarized in Table 1 and Table 2.

Table 1. Characteristics of included study participants and nonparticipants.

Characteristics	Participants				Nonparticipants[a]			
	SPNs[b] (n=101)	FPNs[c] (n=340)	Controls (n=150)	Total (n=591)	SPNs (n=146)	FPNs (n=1389)	Controls (n=96)	Total (n=1631)
Female, n (%)	50 (49.5)	189 (55.6)	62 (41.3)	301 (50.9)	71 (48.6)	606 (43.6)	42 (43.8)	719 (44.1)
Male, n (%)	51 (50.5)	151 (44.4)	88 (58.7)	290 (49.1)	65 (44.5)	657 (47.3)	54 (56.2)	776 (47.6)
Sex missing, n (%)	N/A[d]	N/A	N/A	N/A	10 (6.8)	126 (9.1)	0 (0)	136 (8.3)
Age at recruitment (years), mean (range)	32 (19-51)	34 (19-53)	29 (18-48)	32 (19-53)	34 (18-49)	34 (18-51)	31 (18-51)	33 (18-51)
<25 years old, n (%)	19 (18.8)	44 (12.9)	57 (38.0)	120 (20.3)	18 (12.3)	111 (8.0)	17 (17.7)	146 (9.0)
25-29 years old, n (%)	25 (24.8)	69 (20.3)	40 (26.7)	134 (22.7)	18 (12.3)	234 (16.8)	25 (26.0)	277 (17.0)
30-34 years old, n (%)	19 (18.8)	78 (22.9)	20 (13.2)	117 (19.8)	24 (16.4)	245 (17.6)	19 (29.8)	288 (17.7)
≥35 years old, n (%)	38 (37.6)	149 (43.8)	33 (22.0)	220 (37.2)	75 (51.4)	672 (48.4)	30 (31.3)	777 (47.6)
Age missing, n (%)	N/A	N/A	N/A	N/A	11 (7.5)	127 (9.1)	5 (5.2)	143 (8.8)
Age at 1st diagnosis (years), mean (range)	7 (0-14)	8 (0-16)	N/A	N/A	8 (0-14)	7 (0-15)	N/A	N/A
Year of 1st diagnosis	1980-2011	1980-2012	N/A	N/A	1980-2005	1980-2012	N/A	N/A
Years between 1st and 2nd diagnoses, mean (range)	16 (2-35)	N/A	N/A	N/A	16 (1-30)	N/A	N/A	N/A
Age at 2nd diagnosis (years), mean (range)	23 (5-46)	N/A	N/A	N/A	24 (5-41)	N/A	N/A	N/A
Year of 2nd diagnosis	1986-2018	N/A	N/A	N/A	1989-2014	N/A	N/A	N/a

[a]Information available only for nonparticipants from the main study.

[b]SPNs: second primary neoplasms.

[c]FPNs: first primary neoplasms.

[d]N/A: not applicable.

Table 2. Cancer sites and cancer therapies of the included study participants and nonparticipants.

Cancer site (International Classification of Childhood Cancer 3rd Edition)	Participants		Nonparticipants[a]	
	SPNs[b] (n=101)	FPNs[c] (n=340)	SPNs (n=146)	FPNs (n=1389)
1st neoplasm, n (%)				
Leukemia (I(a), I(b), I(c), I(d))	41 (40.6)	166 (48.8)	66 (45.2)	641 (46.1)
Lymphoma (II(a), II(b), II(c))	41 (40.6)	135 (39.7)	40 (27.4)	485 (34.9)
Central/peripheral nervous system (III(a), III(b), III(c), III(d), IV(a))	15 (14.9)	35 (10.3)	29 (19.9)	138 (9.9)
Other tumors V, VI(a), IX(a), IX(e)	4 (4.0)	4 (1.2)	0 (0.0)	0 (0.0)
2nd neoplasm, n (%)				
Thyroid cancer (XI(b))	30 (29.7)	N/A[d]	55 (37.7)	N/A
Skin carcinoma (XI(e))	32 (31.7)	N/A	53 (36.3)	N/A
Malignant melanoma (XI(d))	4 (4.0)	N/A	11 (7.5)	N/A
Leukemia (I(a), I(b), I(d))	9 (8.9)	N/A	16 (11.0)	N/A
Lymphoma (II(a), II(b))	6 (5.9)	N/A	N/A	N/A
Central nervous system (III(a), III(b), III(e))	9 (8.9)	N/A	N/A	N/A
Breast cancer (XI(f))	3 (3.0)	N/A	N/A	N/A
Other unspecific carcinoma (XI(f))	6 (5.9)	N/A	N/A	N/A
Sarcoma (IX(d), IX(e))	2 (2.0)	N/A	N/A	N/A
3rd neoplasm, n (%)				
Renal carcinomas (VI(b))	1 (1.0)	N/A	__[e]	—
Skin carcinoma (XI(e))	2 (2.0)	N/A	—	—
Breast cancer (XI(f))	1 (1.0)	N/A	—	—
Other and unspecified carcinomas (XI(f))	2 (2.0)	N/A	—	—
Other specified intracranial and intraspinal neoplasms (III(e))	2 (2.0)	N/A	—	—
4th neoplasm, n (%)				
Thyroid cancer (XI(b))	1 (1.0)	N/A	—	—
Cancer therapies for the 1st neoplasm, n (%)				
Chemotherapy	93 (92.1)	312 (91.8)	—	—
Radiation therapy	74 (73.3)	225 (66.2)	—	—
Surgery	25 (24.8)	64 (18.8)	—	—
Cancer therapies for the 2nd neoplasm, n (%)				
Chemotherapy	22 (21.8)	N/A	—	—
Radiation therapy	21 (20.8)	N/A	—	—
Surgery	56 (55.4)	N/A	—	—
Cancer therapies for the 3rd neoplasm, n (%)				
Chemotherapy	1 (1.0)	N/A	—	—
Surgery	2 (2.0)	N/A	—	—
Cancer therapies for the 4th neoplasm, n (%)				
Surgery	1 (1.0)	N/A	—	—

[a]Information available only for nonparticipants from the main study.

[b]SPNs: second primary neoplasms.

[c]FPNs: first primary neoplasms.

[d]N/A: not applicable.

[e]Information on 3rd and 4th diagnoses were obtained only from participants; therefore, this information is not available for nonparticipants.

For 95% (87/91) of participating SPN cases, suitable FPN controls with a maximum difference of 3 calendar years between first diagnoses could be identified (Multimedia Appendix 1). For the remaining 5%, the time difference was increased to 4-7 calendar years. The matching rate was comparable to the age at first diagnosis: 98% of SPN cases and FPN controls were diagnosed within 3 years of age, and 100% were diagnosed within 4 years of age. Matching for age at recruitment was accomplished within a 3-year age range for 93% (85/91) of participating SPN cases and FPN controls. The remaining 7% were matched by a maximum age range of 5 years. For 7 SPN cases (7/101, 6.9%), no suitable FPN cases participated in the study. However, their information from genetic analyses and questionnaires as well as the information from all other incomplete matching groups will also be included in the analyses.

Cancer-free controls (n=150) were recruited during their stay in the orthopedic surgery department and matched by age and sex to participating SPN cases and FPN controls. Participation proportion for cancer-free controls was originally 66.3% (163 participants of 246 directly contacted persons), but 6 cancer-free controls were excluded due to cancer diagnoses, 4 cancer-free controls actively withdrew from participation during the study period, 2 had to be excluded due to nonresponse, and 1 was excluded due to diabetes (Figure 1). An additional cancer-free control took part in both the pilot study and the main study, and therefore, this participant was excluded from the pilot data.

The difference in age at recruitment for participating SPN cases and cancer-free controls was not larger than 3 years for 95% (76/81) of cancer-free controls and not more than 5 years for 98% (79/81; Multimedia Appendix 1). Only 2 cancer-free controls (2/81, 2%) could not be matched within this age range. Included controls had a short hospital stay due to injuries or their consequences (87/150, 58.0%), joint diseases (17/150, 11.3%), osteopathy and chondropathy (14/150, 9.3%), diseases of the soft tissue (9/150, 6.0%), arthrosis (6/150, 4.0%), orthopedic after treatments (2/150, 1.3%), diseases of the skin and subcutaneous tissue (2/150, 1.3%), congenital malformations or deformities of the musculoskeletal system (1/150, 0.7%), diseases of the musculoskeletal system and connective tissue (1/150, 0.7%), or diseases of nerves, nerve roots, and nerve plexus (1/150, 0.7%). For 6.7% (10/150) of controls, no reason for the hospital stay was given.

Taking group changes from FPN to SPN into account, final participation proportions were 40.9% (101 participants out of 247 invited persons) for SPN cases, 19.7% (340 participants out of 1729 invited persons) for FPN controls, and 61.0% (150 participants out of 246 contacted persons) for cancer-free controls (Table 1). Mentioned reasons for refusal to participate were lack of interest or perceived lack of personal benefit (7 SPN, 49 FPN, 34 cancer-free controls), expenditure of time (36 SPN, 130 FPN, 14 cancer-free controls), illnesses (12 SPN, 20 FPN, 5 cancer-free controls), fear of skin biopsy (12 SPN, 50 FPN, 14 cancer-free controls), and unavailability due to insufficient language skills or problems of comprehension or incorrect contact information (1 SPN, 6 FPN, 5 cancer-free controls). All other participants (1235/1631, 75.7%) provided no reason for their refusal to participate.

In summary, this study successfully obtained questionnaire data for 85 SPN cases (84.2% of 101 participating SPN), 325 FPN controls (95.6% of 340 participating FPN), and 146 cancer-free controls (97.3% of 150 participating cancer-free controls). Skin biopsies were available from 92 SPN cases (91.1% of 101 participating SPN), 307 FPN controls (90.3% of 340 participating FPN), and 100 cancer-free controls (66.7% of 150 participating cancer-free controls). Overall, 3886 cryogenic tubes with primary skin fibroblasts were cryopreserved in liquid nitrogen for further experiments with a mean of 6.8 tubes per participant (SD 4.2, range: 0-28). In total, saliva samples were dispensed from 84 SPN cases (83.2% of 101 participating SPN) and 319 FPN controls (93.8% of 340 participating FPN), as well as from 108 cancer-free controls (72.0% of 150 participating cancer-free controls). Only 2 SPN cases, 3 FPN controls, and 13 cancer-free controls were unwilling to provide any biosamples for RNA and DNA analyses. Further, 2 FPN controls were excluded from the extraction of biosamples because of former hepatitis infections. Details on available survey modules and biosamples for participants are shown in Table 3 for each donor group.

Table 3. Actual available survey modules and biosamples for participants in each donor group.

Type of data	SPNs[a] (n=101)	FPNs[b] (n=340)	Controls (n=150)	Total (n=591)
Questionnaire data, n (%)				
Participant information	85 (84.2)	325 (95.6)	144 (96.0)	554 (93.7)
Family history of diseases	85 (84.2)	325 (95.6)	146 (97.3)	556 (94.1)
Both questionnaires	85 (84.2)	325 (95.6)	144 (96.0)	554 (93.7)
Biosamples, n (%)				
Biopsy	92 (91.1)	307 (90.3)	100 (66.7)	499 (84.4)
Saliva	84 (83.2)	319 (93.8)	108 (72.0)	511 (86.5)
Biopsy and saliva	77 (76.2)	291 (85.6)	71 (47.3)	439 (74.3)
Biopsy or saliva	99 (98.0)	335 (98.5)	137 (91.3)	571 (96.6)
No bio-samples	2 (2.0)	5 (1.5)	13 (8.7)	20 (3.4)
Cryopreserved tubes of fibroblasts				
Total, n	757	2179	950	3886
Tubes per participant, mean (SD)	7.7 (4.3)	6.5 (3.1)	6.9 (5.9)	6.8 (4.2)
Tubes per participant, minimum	0	0	0	0
Tubes per participant, maximum	20	16	28	28
DNA extracts, n (%)				
From fibroblasts	90 (89.1)	301 (88.5)	97 (64.7)	488 (82.6)
From saliva	84 (83.2)	319 (93.8)	107 (71.3)	510 (86.3)

[a]SPNs: second primary neoplasms.

[b]FPNs: first primary neoplasms.

Discussion

Principal Findings

Our molecular-epidemiological study is the first attempting to analyze observational data from questionnaires and molecular-biological factors associated with ionizing radiation in primary human fibroblasts of a unique childhood cancer survivor cohort. To study molecular-biological factors, we succeeded in obtaining fibroblasts derived from 499 skin biopsies and 511 saliva samples of former childhood cancer patients (SPNs and FPNs) and cancer-free controls. With this source, we can measure individual reactions to ionizing radiation in primary human skin fibroblasts. We will use these data for an informed analysis of potential genetic predispositions. Predispositions defined through DNA mutations can be identified using the DNA extracted from fibroblasts as well as saliva samples. Combining these results with observational data from questionnaires allows us to control for several confounding factors. During the recruitment process, we invited all former SPN and matched FPN patients from the German Childhood Cancer Registry who met our inclusion criteria. However, the number of eligible former childhood cancer patients was limited to 1990 even in such a large and long-running childhood cancer survivor cohort. While the participation of cancer-free controls was high (61%), the rate of participation among former childhood cancer patients was rather low (SPN 41%, FPN 20%). Different participation proportions can be explained by the nature of this study's sampling strategy. Cancer-free controls were contacted in the hospital before undergoing surgery. Biopsies were then taken during that procedure without further effort for the patient. In contrast, SPN and FPN patients needed to travel or keep set appointments made for the biopsy. In general, the study involved complex logistics and high time expenditure for participants, especially for SPN and FPN participants. By implementing the possibility for former childhood cancer patients to participate near their residence, we reduced their effort and time spent on recruitment to a minimum. Our design required immense efforts in recruitment and data collection for the study centers. These efforts were worthwhile as they increased the rate of participation, even though an invasive procedure, such as skin biopsy, was demanded from more or less healthy individuals, and individual genetic analyses were performed. In summary, our study provides a new way of exploring the interplay between childhood cancer and second primary cancer predisposition and ionization radiation. We hope that this study will set a precedent and encourage others to perform similar projects on the international scale, requiring primary fibroblasts for experiments from large childhood cancer survivor cohorts and to investigate the underlying reasons for childhood cancer. This would help to improve therapeutic strategies, reduce the risk of developing a second primary cancer, and enhance the quality of the patients' lives.

To identify molecular mechanisms potentially related to radiation and the development of childhood cancer, analyses at different levels are required to increase our knowledge. On the genomic level, single nucleotide polymorphisms (SNPs) can

and should be analyzed in a population-based sample as it is common in genome-wide association studies (GWAS). Our sample size is limited by the number of available SPN cases and thus corresponds more to the size of a clinical cohort, which does not allow direct transfer of a GWAS approach. However, such clinical cohorts often consider gene expression and less frequently SNPs, which makes direct transmission difficult [92]. Additionally, the investigation of radiation-induced effects will be carried out experimentally by gene expression measurement before and after irradiation. To investigate the connection between radiation and childhood cancer, statistical techniques from these 3 perspectives — GWAS, clinical cohorts, and experiments — must be combined. With this combination, an increase in statistical power can be achieved. However, sufficient statistical power will still be limited to strong associations.

Strengths and Limitations

In contrast to previously conducted studies that investigated the association between ionizing radiation and cancer risk [35,62-69,93-106], this epidemiological study is one of the first enabling the collection of detailed molecular-biological information before and after exposure of primary fibroblasts from a large number of participants exposed to diagnostic and therapeutic doses of ionizing radiation to investigate innate genetic radiation responses in the patients' normal somatic cells [60,61]. We chose to perform experiments with primary fibroblasts, although lymphocytes used in other studies [107] would have been easier to attain by venipuncture. However, their survival and prolonged cultivation without immortalization by Epstein-Barr virus transformation are very limited [108]. Moreover, as some of our SPN and FPN donors have received bone marrow transplants, blood samples would have contained foreign blood cells of the bone marrow donors [109], which makes it impossible to analyze germline mutations of included cases. By measuring individual reactions to different exposures of radiation in normal somatic cells of the same person, our design enables us to create several exposure scenarios for the same participant simultaneously and therefore to trick the problem of counterfactual thinking and to avoid some confounding and bias [70]. The combination with observational data from questionnaires on medical radiation history, health, and family history of diseases allows comprehensive control for important confounders in the development of cancer. With additional collection of saliva samples from participants, DNA from an independent source is available for the validation and replication of results.

There are also several limitations to our study design. Given that we will analyze primary fibroblasts as monolayer cell cultures in vitro, this approach does not allow consideration of nontargeted radiation responses, such as the intercellular transmission of primarily adverse radiation effects to unirradiated neighboring cells via the so-called bystander effect, and their role in the development of therapy-related SPN [110]. Thus, the complexity of the 3D interaction of the in vivo radiation response and its clinical manifestation cannot be adequately represented by experiments in our study with monolayers of a single cell type. In addition, gene expression and radiation response of the chosen primary fibroblasts might not be representative of cells of various target organs and all cancer subtypes. However, the experiments conducted in this study enable first and very important insights into the etiology of childhood cancer and SPN. Moreover, the biological endpoints of this study might be influenced by the exposure history of the fibroblasts to possible carcinogenic factors (eg, cancer therapy, alcohol, tobacco, medication). To deal with this problem, our questionnaires cover a broad spectrum of possible confounding factors and allow us to control for them. As with all epidemiological studies requiring biological material from patients, our study underlies an inherent survivor bias, as solely living patients could be recruited. Severe cases with high mortality (eg, acute myeloid leukemia after acute lymphoid leukemia or 2 diagnoses in rapid succession) cannot be captured to a full extent by this study. A selection bias cannot be ruled out in this study, as individuals, either without long-term health damages or with severe health problems, might be less motivated to participate. Moreover, a family history of cancer might influence the willingness to participate, and the statistical power might be limited by the sample size of available former childhood cancer cases. However, the invitations to this study included the maximum number of former childhood cancer patients registered in the German Childhood Cancer Registry that met the inclusion criteria. The recruitment of living patients several years after their diagnosis for the study further limited our analysis to particular patients that suffered from first and second malignancies with a good prognosis. The source population of hospital-based, cancer-free controls is regionally limited to the rural and urban areas around the University Medical Center in Mainz, while population-based cases were recruited all over Germany. However, we do not expect any major differences in the source populations since we expect that neither the interplay between hereditary dispositions and radiation nor cancer have any causal effect on hospitalization after an accident in the Mainz area. Thus, restricting the majority to these controls is equivalent to taking a simple random sample of the original population [74]. In addition, it is known that participation decreases in populations with lower education as well as in very high-income groups. Even though there is no information on socioeconomic status for nonparticipants, we were able to compare the available information of the nonparticipants with the obtained information of the participants. The distribution of sex, age, and age at first diagnosis was similar among participants and nonparticipants and is representative for former childhood cancer patients with these diagnoses in Germany [32].

Conclusions

To our knowledge, this is the first molecular-epidemiological study on radiation, childhood cancer, and second primary cancer providing a large number of primary fibroblasts from skin biopsies of well-characterized and carefully matched participants for irradiation experiments. In this study, we were able to successfully recruit 441 former SPN and FPN patients from the large survivor cohort of the German Childhood Cancer Registry long after their diagnosis and 150 cancer-free control patients from the Department of Orthopedics and Traumatology of the University Medical Center Mainz. In future projects, the combination of experimental and observational data with a

unique study sample, including primary normal somatic cells from former childhood cancer patients and cancer-free controls, will forward research on radiation-related risk factors for childhood cancer, SPNs, and its underlying genetics. Using the gained knowledge from irradiation experiments and analyses on different molecular levels (eg, DNA, RNA, epigenetics), we aim to overcome challenges of personalized childhood cancer therapies and gain insight into the detrimental cellular responses and potential mechanisms of low medically applied radiation doses.

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Authors' Contributions

MM is a principal investigator of the KiKme study and developed its design, which was implemented and monitored by MM and LKB. PK supported the development of strategies for the recruitment of former childhood cancer patients. MM, LKB, IS, and DG conducted the recruitment of the participants, which was organized and planned by MM, LKB, and IS. MM, LKB, HS, and PD monitored the recruitment of controls. DG, SZ, and HS established the method of fibroblast sampling. CG, PD, and JH were responsible for biopsy sampling. They were trained and supervised by MM and HS. In the study, HSZ takes care of the project´s biobank and controls for the quality of all biosamples. IS conducts the work in the laboratory, including the processing of saliva samples and skin biopsies. LKB and SZ were responsible for the pseudonymization of all biosamples. MM, HB, MH, and AP developed the analyses pipelines for the project. Analysis data of biosamples are processed by AP and TH. LKB and WHB are responsible for data management. HSZ, SZ, DG, IS, JM, PSK, PK, AP, HB, TH, MB, and HS contributed to the writing process, which was initially prepared by MM and LKB. All authors revised the manuscript and agreed to be accountable for all aspects of the work.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Number of matching groups and time spans for matching between patient groups of participants.
[DOCX File , 19 KB - resprot_v10i11e32395_app1.docx]

References

1. Thun M, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D. Cancer Epidemiology and Prevention, 4th edition. Oxford, England: Oxford University Press; 2017.
2. Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F, IICC-3 contributors. International incidence of childhood cancer, 2001-10: a population-based registry study. Lancet Oncol 2017 Jun;18(6):719-731 [FREE Full text] [doi: 10.1016/S1470-2045(17)30186-9] [Medline: 28410997]
3. Spector LG, Pankratz N, Marcotte EL. Genetic and nongenetic risk factors for childhood cancer. Pediatr Clin North Am 2015 Feb;62(1):11-25 [FREE Full text] [doi: 10.1016/j.pcl.2014.09.013] [Medline: 25435109]
4. Matsuse M, Takahashi M, Mitsutake N, Nishihara E, Hirokawa M, Kawaguchi T, et al. The FOXE1 and NKX2-1 loci are associated with susceptibility to papillary thyroid carcinoma in the Japanese population. J Med Genet 2011 Sep;48(9):645-648. [doi: 10.1136/jmedgenet-2011-100063] [Medline: 21730105]
5. Johansson G, Andersson U, Melin B. Recent developments in brain tumor predisposing syndromes. Acta Oncol 2016;55(4):401-411. [doi: 10.3109/0284186X.2015.1107190] [Medline: 26634384]

6. Giacomazzi CR, Giacomazzi J, Netto CBO, Santos-Silva P, Selistre SG, Maia AL, et al. Pediatric cancer and Li-Fraumeni/Li-Fraumeni-like syndromes: a review for the pediatrician. Rev Assoc Med Bras (1992) 2015;61(3):282-289 [FREE Full text] [doi: 10.1590/1806-9282.61.03.282] [Medline: 26248253]
7. Saletta F, Dalla Pozza L, Byrne JA. Genetic causes of cancer predisposition in children and adolescents. Transl Pediatr 2015 Apr;4(2):67-75 [FREE Full text] [doi: 10.3978/j.issn.2224-4336.2015.04.08] [Medline: 26835363]
8. Zhang J, Walsh MF, Wu G, Edmonson MN, Gruber TA, Easton J, et al. Germline mutations in predisposition genes in pediatric cancer. N Engl J Med 2015 Dec 10;373(24):2336-2346 [FREE Full text] [doi: 10.1056/NEJMoa1508054] [Medline: 26580448]
9. Mateos MK, Barbaric D, Byatt S, Sutton R, Marshall GM. Down syndrome and leukemia: insights into leukemogenesis and translational targets. Transl Pediatr 2015 Apr;4(2):76-92 [FREE Full text] [doi: 10.3978/j.issn.2224-4336.2015.03.03] [Medline: 26835364]
10. Takeuchi S, Koike M, Park S, Seriu T, Bartram CR, Taub HE, et al. The ATM gene and susceptibility to childhood T-cell acute lymphoblastic leukaemia. Br J Haematol 1998 Nov;103(2):536-538. [doi: 10.1046/j.1365-2141.1998.00993.x] [Medline: 9827931]
11. Mansur MB, van Delft FW, Colman SM, Furness CL, Gibson J, Emerenciano M, et al. Distinctive genotypes in infants with T-cell acute lymphoblastic leukaemia. Br J Haematol 2015 Nov;171(4):574-584 [FREE Full text] [doi: 10.1111/bjh.13613] [Medline: 26205622]
12. Cavé H, Caye A, Strullu M, Aladjidi N, Vignal C, Ferster A, et al. Acute lymphoblastic leukemia in the context of RASopathies. Eur J Med Genet 2016 Mar;59(3):173-178. [doi: 10.1016/j.ejmg.2016.01.003] [Medline: 26855057]
13. Kratz CP, Franke L, Peters H, Kohlschmidt N, Kazmierczak B, Finckh U, et al. Cancer spectrum and frequency among children with Noonan, Costello, and cardio-facio-cutaneous syndromes. Br J Cancer 2015 Apr 14;112(8):1392-1397 [FREE Full text] [doi: 10.1038/bjc.2015.75] [Medline: 25742478]
14. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016 May 19;127(20):2391-2405 [FREE Full text] [doi: 10.1182/blood-2016-03-643544] [Medline: 27069254]
15. Czuchlewski DR, Peterson LC. Myeloid neoplasms with germline predisposition: A new provisional entity within the World Health Organization Classification. Surg Pathol Clin 2016 Mar;9(1):165-176. [doi: 10.1016/j.path.2015.09.010] [Medline: 26940275]
16. Lakshmi Narendra B, Eshvendar Reddy K, Shantikumar S, Ramakrishna S. Immune system: a double-edged sword in cancer. Inflamm Res 2013 Sep 19;62(9):823-834. [doi: 10.1007/s00011-013-0645-9] [Medline: 23868500]
17. Ward G. The infective theory of acute leukaemia. British Journal of Childhood Diseases 1917:1.
18. Greaves M. Infection, immune responses and the aetiology of childhood leukaemia. Nat Rev Cancer 2006 Mar 9;6(3):193-203. [doi: 10.1038/nrc1816] [Medline: 16467884]
19. Adami HO, Hunter D, Trichopoulos D. Textbook of Cancer Epidemiology, 2nd edition. Oxford, England: Oxford University Press; 2008.
20. Villumsen M, Sørup S, Jess T, Ravn H, Relander T, Baker JL, et al. Risk of lymphoma and leukaemia after bacille Calmette-Guérin and smallpox vaccination: a Danish case-cohort study. Vaccine 2009 Nov 16;27(49):6950-6958. [doi: 10.1016/j.vaccine.2009.08.103] [Medline: 19747577]
21. Caputo M, Raupach-Rosin H, Karch A, Borte M, Lehmann I, Liebert UG, et al. Vaccinations and infections are associated with unrelated antibody titers: An analysis from the German Birth Cohort Study LISA. Front Pediatr 2019 Jun 25;7:254 [FREE Full text] [doi: 10.3389/fped.2019.00254] [Medline: 31294004]
22. Marcotte EL, Thomopoulos TP, Infante-Rivard C, Clavel J, Petridou ET, Schüz J, et al. Caesarean delivery and risk of childhood leukaemia: a pooled analysis from the Childhood Leukemia International Consortium (CLIC). Lancet Haematol 2016 Apr;3(4):e176-e185 [FREE Full text] [doi: 10.1016/S2352-3026(16)00002-8] [Medline: 27063976]
23. Rudant J, Orsi L, Menegaux F, Petit A, Baruchel A, Bertrand Y, et al. Childhood acute leukemia, early common infections, and allergy: The ESCALE Study. Am J Epidemiol 2010 Nov 01;172(9):1015-1027. [doi: 10.1093/aje/kwq233] [Medline: 20807738]
24. Rudant J, Lightfoot T, Urayama KY, Petridou E, Dockerty JD, Magnani C, et al. Childhood acute lymphoblastic leukemia and indicators of early immune stimulation: a Childhood Leukemia International Consortium study. Am J Epidemiol 2015 Apr 15;181(8):549-562 [FREE Full text] [doi: 10.1093/aje/kwu298] [Medline: 25731888]
25. Urayama KY, Buffler PA, Gallagher ER, Ayoob JM, Ma X. A meta-analysis of the association between day-care attendance and childhood acute lymphoblastic leukaemia. Int J Epidemiol 2010 Jun;39(3):718-732 [FREE Full text] [doi: 10.1093/ije/dyp378] [Medline: 20110276]
26. UK Childhood Cancer Study Investigators. Breastfeeding and childhood cancer. Br J Cancer 2001 Nov 30;85(11):1685-1694 [FREE Full text] [doi: 10.1054/bjoc.2001.2110] [Medline: 11742489]
27. Maia RDRP, Wunsch Filho V. Infection and childhood leukemia: review of evidence. Rev. Saude Publica 2013 Dec;47(6):1172-1185. [doi: 10.1590/s0034-89102013000901172]

28. Morra ME, Kien ND, Elmaraezy A, Abdelaziz OAM, Elsayed AL, Halhouli O, et al. Early vaccination protects against childhood leukemia: A systematic review and meta-analysis. Sci Rep 2017 Nov 22;7(1):15986 [FREE Full text] [doi: 10.1038/s41598-017-16067-0] [Medline: 29167460]
29. Schottenfeld DL, Beebe-Dimmer J. Multiple Primary Cancers. In: Schottenfeld D, Fraumeni JF, editors. Cancer Epidemiology and Prevention. Oxford, England: Oxford University Press; 2009.
30. Ross J, Spector L. Cancers in Children. In: Schoettenfeld D, Fraumeni JF, editors. Cancer Epidemiology and Prevention. Oxford, England: Oxford University Press; 2006:1251-1268.
31. Nikiforova MN, Stringer JR, Blough R, Medvedovic M, Fagin JA, Nikiforov YE. Proximity of chromosomal loci that participate in radiation-induced rearrangements in human cells. Science 2000 Oct 6;290(5489):138-141. [doi: 10.1126/science.290.5489.138] [Medline: 11021799]
32. Kaatsch PG, Spix C. German Childhood Cancer Registry - Annual Report 2016 (1980-2015). Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI) at the University Medical Center of the Johannes Gutenberg University, Mainz. 2016. URL: https://www.unimedizin-mainz.de/fileadmin/kliniken/dkkr/pdf/jb/jb2016/jb2016_s.pdf [accessed 2021-09-24]
33. Ron E, Modan B, Boice JD, Alfandary E, Stovall M, Chetrit A, et al. Tumors of the brain and nervous system after radiotherapy in childhood. N Engl J Med 1988 Oct 20;319(16):1033-1039. [doi: 10.1056/NEJM198810203191601] [Medline: 3173432]
34. Albert R, Shore R, Harley N, Omran A. Follow-up Studies of Patients Treated by X-Ray Epilation for Tinea Capitis. In: Burns FJ, Upton AC, Silini G, editors. Radiation Carcinogenesis and DNA Alterations. Boston, MA: Springer; 1986:1-25.
35. Tucker MA, Jones PH, Boice JD, Robison LL, Stone BJ, Stovall M, et al. Therapeutic radiation at a young age is linked to secondary thyroid cancer. The Late Effects Study Group. Cancer Res 1991 Jun 01;51(11):2885-2888 [FREE Full text] [Medline: 1851664]
36. Travis LB, Ng AK, Allan JM, Pui C, Kennedy AR, Xu XG, et al. Second malignant neoplasms and cardiovascular disease following radiotherapy. J Natl Cancer Inst 2012 Mar 07;104(5):357-370 [FREE Full text] [doi: 10.1093/jnci/djr533] [Medline: 22312134]
37. Boice JD. Cancer following irradiation in childhood and adolescence. Med Pediatr Oncol Suppl 1996;1:29-34. [Medline: 8643045]
38. Hennewig U, Kaatsch P, Blettner M, Spix C. Local radiation dose and solid second malignant neoplasms after childhood cancer in Germany: a nested case-control study. Radiat Environ Biophys 2014 Aug 27;53(3):485-493. [doi: 10.1007/s00411-014-0550-9] [Medline: 24859016]
39. Tukenova M, Guibout C, Hawkins M, Quiniou E, Mousannif A, Pacquement H, et al. Radiation therapy and late mortality from second sarcoma, carcinoma, and hematological malignancies after a solid cancer in childhood. Int J Radiat Oncol Biol Phys 2011 Jun 01;80(2):339-346. [doi: 10.1016/j.ijrobp.2010.02.004] [Medline: 20646844]
40. Thun M, Linet M, Cerhan J, Haiman C, Schottenfeld D. Cancer Epidemiology and Prevention. In: 2017 (4). Oxford, England: Oxford University Press; 2017.
41. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 100D. World Health Organization International Agency for Research on Cancer. 2012. URL: https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Radiation-2012 [accessed 2021-09-24]
42. Takahashi M, Saenko VA, Rogounovitch TI, Kawaguchi T, Drozd VM, Takigawa-Imamura H, et al. The FOXE1 locus is a major genetic determinant for radiation-related thyroid carcinoma in Chernobyl. Hum Mol Genet 2010 Jun 15;19(12):2516-2523. [doi: 10.1093/hmg/ddq123] [Medline: 20350937]
43. Sherborne AL, Lavergne V, Yu K, Lee L, Davidson PR, Mazor T, et al. Somatic and germline TP53 alterations in second malignant neoplasms from pediatric cancer survivors. Clin Cancer Res 2017 Apr 01;23(7):1852-1861 [FREE Full text] [doi: 10.1158/1078-0432.CCR-16-0610] [Medline: 27683180]
44. Morton LM, Sampson JN, Armstrong GT, Chen T, Hudson MM, Karlins E, et al. Genome-wide association study to identify susceptibility loci that modify radiation-related risk for breast cancer after childhood cancer. J Natl Cancer Inst 2017 Nov 01;109(11):1 [FREE Full text] [doi: 10.1093/jnci/djx058] [Medline: 29059430]
45. Hodgson D, van Leeuwen F, Ng A, Morton L, Henderson TO. Breast cancer after childhood, adolescent, and young adult cancer: it's not just about chest radiation. Am Soc Clin Oncol Educ Book 2017;37:736-745 [FREE Full text] [doi: 10.1200/EDBK_175668] [Medline: 28561716]
46. Meadows AT, Strong LC, Li FP, D'Angio GJ, Schweisguth O, Freeman AI, et al. Bone sarcoma as a second malignant neoplasm in children: influence of radiation and genetic predisposition for the Late Effects Study Group. Cancer 1980 Dec 15;46(12):2603-2606. [doi: 10.1002/1097-0142(19801215)46:12<2603::aid-cncr2820461212>3.0.co;2-4] [Medline: 7448699]
47. Lin EC. Radiation risk from medical imaging. Mayo Clin Proc 2010 Dec;85(12):1142-6; quiz 1146 [FREE Full text] [doi: 10.4065/mcp.2010.0260] [Medline: 21123642]
48. Diallo I, Haddy N, Adjadj E, Samand A, Quiniou E, Chavaudra J, et al. Frequency distribution of second solid cancer locations in relation to the irradiated volume among 115 patients treated for childhood cancer. Int J Radiat Oncol Biol Phys 2009 Jul 01;74(3):876-883. [doi: 10.1016/j.ijrobp.2009.01.040] [Medline: 19386434]

49. Bithell JF, Stiller CA. A new calculation of the carcinogenic risk of obstetric X-raying. Stat Med 1988 Aug;7(8):857-864. [doi: 10.1002/sim.4780070804] [Medline: 3413365]
50. Boice JD, Miller RW. Childhood and adult cancer after intrauterine exposure to ionizing radiation. Teratology 1999 Apr;59(4):227-233. [doi: 10.1002/(SICI)1096-9926(199904)59:4<227::AID-TERA7>3.0.CO;2-E] [Medline: 10331524]
51. Giles D, Hewitt D, Stewart A, Webb J. Malignant disease in childhood and diagnostic irradiation in utero. Lancet 1956 Sep 01;271(6940):447. [doi: 10.1016/s0140-6736(56)91923-7] [Medline: 13358242]
52. Graham S, Levin ML, Lilienfeld AM, Schuman LM, Gibson R, Dowd JE, et al. Preconception, intrauterine, and postnatal irradiation as related to leukemia. Natl Cancer Inst Monogr 1966 Jan;19:347-371. [Medline: 5905674]
53. Linet MS, Slovis TL, Miller DL, Kleinerman R, Lee C, Rajaraman P, et al. Cancer risks associated with external radiation from diagnostic imaging procedures. CA Cancer J Clin 2012;62(2):75-100 [FREE Full text] [doi: 10.3322/caac.21132] [Medline: 22307864]
54. MacMahon B. Prenatal x-ray exposure and childhood cancer. J Natl Cancer Inst 1962 May;28:1173-1191. [Medline: 14468031]
55. Stewart A, Webb J. A survey of childhood malignancies. Br Med J 1958 Jun 28;1(5086):1495-1508 [FREE Full text] [doi: 10.1136/bmj.1.5086.1495] [Medline: 13546604]
56. Wakeford R. Childhood leukaemia following medical diagnostic exposure to ionizing radiation in utero or after birth. Radiat Prot Dosimetry 2008;132(2):166-174. [doi: 10.1093/rpd/ncn272] [Medline: 18922822]
57. Austin LM, Frush DP. Compendium of national guidelines for imaging the pregnant patient. AJR Am J Roentgenol 2011 Oct;197(4):W737-W746. [doi: 10.2214/AJR.10.6351] [Medline: 21940547]
58. Rajaraman P, Simpson J, Neta G, Berrington de Gonzalez A, Ansell P, Linet MS, et al. Early life exposure to diagnostic radiation and ultrasound scans and risk of childhood cancer: case-control study. BMJ 2011 Feb 10;342:d472 [FREE Full text] [doi: 10.1136/bmj.d472] [Medline: 21310791]
59. Baaken D, Hammer GP, Seidenbusch MC, Schneider K, Spix C, Blettner M, et al. Second follow-up of a German cohort on childhood cancer incidence after exposure to postnatal diagnostic x-ray. J Radiol Prot 2019 Jul 25;39(4):1074-1091. [doi: 10.1088/1361-6498/ab3506] [Medline: 31342929]
60. Pernot E, Hall J, Baatout S, Benotmane MA, Blanchardon E, Bouffler S, et al. Ionizing radiation biomarkers for potential use in epidemiological studies. Mutat Res 2012;751(2):258-286 [FREE Full text] [doi: 10.1016/j.mrrev.2012.05.003] [Medline: 22677531]
61. Hall J, Jeggo PA, West C, Gomolka M, Quintens R, Badie C, et al. Ionizing radiation biomarkers in epidemiological studies - An update. Mutat Res Rev Mutat Res 2017;771:59-84. [doi: 10.1016/j.mrrev.2017.01.001] [Medline: 28342453]
62. Krille L, Dreger S, Schindel R, Albrecht T, Asmussen M, Barkhausen J, et al. Risk of cancer incidence before the age of 15 years after exposure to ionising radiation from computed tomography: results from a German cohort study. Radiat Environ Biophys 2015 Mar 8;54(1):1-12. [doi: 10.1007/s00411-014-0580-3] [Medline: 25567615]
63. Krille L, Jahnen A, Mildenberger P, Schneider K, Weisser G, Zeeb H, et al. Computed tomography in children: multicenter cohort study design for the evaluation of cancer risk. Eur J Epidemiol 2011 Mar 12;26(3):249-250. [doi: 10.1007/s10654-011-9549-6] [Medline: 21318426]
64. Krille L, Zeeb H, Jahnen A, Mildenberger P, Seidenbusch M, Schneider K, et al. Computed tomographies and cancer risk in children: a literature overview of CT practices, risk estimations and an epidemiologic cohort study proposal. Radiat Environ Biophys 2012 May 5;51(2):103-111. [doi: 10.1007/s00411-012-0405-1] [Medline: 22310909]
65. Spycher BD, Lupatsch JE, Zwahlen M, Röösli M, Niggli F, Grotzer MA, Swiss Pediatric Oncology Group, Swiss National Cohort Study Group. Background ionizing radiation and the risk of childhood cancer: a census-based nationwide cohort study. Environ Health Perspect 2015 Jun;123(6):622-628 [FREE Full text] [doi: 10.1289/ehp.1408548] [Medline: 25707026]
66. Hammer GP, Seidenbusch MC, Regulla DF, Spix C, Zeeb H, Schneider K, et al. Childhood cancer risk from conventional radiographic examinations for selected referral criteria: Results from a large cohort study. American Journal of Roentgenology 2011 Jul;197(1):217-223. [doi: 10.2214/ajr.10.4979]
67. Spix C, Schmiedel S, Kaatsch P, Schulze-Rath R, Blettner M. Case-control study on childhood cancer in the vicinity of nuclear power plants in Germany 1980-2003. Eur J Cancer 2008 Jan;44(2):275-284. [doi: 10.1016/j.ejca.2007.10.024] [Medline: 18082395]
68. Zeeb H, Blettner M, Hammer GP, Langner I. Cohort mortality study of German cockpit crew, 1960-1997. Epidemiology 2002 Nov;13(6):693-699. [doi: 10.1097/01.EDE.0000029605.69271.8E] [Medline: 12410011]
69. Spix C, Grosche B, Bleher M, Kaatsch P, Scholz-Kreisel P, Blettner M. Background gamma radiation and childhood cancer in Germany: an ecological study. Radiat Environ Biophys 2017 May;56(2):127-138. [doi: 10.1007/s00411-017-0689-2] [Medline: 28337585]
70. Rothman KJ, Greenland S. Modern Epidemiology. Philadelphia, PA: Lippincott Williams & Wilkins; 2009.
71. Kaatsch P, Grabow D, Spix C. German Childhood Cancer Registry - Annual Report 2017 (1980-2016). Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI) at the University Medical Center of the Johannes Gutenberg, University Mainz. 2018. URL: https://www.unimedizin-mainz.de/fileadmin/kliniken/dkkr/pdf/jb/jb2017/jb2017_s.pdf [accessed 2021-09-24]

72. Debling D, Spix C, Blettner M, Michaelis J, Kaatsch P. The cohort of long-term survivors at the German childhood cancer registry. Klin Padiatr 2008;220(6):371-377. [doi: 10.1055/s-0028-1086027] [Medline: 18949673]
73. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. Cancer 2005 Apr 01;103(7):1457-1467 [FREE Full text] [doi: 10.1002/cncr.20910] [Medline: 15712273]
74. Westreich D. Berkson's bias, selection bias, and missing data. Epidemiology 2012 Jan;23(1):159-164 [FREE Full text] [doi: 10.1097/EDE.0b013e31823b6296] [Medline: 22081062]
75. Brackmann L, Grandt C, Schwarz H, Schmidtmann I, Hankeln T, Galetzka D, et al. Exposure assessment among an adult population on radiation therapy, chemotherapy, and other cancer therapies in childhood. In: Cancer Research. 2020 Presented at: AACR Special Conference on the Advances in Pediatric Cancer Research; September 17-20, 2019; Montreal, QC, Canada. [doi: 10.1158/1538-7445.pedca19-b60]
76. Brackmann LK, Poplawski A, Grandt CL, Schwarz H, Hankeln T, Rapp S, et al. Comparison of time and dose dependent gene expression and affected pathways in primary human fibroblasts after exposure to ionizing radiation. Mol Med 2020 Sep 09;26(1):85 [FREE Full text] [doi: 10.1186/s10020-020-00203-0] [Medline: 32907548]
77. Law CW, Chen Y, Shi W, Smyth GK. voom: Precision weights unlock linear model analysis tools for RNA-seq read counts. Genome Biol 2014 Feb 03;15(2):R29 [FREE Full text] [doi: 10.1186/gb-2014-15-2-r29] [Medline: 24485249]
78. Ritchie ME, Phipson B, Wu D, Hu Y, Law CW, Shi W, et al. limma powers differential expression analyses for RNA-sequencing and microarray studies. Nucleic Acids Res 2015 Apr 20;43(7):e47 [FREE Full text] [doi: 10.1093/nar/gkv007] [Medline: 25605792]
79. Krämer A, Green J, Pollard J, Tugendreich S. Causal analysis approaches in Ingenuity Pathway Analysis. Bioinformatics 2014 Feb 15;30(4):523-530 [FREE Full text] [doi: 10.1093/bioinformatics/btt703] [Medline: 24336805]
80. Xu H, Liu Y, Li Y, Diao L, Xun Z, Zhang Y, et al. RadAtlas 1.0: a knowledgebase focusing on radiation-associated genes. Int J Radiat Biol 2020 Aug;96(8):980-987. [doi: 10.1080/09553002.2020.1761567] [Medline: 32338561]
81. Zhang J, Baran J, Cros A, Guberman JM, Haider S, Hsu J, et al. International Cancer Genome Consortium Data Portal--a one-stop shop for cancer genomics data. Database (Oxford) 2011;2011:bar026 [FREE Full text] [doi: 10.1093/database/bar026] [Medline: 21930502]
82. Jeanquartier F, Jean-Quartier C, Holzinger A. Use case driven evaluation of open databases for pediatric cancer research. BioData Min 2019;12:2 [FREE Full text] [doi: 10.1186/s13040-018-0190-8] [Medline: 30675185]
83. GTEx Consortium. Human genomics. The Genotype-Tissue Expression (GTEx) pilot analysis: multitissue gene regulation in humans. Science 2015 May 08;348(6235):648-660 [FREE Full text] [doi: 10.1126/science.1262110] [Medline: 25954001]
84. Li X, Kim Y, Tsang EK, Davis JR, Damani FN, Chiang C, GTEx Consortium, Laboratory, Data Analysis Center (LDACC)—Analysis Working Group, Statistical Methods groups—Analysis Working Group, Enhancing GTEx (eGTEx) groups, NIH/NCI, NIH/NHGRI, NIH/NIMH, NIH/NIDA, Biospecimen Collection Source Site—NDRI, Biospecimen Collection Source Site—RPCI, Biospecimen Core Resource—VARI, Brain Bank Repository—University of Miami Brain Endowment Bank, Leidos Biomedical—Project Management, ELSI Study, Genome Browser Data Integration —EBI, Genome Browser Data Integration —UCSC Genomics Institute, University of California Santa Cruz, et al. The impact of rare variation on gene expression across tissues. Nature 2017 Oct 11;550(7675):239-243 [FREE Full text] [doi: 10.1038/nature24267] [Medline: 29022581]
85. Tutz G, Binder H. Generalized additive modeling with implicit variable selection by likelihood-based boosting. Biometrics 2006 Dec;62(4):961-971. [doi: 10.1111/j.1541-0420.2006.00578.x] [Medline: 17156269]
86. Zhan X, Hu Y, Li B, Abecasis GR, Liu DJ. RVTESTS: an efficient and comprehensive tool for rare variant association analysis using sequence data. Bioinformatics 2016 May 01;32(9):1423-1426 [FREE Full text] [doi: 10.1093/bioinformatics/btw079] [Medline: 27153000]
87. Li B, Leal SM. Methods for detecting associations with rare variants for common diseases: application to analysis of sequence data. Am J Hum Genet 2008 Sep;83(3):311-321 [FREE Full text] [doi: 10.1016/j.ajhg.2008.06.024] [Medline: 18691683]
88. Wu MC, Lee S, Cai T, Li Y, Boehnke M, Lin X. Rare-variant association testing for sequencing data with the sequence kernel association test. Am J Hum Genet 2011 Jul 15;89(1):82-93 [FREE Full text] [doi: 10.1016/j.ajhg.2011.05.029] [Medline: 21737059]
89. Price AL, Kryukov GV, de Bakker PI, Purcell SM, Staples J, Wei L, et al. Pooled association tests for rare variants in exon-resequencing studies. The American Journal of Human Genetics 2010 Jun;86(6):982. [doi: 10.1016/j.ajhg.2010.05.014]
90. Hill J. A survey of cancer sites by kinship in the Utah Mormon population. Cancer Incidence in Defined Populations: Banbury Report 1980;4:299.
91. Rainer J, Taliun D, D'Elia Y, Pattaro C, Domingues FS, Weichenberger CX. FamAgg: an R package to evaluate familial aggregation of traits in large pedigrees. Bioinformatics 2016 May 15;32(10):1583-1585 [FREE Full text] [doi: 10.1093/bioinformatics/btw019] [Medline: 26803158]
92. Binder H, Benner A, Bullinger L, Schumacher M. Tailoring sparse multivariable regression techniques for prognostic single-nucleotide polymorphism signatures. Stat Med 2013 May 10;32(10):1778-1791. [doi: 10.1002/sim.5490] [Medline: 22786659]

93. Pokora R, Krille L, Dreger S, Lee C, Günster C, Zeeb H, et al. Computed Tomography in Germany. Dtsch Arztebl Int 2016 Oct 28;113(43):721-728 [FREE Full text] [doi: 10.3238/arztebl.2016.0721] [Medline: 27866569]
94. Pierce DA, Shimizu Y, Preston DL, Vaeth M, Mabuchi K. Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950-1990. Radiat Res 1996 Jul;146(1):1-27. [Medline: 8677290]
95. Cardis E, Gilbert ES, Carpenter L, Howe G, Kato I, Armstrong BK, et al. Effects of low doses and low dose rates of external ionizing radiation: cancer mortality among nuclear industry workers in three countries. Radiat Res 1995 May;142(2):117-132. [Medline: 7724726]
96. Preston DL, Kusumi S, Tomonaga M, Izumi S, Ron E, Kuramoto A, et al. Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950-1987. Radiat Res 1994 Feb;137(2 Suppl):S68-S97. [Medline: 8127953]
97. Thompson DE, Mabuchi K, Ron E, Soda M, Tokunaga M, Ochikubo S, et al. Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958-1987. Radiat Res 1994 Feb;137(2 Suppl):S17-S67. [Medline: 8127952]
98. Boice JD, Blettner M, Kleinerman RA, Stovall M, Moloney WC, Engholm G, et al. Radiation dose and leukemia risk in patients treated for cancer of the cervix. J Natl Cancer Inst 1987 Dec;79(6):1295-1311. [Medline: 3480381]
99. Boice JD, Engholm G, Kleinerman RA, Blettner M, Stovall M, Lisco H, et al. Radiation dose and second cancer risk in patients treated for cancer of the cervix. Radiat Res 1988 Oct;116(1):3-55. [Medline: 3186929]
100. Boice JD, Preston D, Davis FG, Monson RR. Frequent chest X-ray fluoroscopy and breast cancer incidence among tuberculosis patients in Massachusetts. Radiat Res 1991 Feb;125(2):214-222. [Medline: 1996380]
101. Tucker MA, D'Angio GJ, Boice JD, Strong LC, Li FP, Stovall M, et al. Bone sarcomas linked to radiotherapy and chemotherapy in children. N Engl J Med 1987 Sep 03;317(10):588-593. [doi: 10.1056/NEJM198709033171002] [Medline: 3475572]
102. Hawkins MM, Wilson LM, Burton HS, Potok MH, Winter DL, Marsden HB, et al. Radiotherapy, alkylating agents, and risk of bone cancer after childhood cancer. J Natl Cancer Inst 1996 Mar 06;88(5):270-278. [doi: 10.1093/jnci/88.5.270] [Medline: 8614005]
103. Wong FL, Boice JD, Abramson DH, Tarone RE, Kleinerman RA, Stovall M, et al. Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. JAMA 1997 Oct 15;278(15):1262-1267. [doi: 10.1001/jama.278.15.1262] [Medline: 9333268]
104. de Vathaire F, Hardiman C, Shamsaldin A, Campbell S, Grimaud E, Hawkins M, et al. Thyroid carcinomas after irradiation for a first cancer during childhood. Arch Intern Med 1999;159(22):2713-2719. [doi: 10.1001/archinte.159.22.2713] [Medline: 10597762]
105. Juerß D, Zwar M, Giesen U, Nolte R, Kriesen S, Baiocco G, et al. Comparative study of the effects of different radiation qualities on normal human breast cells. Radiat Oncol 2017 Sep 25;12(1):159 [FREE Full text] [doi: 10.1186/s13014-017-0895-8] [Medline: 28946898]
106. Yang XR, Killian JK, Hammond S, Burke LS, Bennett H, Wang Y, et al. Characterization of genomic alterations in radiation-associated breast cancer among childhood cancer survivors, using comparative genomic hybridization (CGH) arrays. PLoS One 2015;10(3):e0116078 [FREE Full text] [doi: 10.1371/journal.pone.0116078] [Medline: 25764003]
107. Haddy N, Tartier L, Koscielny S, Adjadj E, Rubino C, Brugières L, et al. Repair of ionizing radiation-induced DNA damage and risk of second cancer in childhood cancer survivors. Carcinogenesis 2014 Aug;35(8):1745-1749. [doi: 10.1093/carcin/bgu077] [Medline: 24670918]
108. Neitzel H. A routine method for the establishment of permanent growing lymphoblastoid cell lines. Hum Genet 1986 Aug;73(4):320-326. [doi: 10.1007/BF00279094] [Medline: 3017841]
109. Victor A, Weis E, Messow CM, Marron M, Haaf T, Spix C, et al. Searching for gene expression differences in primary fibroblasts between patients with one and two neoplasms in childhood. Pediatr Hematol Oncol 2013 Feb 09;30(1):33-45. [doi: 10.3109/08880018.2012.735747] [Medline: 23140311]
110. Sokolov M, Neumann R. Global gene expression alterations as a crucial constituent of human cell response to low doses of ionizing radiation exposure. Int J Mol Sci 2015 Dec 31;17(1):1 [FREE Full text] [doi: 10.3390/ijms17010055] [Medline: 26729107]

Abbreviations

CMC: combined multivariate and collapsing
eQTLs: expression quantitative trait loci
FDR: false discovery rate
FPN: first primary neoplasm
GTEx: genotype-tissue expression
GWAS: genome-wide association study
Gy: Gray
ICCC-3: International Classification of Childhood Cancer, Third edition
ICGC: International Cancer Genome Consortium

IPA: Ingenuity Pathway Analysis
OR: odds ratio
PeCan: Pediatric Cancer Genomic Data Portal
Pedican: Pediatric cancer gene database
RVTEST: forest tests
SKAT: sequence Kernel association test
SNP: single nucleotide polymorphism
SNV: single-nucleotide variant
SPN: second primary neoplasm

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Protocol

Discovery of Arthritis in Psoriasis Patients for Early Rheumatological Referral (DAPPER): Protocol for a Longitudinal Observational Study

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Abstract

Background: One in three patients with psoriasis will develop psoriatic arthritis (PsA). If left untreated, this can lead to pain, impaired function, and irreversible joint damage. Timely recognition and referral to a rheumatologist are therefore key. However, current methods used to screen patients with psoriasis for those who might benefit from referral to a rheumatologist are not performing well enough.

Objective: The Discovery of Arthritis in Psoriasis Patients for Early Rheumatological Referral (DAPPER) study is designed to determine the prevalence of PsA in a psoriasis population and to find parameters that can be used to develop a new or enhance an existing instrument for a rheumatological referral.

Methods: DAPPER is a longitudinal observational study with a 1-year follow-up. Patients with psoriasis (N=300) who are treated at an outpatient dermatological clinic will be screened extensively for signs and symptoms of PsA by a trained rheumatologist. If there is clinical suspicion of PsA and the patient is not yet treated by a rheumatologist, referral to the Department of Rheumatology will follow for confirmation of the diagnosis and further care. After 1 year, data on changes in quality of life and PsA and psoriasis disease activity will be collected from the referred patients. The screening visit will be used to gather demographical and medical data, which can later be used to develop the aforementioned screening instrument.

Results: Inclusion started in June 2019 and finished in June 2021. Follow-up with newly discovered patients with PsA is ongoing.

Conclusions: The DAPPER study is specifically designed to improve the detection of existing PsA in a dermatologic outpatient setting. Although internal validity will be tested, external validity will have to be checked using a second validation cohort. To predict the development of PsA in the future, longitudinal/prospective data collection is required and will be performed in a follow-up study (DAPPER-i).

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KEYWORDS

psoriasis; psoriatic arthritis; screening

Introduction

Psoriasis is a common immune-mediated skin disease. Besides skin and nails, psoriatic disease can also involve several other domains such as the entheses and the peripheral as well as the axial joints. This involvement of the musculoskeletal system defines psoriatic arthritis (PsA). PsA is an inflammatory rheumatic disease, related to other spondyloarthritides such as reactive arthritis, ankylosing spondylitis, or inflammatory bowel disease–associated arthritis. About one in three patients with psoriasis in the dermatological outpatient clinic will eventually develop PsA [1,2]. The order and amount of domains involved display a large variation in different patients and at different time points [3]. However, the musculoskeletal symptoms often develop after the disease shows itself in skin or nails. On average, the lag time between skin and joint involvement is 10 years [4].

When joints or entheses become inflamed, these can cause significant pain and have a large impact on the quality of life [5]. Moreover, ongoing inflammation of joints can lead to irreversible joint damage and disability [6,7]. Early and adequate treatment of arthritis leads to an improvement of both joint function and quality of life [8,9]. Therefore, it is important to recognize and treat patients with concomitant arthritis as soon as possible.

The treatment strategies for psoriasis and PsA show considerable overlap [10,11]. Several pharmacological options are effective and recommended to treat both skin and joints. These encompass, for example, conventional systemic drugs such as methotrexate and several biological drugs such as tumor necrosis factor alpha inhibitors and interleukin-17 inhibitors. However, some options are only available for one of these disease entities. This may be because of the delivery mode (eg, topical application of creams for psoriasis or local injections of corticosteroids for PsA) or because of a difference in efficacy in controlling either joint or skin disease (eg, retinoids for psoriasis and leflunomide for PsA). This could mean that the therapy a patient uses for their skin can also be effective for their musculoskeletal complaints.

To ensure early adequate treatment and prevent (irreversible) morbidity, early recognition and early referral to a rheumatologist are key. The combined guidelines of the American Association of Dermatologist and the National Psoriasis Foundation calls screening of patients with psoriasis for PsA “essential at each visit” [12]. However, recognition of inflammatory joint complaints is not part of the dermatological scope. In addition, due to a large prevalence of noninflammatory joint complaints, referral of all patients with musculoskeletal pain is considered an unnecessary drain of resources. Therefore, about one in three patients with PsA remain unrecognized in the dermatological clinic [1] and are at risk for irreversible damage.

To aid the recognition of PsA by dermatologists, several screening questionnaires have been developed [13-16]. Most of these are based on multiple patient-reported signs or symptoms and result in a cumulative score. Referral to a rheumatologist is recommended when a certain score is reached. Unfortunately, testing of these questionnaires in new cohorts often had disappointing results [17,18]. The long average lag time between psoriasis and PsA also necessitates repeated use of a screening tool on a regular basis. However, none of the questionnaires were validated for reuse. These are all clues that current referral strategies are inadequate.

By screening a psoriasis population for the presence of concomitant PsA, we want to determine the prevalence of (undiscovered) PsA in this group. During this screening visit, we will gather data about several clinical characteristics. These will be used to ultimately develop a new or enhance an existing instrument for rheumatologic referral. This study is therefore called the Discovery of Arthritis in Psoriasis Patients for Early Rheumatology Referral (DAPPER).

Methods

Aim

The aim of this study is to determine the number of patients with (untreated) PsA in a group of psoriasis patients in a dermatological outpatient clinic. Furthermore, we want to optimize the detection of PsA in patients with psoriasis in a dermatological outpatient clinic. For this purpose, we defined the following research questions.

The primary objective is to determine the prevalence of very early, newly-discovered, and known PsA in a cohort of patients with psoriasis treated at a dermatology outpatient clinic.

The secondary objectives include determining if, in newly diagnosed patients with PsA, PsA disease activity and quality of life differ before and 1 year after rheumatological referral in case of PsA; discovering clinical parameters that are associated with the presence of PsA in a cohort of patients with psoriasis; and using the aforementioned parameters to develop a new or enhance an existing screening tool for concomitant PsA in patients with psoriasis.

Design

The DAPPER study is a monocenter observational study with a follow-up of 1 year. We will examine 300 patients stratified 1:1:1 according to current dermatological treatment (topical or UV therapy only, conventional systemic medication but no biologicals, biological therapy).

The initial screening at the dermatology department will include a 68 tender joint count, 66 swollen joint count, a dactylitis count (0-20), and enthesitis scores (Leeds Enthesitis Index [LEI] [19] and the enthesitis score of the Spondyloarthritis Research Consortium of Canada [SPARCC] [20]). Inflammatory back pain will be assessed via the criteria of the Assessment of Spondyloarthritis International Society [21]. At this study visit, no laboratory tests or imaging will be performed for diagnostic purposes.

To investigate possible identifying characteristics or confounders for the detection of PsA, the study visit will also be used to gather demographical data (comorbidity, treatment data, and clinical characteristics of the skin). An example of the interview guide used is shown in Multimedia Appendix 1.

Referral and Referral Criteria

If there is a clinical suspicion of PsA in the study visit according to the study physician (trained rheumatologist), the patient will be referred to the Department of Rheumatology. Referral to a rheumatologist will be at the discretion of the investigator. A patient will be referred when not under current rheumatological care and when meeting one of the following criteria: one or more swollen joints, clinical evidence of inflammatory enthesitis, and/or inflammatory back pain. Other reasons to suspect PsA can also give rise to referral (eg, restricted movement in a joint or prolonged morning stiffness). From there on, these patients will be investigated and treated as in regular PsA care. This will include confirmation of the diagnosis with additional laboratory tests and imaging, and treat-to-target via the Psoriatic Arthritis Disease Activity Score (PASDAS) [22].

Follow-up

Only those patients with a newly discovered PsA, as confirmed by a rheumatologist after referral, will be approached for follow-up after 1 year. At that moment, changes in treatment, disease activity, and health-related quality of life (HR-QoL) will be noted.

Study Setting

This study will be carried out in the outpatient clinic of the Department of Dermatology in an academic center in the Netherlands (Radboud University Medical Center, Nijmegen). This department is a national psoriasis expertise center. Patients will initially be screened at the Department of Dermatology for signs or symptoms of enthesitis, dactylitis, arthritis, or inflammatory back pain by a trained rheumatologist. When additional rheumatological evaluation is required, patients are preferentially referred to the Department of Rheumatology of the Sint Maartenskliniek in Nijmegen. Here, the patient will be assessed by a rheumatologist with special expertise in PsA. When requested by the patient, a referral to another rheumatologic center is also possible.

Participants

All patients with a clinical diagnosis of psoriasis who are treated at the outpatient clinic are eligible for this study. Neither current nor previous treatment by a rheumatologist nor a previous diagnosis of PsA are exclusion criteria. Patients must be 18 years or older and be able to give written informed consent.

Study Size

For the logistic model, we aim to use 5 to 10 independent variables. The number of independent variables used in the model will be restricted to 1 per 10 events (ie, 1 per 10 PsA cases). Therefore, we aim to have 50 to 100 PsA cases. Assuming a prevalence of PsA of 20% to 30% [1], this means we need 167 (prevalence 30%, 5 predictors) to 500 (prevalence 20%, 10 predictors) patients with psoriasis. Using a total number of 300 patients, we expect to find up to 60 to 90 PsA cases, ensuring we can incorporate 6 to 9 independent variables.

Recruitment

All patients eligible for the study will be asked for study participation by their dermatologist. Written and oral information about the study will be given by the investigator. A study visit will be planned adjacent to a regular outpatient visit with the dermatologist. Before the study visit starts, written informed consent is obtained from the patients.

Outcome Measures

The primary outcome measure will be the percentage of investigated patients with the diagnosis of PsA. This diagnosis will be accepted if it was confirmed by a rheumatologist in correspondence. Fulfillment of Classification Criteria for Psoriatic Arthritis (CASPAR) is not required [23]. After 1 year, patient files of the referred patients will be checked to confirm the diagnosis. If the suspicion of active PsA is confirmed, treatment changes and their effect on disease activity will be noted. Alternatively, the other rheumatological diagnosis will be noted.

In the referred patients with PsA, HR-QoL will be assessed via two disease-specific questionnaires at referral and 1 year thereafter. Skin-related impact will be explored via the Dermatological Life Quality Index (DLQI) [24]. Joint-related impact will be explored via the Psoriatic Arthritis Impact of Disease (PsAID) [25].

Outcome Variables

Prevalence of PsA

To ascertain the presence of PsA, we will ask the patient about joint and enthesis complaints (location, pattern, and intensity), morning stiffness (duration), and whether or not they ever had a diagnosis of arthritis. For confirmation of arthritis, dactylitis, or enthesitis, we will perform joint counts (swollen, tender, and dactylitis) and enthesitis indices (LEI and SPARCC). After referral, the diagnosis of PsA or alternative diagnosis will be retrieved from (the correspondence gathered in) the electronic patient file.

Effect of Referral

In referred patients with confirmed PsA, we will retrieve data at time of referral and 1 year later. We will use the PASDAS as a disease activity score, which gives a full overview of the PsA disease spectrum. We will evaluate both the combined disease activity score and the specific scores of tender and/or swollen joints, dactylitis, and enthesitis. In addition, treatment changes (either instigated by rheumatologist or dermatologist) will be retrieved from the electronic patient file. Impact on HR-QoL will be assessed by questionnaires before referral and after 1 year (DLQI [24], PsAID12 [25]).

Possible Identifying Characteristics for the Presence of PsA in Psoriasis

We will gather information about demographic variables, comorbidity, intoxications, and family history. Family history and comorbidity will be targeted at diseases that are associated with spondyloarthritis, such as uveitis, psoriasis, and inflammatory bowel disease. Next to that, the Charlson Comorbidity Index [26] and Functional Comorbidity Index [27] will be used to evaluate a total comorbidity burden. Data about comorbidity specifically associated with either psoriasis or PsA (eg, hepatic [28], psychological [29], and cardiovascular [30]

diseases) will be added. In addition, current and previous treatment for either PsA or psoriasis will be noted. Severity and location of psoriasis (via Psoriasis Area and Severity Index [31] and body surface amount will be noted. Nail involvement will be assessed via Nail Psoriasis Severity Index [32] and Nijmegen Nail Psoriasis Activity Index Tool [33]. Three of the currently used screening questionnaires (ie, Psoriasis Epidemiology Screening Tool [PEST], Toronto Psoriatic Arthritis Screen [ToPAS], and Psoriatic Arthritis Screening and Evaluation [PASE]) will be used to collect clinical characteristics that have been previously discovered in their development [13-15].

Statistics

Prevalence

The primary outcome of this study will be the point prevalence (number per 100 patients) of PsA in established patients with psoriasis. Sensitivity analyses will be performed by including or excluding patients with an uncertain diagnosis after 1 year, patients who refuse referral, or patients who are otherwise lost to follow-up.

Effect of Referral

The effect of referral on treatment changes, disease activity, and HR-QoL will be assessed qualitatively in an explorative descriptive matter. No formal statistical analyses will be applied.

Possible Identifying Characteristics for the Presence of PsA in Psoriasis

The identifying value of various clinical markers for the presence of PsA in psoriasis will be processed as independent variables in a univariate logistic regression model. Diagnosis of PsA (yes/no) will be the dependent variable. Variables that are statistically related to the outcome ($P \leq .20$ in univariate modeling) and are clinically and methodologically feasible (based on a favorable balance between prevalence in the cohort, effect size, and ease of measurement) will be selected. The subsequent selection of variables will be tested in a multivariable logistic regression model with backward stepwise selection. Sensitivity analysis will be performed by reclassifying patients with an uncertain diagnosis as cases. The number of possible independent variables will be limited based on a minimum of 10 events (PsA diagnoses) per variable. Bootstrapping will be used to assess the internal validity of the model in terms of overoptimism and shrinkage.

Data Handling

The collected data will be entered in CASTOR, an electronic database set up for clinical trials. Data will be coded and kept by personnel trained in Good Clinical Practice. Handling of personal data will comply with the Data Protection Law.

During the informed consent procedure, patients will be asked if gathered data can be used for further research involving psoriasis or PsA. Only data from patients who gave consent for this can be reused in accordance to FAIR (Findable, Accessible, Interoperable, Reusable) principles.

Monitoring will be performed by certified personnel from the Radboud University Medical Center, according to the guidelines of the NFU (Dutch Federation of University Medical Centers).

Ethical Considerations

DAPPER has been approved by the Ethical Committee of the region Arnhem-Nijmegen, Radboud University Medical Centre (NL68137.091.18). It has been registered in the Dutch Trial Register (NTR 7604). All study procedures will be performed in accordance with the ICH guidelines on Good Clinical Practice and the principles of the Declaration of Helsinki.

Results

Ethical approval was obtained by the Ethical Committee of the region Arnhem-Nijmegen, Radboud University Medical Centre (NL68137.091.18) in April 2019. Inclusion started in June 2019 and finished in June 2021. Follow-up is expected to be finished in December 2022, thereby ending the study.

Discussion

PsA is an inflammatory disease of joints and entheses, which can cause pain, disability, and a diminished quality of life. Moreover, prolonged arthritis can lead to permanent irreversible joint damage [6,7]. Early recognition, for example, by screening populations at high risk for PsA, may be able to prevent joint damage by facilitating timely treatment. The high prevalence of PsA in patients with psoriasis and the fact that skin complaints mostly appear years before joint involvement make this population suitable for the implementation of screening. However, current screening questionnaires are not sufficient. Therefore, we wish to determine if current screening and referral strategies are satisfactory, and to improve them if necessary.

In our study, we used three of the previously developed questionnaires: PASE, PEST, and ToPAS [13-15]. Although their sensitivity and specificity could be improved, we feel that the possibly identifying variables used in these questionnaires warrant further evaluation [17,18]. Our study has several strengths that may overcome the suboptimal performance of the beforementioned questionnaires. First, the PASE and PEST development studies were hampered by a low amount of PsA cases (17 and 12, respectively) [13,14]. Second, the setting of our study in the Dermatology Department ensures access to the target population with minimal extra burden for the patient. Although the ToPAS study included 164 patients with PsA, most of these were recruited via the Rheumatology Department. Only 123 study participants were recruited via the Dermatology Department, giving rise to 30 PsA cases [15]. As stated in the study size, we expect to find 60 to 90 PsA cases in our cohort. Therefore, we expect our model to be more precise.

To develop a good referral tool, the patient population on which development of the model is based is crucial. A limitation of our study could be the academic setting. However, to ensure a more representative case mix, we stratified for current treatment. By using treatment modality as a proxy for severity and by limiting the amount of patients using third-line therapy (eg, biological and targeted therapies), we aim to simulate a population representative of an average dermatological outpatient clinic. Noteworthy in this context is the fact that this study does not provide a validation cohort. Internal validity will be checked by bootstrapping. Before implementing the referral

tool, external validity has to be assessed via a second (validation) cohort. Ideally, this second cohort will be found at one or more other centers, both academic and nonacademic.

A second important choice is the definition of the outcome. In this cohort, we choose not to use the CASPAR criteria [23]. These classification criteria are designed to ensure a homogenous PsA population at the start of the trial. However, these criteria are not meant to be used as diagnostic criteria. In clinical practice, the diagnosis made by the rheumatologist (expert opinion) remains the gold standard. However, since all referred patients in this cohort will have clinical psoriasis, they only need one more point (ie, nail psoriasis, negative rheumatoid factor, dactylitis, or PsA-specific lesions on imaging) to fulfill the criteria (assuming that there is an inflammatory joint or entheseal lesion). Therefore, we expect that (almost) all patients diagnosed with PsA from this cohort will fulfill CASPAR criteria.

The long lag time between skin and joint involvement (on average, 10 years [4]) also has several consequences for a referral tool. When screening for current concomitant PsA, a tool must be applied several times during follow-up. Ideally, every contact moment between treating dermatologist and patient would be an opportunity to check for suspicion of PsA. This means that the investment to use the tool must be minimal, both in time and in money. Therefore, we choose to use only clinical parameters in our data collection. It will be easy for a dermatologist to gather this data from a patient without the necessity for further laboratory or imaging techniques.

A second consequence of the repeated use of the referral tool is that its validity in reuse must be evaluated. With this study design, we cannot assess this validity in repeated use. Implementation of the developed tool in the follow-up of this cohort can be a way to test this.

Ideally, one would want to predict the development of PsA before symptoms or damage arise. However, it is important to realize that the aforementioned design of the DAPPER is focused on *detection* rather than *prediction*. We believe that prediction is a much desired goal, and several studies have reported about signs and symptoms that may present themselves some time before development of full-blown PsA [34,35]. However, the long lag time of PsA in patients with psoriasis means that development and validation of a prediction tool takes a decade or longer. Therefore, we choose to focus on improving the detection of PsA until such prediction tools are available.

In conclusion, the DAPPER study will help improve psoriasis care by providing us information about the extent of (un)diagnosed arthritis in this population. The gathered data about the patients with and without arthritis can then be used to develop an improved screening and referral tool to ensure adequate and timely care for those patients who need it.

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Authors' Contributions

TWvH, MHW, JMPAvdR, and EMGJdJ conceived the original idea. The statistical plan was designed by JMPAvdR and HMMG. TWvH is in charge of coordination of the study. TWvH did the drafting of the original protocol and paper with support from all other authors. All authors were involved in the design of the study and read and approved the final paper.

Conflicts of Interest

TWvH has acted as a paid speaker for Lily Eli and has received reimbursement for attending a symposium from UCB. JMPAvdR carries out clinical trials for AbbVie, Celgene, and Janssen; has received speaking fees/attended advisory boards from AbbVie, Bristol Myers Squibb, Leo Pharma, Almirall, and Janssen; and has received reimbursement for attending a symposium from Janssen, Pfizer, Celgene, and AbbVie. All funding is not personal but goes to the independent research fund of the Department of Dermatology of Radboud University Medical Center Nijmegen (Radboudumc), the Netherlands. EMGJdJ has received research grants for the independent research fund of the Department of Dermatology of the Radboud University Medical Center Nijmegen, the Netherlands from AbbVie, Pfizer, Novartis, Janssen Pharmaceuticals, and Leo Pharma, and has acted as consultant or paid speaker for or participated in research sponsored by companies that manufacture drugs used for the treatment of psoriasis including AbbVie, Janssen, Novartis, Lily, Celgene, Leo Pharma, UCB, and Almirall. All funding is not personal but goes to the independent research fund of the Department of Dermatology of Radboud University Medical Center Nijmegen (Radboudumc), the Netherlands.

Multimedia Appendix 1
Interview guide.
[DOCX File , 17 KB - resprot_v10i11e31647_app1.docx]

References

1. Mease PJ, Gladman DD, Papp KA, Khraishi MM, Thaçi D, Behrens F, et al. Prevalence of rheumatologist-diagnosed psoriatic arthritis in patients with psoriasis in European/North American dermatology clinics. J Am Acad Dermatol 2013 Nov;69(5):729-735. [doi: 10.1016/j.jaad.2013.07.023] [Medline: 23981683]
2. Henes JC, Ziupa E, Eisfelder M, Adamczyk A, Knaudt B, Jacobs F, et al. High prevalence of psoriatic arthritis in dermatological patients with psoriasis: a cross-sectional study. Rheumatol Int 2014 Feb;34(2):227-234. [doi: 10.1007/s00296-013-2876-z] [Medline: 24114527]
3. Wittkowski KM, Leonardi C, Gottlieb A, Menter A, Krueger GG, Tebbey PW, International Psoriasis Council. Clinical symptoms of skin, nails, and joints manifest independently in patients with concomitant psoriasis and psoriatic arthritis. PLoS One 2011;6(6):e20279 [FREE Full text] [doi: 10.1371/journal.pone.0020279] [Medline: 21673809]
4. Tillett W, Charlton R, Nightingale A, Snowball J, Green A, Smith C, et al. Interval between onset of psoriasis and psoriatic arthritis comparing the UK Clinical Practice Research Datalink with a hospital-based cohort. Rheumatology (Oxford) 2017 Dec 01;56(12):2109-2113. [doi: 10.1093/rheumatology/kex323] [Medline: 28968790]
5. Rosen CF, Mussani F, Chandran V, Eder L, Thavaneswaran A, Gladman DD. Patients with psoriatic arthritis have worse quality of life than those with psoriasis alone. Rheumatology (Oxford) 2012 Mar;51(3):571-576. [doi: 10.1093/rheumatology/ker365] [Medline: 22157469]
6. Haroon M, Gallagher P, FitzGerald O. Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis. Ann Rheum Dis 2015 Jun;74(6):1045-1050. [doi: 10.1136/annrheumdis-2013-204858] [Medline: 24525911]
7. Kane D, Stafford L, Bresnihan B, FitzGerald O. A prospective, clinical and radiological study of early psoriatic arthritis: an early synovitis clinic experience. Rheumatology (Oxford) 2003 Dec;42(12):1460-1468. [doi: 10.1093/rheumatology/keg384] [Medline: 14523223]
8. Coates LC, Moverley AR, McParland L, Brown S, Navarro-Coy N, O'Dwyer JL, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. Lancet 2015 Dec 19;386(10012):2489-2498 [FREE Full text] [doi: 10.1016/S0140-6736(15)00347-5] [Medline: 26433318]
9. Coates LC, Orbai A, Morita A, Benichou O, Kerr L, Adams DH, et al. Achieving minimal disease activity in psoriatic arthritis predicts meaningful improvements in patients' health-related quality of life and productivity. BMC Rheumatol 2018;2:24 [FREE Full text] [doi: 10.1186/s41927-018-0030-y] [Medline: 30886974]
10. Gossec L, Baraliakos X, Kerschbaumer A, de Wit M, McInnes I, Dougados M, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis 2020 Jun;79(6):700-712 [FREE Full text] [doi: 10.1136/annrheumdis-2020-217159] [Medline: 32434812]
11. Menter A, Gelfand JM, Connor C, Armstrong AW, Cordoro KM, Davis DM, et al. Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies. J Am Acad Dermatol 2020 Jun;82(6):1445-1486. [doi: 10.1016/j.jaad.2020.02.044] [Medline: 32119894]
12. Elmets CA, Leonardi CL, Davis DM, Gelfand JM, Lichten J, Mehta NN, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. J Am Acad Dermatol 2019 Apr;80(4):1073-1113. [doi: 10.1016/j.jaad.2018.11.058] [Medline: 30772097]
13. Ibrahim GH, Buch MH, Lawson C, Waxman R, Helliwell PS. Evaluation of an existing screening tool for psoriatic arthritis in people with psoriasis and the development of a new instrument: the Psoriasis Epidemiology Screening Tool (PEST) questionnaire. Clin Exp Rheumatol 2009;27(3):469-474. [Medline: 19604440]
14. Husni ME, Meyer KH, Cohen DS, Mody E, Qureshi AA. The PASE questionnaire: pilot-testing a psoriatic arthritis screening and evaluation tool. J Am Acad Dermatol 2007 Oct;57(4):581-587. [doi: 10.1016/j.jaad.2007.04.001] [Medline: 17610990]
15. Gladman DD, Schentag CT, Tom BDM, Chandran V, Brockbank J, Rosen C, et al. Development and initial validation of a screening questionnaire for psoriatic arthritis: the Toronto Psoriatic Arthritis Screen (ToPAS). Ann Rheum Dis 2009 Apr;68(4):497-501. [doi: 10.1136/ard.2008.089441] [Medline: 18445625]
16. Tinazzi I, Adami S, Zanolin EM, Caimmi C, Confente S, Girolomoni G, et al. The early psoriatic arthritis screening questionnaire: a simple and fast method for the identification of arthritis in patients with psoriasis. Rheumatology (Oxford) 2012 Nov;51(11):2058-2063. [doi: 10.1093/rheumatology/kes187] [Medline: 22879464]
17. Coates LC, Aslam T, Al Balushi F, Burden AD, Burden-Teh E, Caperon AR, et al. Comparison of three screening tools to detect psoriatic arthritis in patients with psoriasis (CONTEST study). Br J Dermatol 2013 Apr;168(4):802-807. [doi: 10.1111/bjd.12190] [Medline: 23311587]
18. Haroon M, Kirby B, FitzGerald O. High prevalence of psoriatic arthritis in patients with severe psoriasis with suboptimal performance of screening questionnaires. Ann Rheum Dis 2013 May;72(5):736-740. [doi: 10.1136/annrheumdis-2012-201706] [Medline: 22730367]
19. Healy PJ, Helliwell PS. Measuring clinical enthesitis in psoriatic arthritis: assessment of existing measures and development of an instrument specific to psoriatic arthritis. Arthritis Rheum 2008 May 15;59(5):686-691. [doi: 10.1002/art.23568] [Medline: 18438903]
20. Maksymowych WP, Mallon C, Morrow S, Shojania K, Olszynski WP, Wong RL, et al. Development and validation of the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index. Ann Rheum Dis 2009 Jun;68(6):948-953. [doi: 10.1136/ard.2007.084244] [Medline: 18524792]

21. Sieper J, van der Heijde D, Landewé R, Brandt J, Burgos-Vagas R, Collantes-Estevez E, et al. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). Ann Rheum Dis 2009 Jun;68(6):784-788. [doi: 10.1136/ard.2008.101501] [Medline: 19147614]
22. Mulder M, den Broeder AA, van Ginneken BTJ, Mahler EAM, van den Hoogen FHJ, Vriezekolk JE, et al. Implementing Psoriatic Arthritis Disease Activity Score-guided treat-to-target in psoriatic arthritis routine clinical practice: (im)possible? Rheumatology (Oxford) 2019 Dec 01;58(12):2330-2331. [doi: 10.1093/rheumatology/kez254] [Medline: 31230083]
23. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006 Aug;54(8):2665-2673. [doi: 10.1002/art.21972] [Medline: 16871531]
24. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol 1994 May;19(3):210-216. [doi: 10.1111/j.1365-2230.1994.tb01167.x] [Medline: 8033378]
25. Gossec L, de Wit M, Kiltz U, Braun J, Kalyoncu U, Scrivo R, EULAR PsAID Taskforce. A patient-derived and patient-reported outcome measure for assessing psoriatic arthritis: elaboration and preliminary validation of the Psoriatic Arthritis Impact of Disease (PsAID) questionnaire, a 13-country EULAR initiative. Ann Rheum Dis 2014 Jun;73(6):1012-1019. [doi: 10.1136/annrheumdis-2014-205207] [Medline: 24790067]
26. Charlson ME, Pompei P, Ales KL, MacKenzie C. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373-383. [doi: 10.1016/0021-9681(87)90171-8] [Medline: 3558716]
27. Groll DL, To T, Bombardier C, Wright JG. The development of a comorbidity index with physical function as the outcome. J Clin Epidemiol 2005 Jun;58(6):595-602. [doi: 10.1016/j.jclinepi.2004.10.018] [Medline: 15878473]
28. Miele L, Vallone S, Cefalo C, La Torre G, Di Stasi C, Vecchio FM, et al. Prevalence, characteristics and severity of non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. J Hepatol 2009 Oct;51(4):778-786. [doi: 10.1016/j.jhep.2009.06.008] [Medline: 19664838]
29. Lewinson RT, Vallerand IA, Lowerison MW, Parsons LM, Frolkis AD, Kaplan GG, et al. Depression is associated with an increased risk of psoriatic arthritis among patients with psoriasis: a population-based study. J Invest Dermatol 2017 Apr;137(4):828-835 [FREE Full text] [doi: 10.1016/j.jid.2016.11.032] [Medline: 28237512]
30. Edson-Heredia E, Zhu B, Lefevre C, Wang M, Barrett A, Bushe C, et al. Prevalence and incidence rates of cardiovascular, autoimmune, and other diseases in patients with psoriatic or psoriatic arthritis: a retrospective study using Clinical Practice Research Datalink. J Eur Acad Dermatol Venereol 2015 May;29(5):955-963. [doi: 10.1111/jdv.12742] [Medline: 25352213]
31. Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. Dermatologica 1978;157(4):238-244. [doi: 10.1159/000250839] [Medline: 357213]
32. Rich P, Scher RK. Nail Psoriasis Severity Index: a useful tool for evaluation of nail psoriasis. J Am Acad Dermatol 2003 Aug;49(2):206-212. [doi: 10.1067/s0190-9622(03)00910-1] [Medline: 12894066]
33. Klaassen KM, van de Kerkhof PC, Bastiaens MT, Plusjé LGJM, Baran RL, Pasch MC. Scoring nail psoriasis. J Am Acad Dermatol 2014 Jun;70(6):1061-1066. [doi: 10.1016/j.jaad.2014.02.010] [Medline: 24698704]
34. Eder L, Haddad A, Rosen CF, Lee K, Chandran V, Cook R, et al. The incidence and risk factors for psoriatic arthritis in patients with psoriasis: a prospective cohort study. Arthritis Rheumatol 2016 Apr;68(4):915-923. [doi: 10.1002/art.39494] [Medline: 26555117]
35. Eder L, Polachek A, Rosen CF, Chandran V, Cook R, Gladman DD. The development of psoriatic arthritis in patients with psoriasis is preceded by a period of nonspecific musculoskeletal symptoms: a prospective cohort study. Arthritis Rheumatol 2017 Mar;69(3):622-629. [doi: 10.1002/art.39973] [Medline: 27792862]

Abbreviations

CASPAR: Classification Criteria for Psoriatic Arthritis
DAPPER: Discovery of Arthritis in Psoriasis Patients for Early Rheumatology Referral
DLQI: Dermatological Life Quality Index
FAIR: Findable, Accessible, Interoperable, Reusable
HR-QoL: health-related quality of life
LEI: Leeds Enthesitis Index
NFU: Dutch Federation of University Medical Centers
PASDAS: Psoriatic Arthritis Disease Activity Score
PASE: Psoriatic Arthritis Screening and Evaluation
PEST: Psoriasis Epidemiology Screening Tool
PsA: psoriatic arthritis
PsAID: Psoriatic Arthritis Impact of Disease
SPARCC: Spondyloarthritis Research Consortium of Canada
ToPAS: Toronto Psoriatic Arthritis Screen

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Protocol

Seroepidemiological Survey on the Impact of Smoking on SARS-CoV-2 Infection and COVID-19 Outcomes: Protocol for the Troina Study

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Abstract

Background: After the global spread of SARS-CoV-2, research has highlighted several aspects of the pandemic, focusing on clinical features and risk factors associated with infection and disease severity. However, emerging results on the role of smoking in SARS-CoV-2 infection susceptibility or COVID-19 outcomes are conflicting, and their robustness remains uncertain.

Objective: In this context, this study aims at quantifying the proportion of SARS-CoV-2 antibody seroprevalence, studying the changes in antibody levels over time, and analyzing the association between the biochemically verified smoking status and SARS-CoV-2 infection.

Methods: The research design involves a 6-month prospective cohort study with a serial sampling of the same individuals. Each participant will be surveyed about their demographics and COVID-19–related information, and blood sampling will be collected upon recruitment and at specified follow-up time points (ie, after 8 and 24 weeks). Blood samples will be screened for the presence of SARS-CoV-2–specific antibodies and serum cotinine, being the latter of the principal metabolite of nicotine, which will be used to assess participants’ smoking status.

Results: The study is ongoing. It aims to find a higher antibody prevalence in individuals at high risk for viral exposure (ie, health care personnel) and to refine current estimates on the association between smoking status and SARS-CoV-2/COVID-19.

Conclusions: The added value of this research is that the current smoking status of the population to be studied will be biochemically verified to avoid the bias associated with self-reported smoking status. As such, the results from this survey may provide an actionable metric to study the role of smoking in SARS-CoV-2 infection and COVID-19 outcomes, and therefore to implement the most appropriate public health measures to control the pandemic. Results may also serve as a reference for future clinical research, and the methodology could be exploited in public health sectors and policies.

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KEYWORDS

antibody persistence; cotinine; COVID-19; SARS-CoV-2; seroprevalence; smoking impact; smoking status

Introduction

Overview

SARS-CoV-2 is the novel coronavirus strain that was first reported as a cluster of viral pneumonia cases of unknown etiology in Wuhan, the capital city of Hubei Province in China, on December 31, 2019. The spreading of SARS-CoV-2 reached pandemic proportion in March 2020, and as of April 2021, more than 141 million cases had been confirmed, and more than 3 million fatalities had occurred worldwide [1].

In late February 2020, the first nonimported cases of COVID-19 were identified in Italy. Since then, SARS-CoV-2 spread rapidly to the community, as reported by national health authorities [2]. On May 23, 2020, at the time of project proposal design, the Italian Ministry of Health reported that, of the 229,327 people who had contracted the virus, 57,752 were still positive, of whom 8695 (15%) were hospitalized with symptoms; 572 (1.0%) were admitted in intensive care units (ICUs); and the remaining 48,485 (84%) were self-isolating at home; 32,735 (14.3%) had died, and 138,840 (60.5%) healed on a total of 2,164,426 tested cases [3]. As of April 2021, 3,870,131 cases and 116,927 deaths have been recorded in the country [4].

Since the beginning of the pandemic, the global scientific community was engaged in intense research efforts to understand all aspects of this public health crisis, from the clinical features of the disease and risk factors for adverse outcome, the patterns of viral spread in the population, the role of asymptomatic or subclinical cases in human-to-human transmission, and the serological response. The clinical features of COVID-19 range from a self-limited flu-like syndrome to progressive lung involvement with respiratory failure and widespread systemic effects [5-7]. Epidemiological surveillance has primarily focused on hospitalized patients with severe disease, and as such, the full spectrum of the disease, including the extent and proportion of mild or asymptomatic infections, is less clear. Evidence suggests that asymptomatic or oligosymptomatic infection is not uncommon [8-11]. A recent review reported that at least one third of SARS-CoV-2 infections are asymptomatic and that almost three quarters of persons who are asymptomatic at the time of a positive polymerase chain reaction (PCR) test result will remain asymptomatic [12]. Remarkably, sequelae of previous viral pneumonia have been reported in chest computed tomography scans of asymptomatic individuals [13], and SARS-CoV-2 transmission from asymptomatic cases to others has been documented [13,14].

In this frame, a seroprevalence study is an ideal attempt for measuring the true infection rates in general or specific populations [11,15,16]. In Italy, a nationwide survey was conducted by the National Institute of Statistics, reporting an IgG seroprevalence of 2.5% [17]. However, there is limited use of seroprevalence studies to retrospectively identify potential predictors of infection susceptibility and disease severity, both in the general population and in specific subgroups (eg, smokers, pediatric populations, or older adults).

Several risk factors for severe COVID-19 have been identified, including cardiovascular disease, diabetes, obesity, and chronic obstructive pulmonary disease [18-21]. Intuitively, one important additional risk factor is expected to be cigarette smoking. Smokers have a higher risk for developing viral and bacterial respiratory infections [22-24], being five times more likely to have influenza and twice more likely to develop pneumonia [25].

However, the role of smoking in SARS-CoV-2 infection susceptibility and COVID-19 outcomes is still unclear. Although there appears to be a higher risk for ICU admission and adverse outcomes [26-28], it has been reported that the prevalence of smoking among hospitalized COVID-19 patients is far lower than would be expected based on population smoking prevalence [29-32]. These findings were initially derived from Chinese case series, and although it is possible that the prevalence of smokers in the Chinese case series may be underrepresented due to inaccurate recording of their smoking status, similar findings have been reported in France [30], Germany [33], Italy [34], and the United States [32,35].

It is not clear how far the underrepresentation of smokers among COVID-19 inpatients reflects problems with poor reporting of the smoking status. Given the challenging circumstances of the pandemic, recall or reporting bias cannot be excluded. The possibility for inaccurate recording, false reporting, or underreporting of the smoking status due to the challenging situations at wards/ICUs with work overloads and operating in a persistent state of emergency should not be underestimated. Improving the quality of clinical and behavioral data mandates the need for an accurate and dedicated recording of the smoking status. Alternatively, population-level data collected outside of hospital settings are required. Another important limitation is

that most of the observations were unadjusted for smoking-related comorbidities, which are known to be associated with higher risk for an adverse outcome in patients with COVID-19 [18]. Lack of adjustment for relevant confounders means it is not possible to disentangle the effect of smoking. Addressing all these limitations is important for evaluating clinical risk, developing clear public health messages, and identifying targets for intervention.

Research Objectives

Surveillance of antibody seropositivity in a population can allow inferences to be made about the cumulative incidence of infection in the population. Additionally, little is currently known about antibody kinetics. Asymptomatic infected persons may clear the virus more quickly than do symptomatic patients, and antibody titers in the former are likely to be lower, if they seroconvert at all, than in infected symptomatic patients [11,36]. Furthermore, understanding the association between smoking and SARS-CoV-2 infection susceptibility or COVID-19 outcomes is generally limited and of poor quality.

To summarize, there is a need for robust population-based evidence on the association of smoking with SARS-CoV-2 infection and COVID-19 outcomes, adjusting for potential confounding variables (eg, sociodemographic characteristics, key worker status, and comorbid health conditions), and a population seroprevalence study could be useful for this goal. The following key research questions will be addressed:

- Does smoking increase susceptibility to SARS-CoV-2 infection?
- Does smoking increase susceptibility to COVID-19 outcomes?
- Does smoking affect the serological response after SARS-CoV-2 infection?

Research Proposal

We propose a 6-month prospective study using in combination a random population sample (taken from residents of the town of Troina; the town with the highest prevalence of positive SARS-CoV-2 cases in Sicily at the time of drafting the protocol in March-May 2020) and a convenience sample (taken from staff of the Troina's main health care establishment, reported to have high infectious levels in the same time period) to investigate the prevalence of past infection, as determined by seropositivity (anti–SARS-CoV-2–specific IgG by enzyme-linked immunosorbent assay [ELISA]). The biochemically verified smoking status of the study population (ie, serum cotinine) will be correlated with serological data and COVID-19 outcomes (ie, clinical symptoms and hospitalization).

Study Aim

Epidemiological exposure data and venous blood (for measurements of anti–SARS-CoV-2–specific IgG and serum cotinine levels) will be systematically collected. Demographic, medical history, and epidemiological exposure data will be recorded from specifically designed questionnaires (for COVID-19 outcomes, relevant comorbidities, and smoking status) and shared rapidly in a format that can be easily aggregated, tabulated, and analyzed across many different regional (or national and international) settings for timely estimates of COVID-19 virus infection and its immunologic response rates according to the smoking status, and to inform public health responses and policy decisions.

Methods

Specific Aims

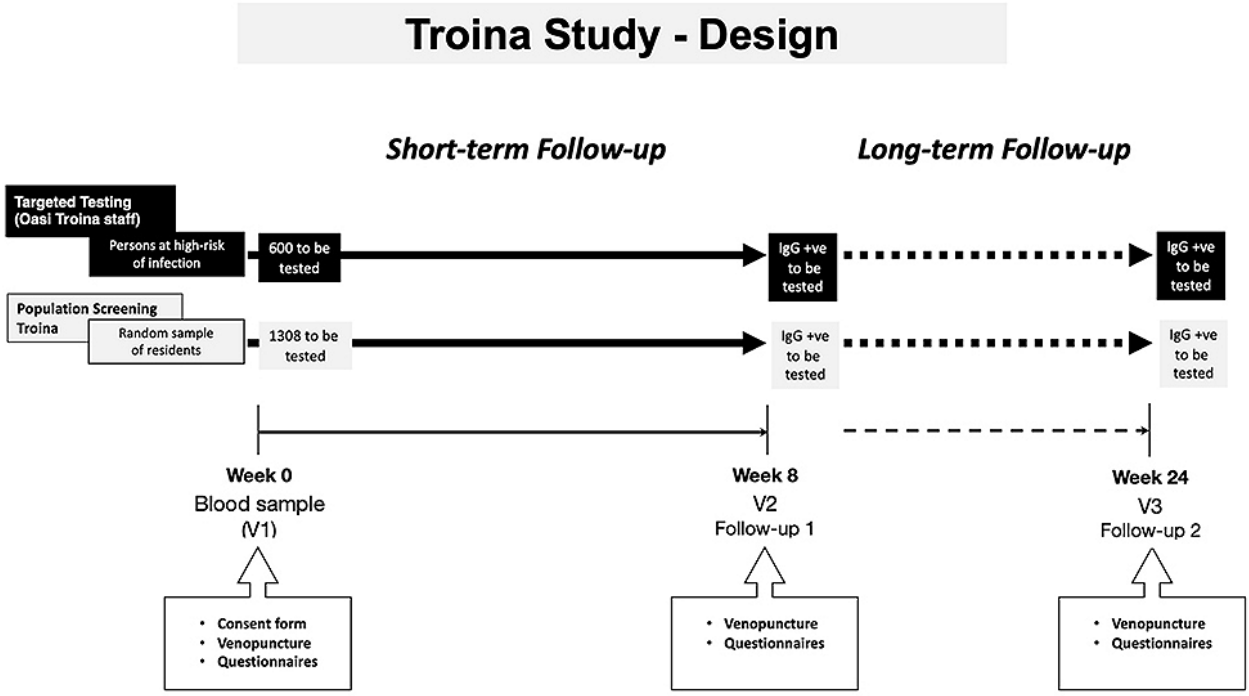
In summary, the main objectives of the study will be to:

- Quantify the proportion of SARS-CoV-2–infected people (by serology assessment of anti–SARS-CoV-2 IgG levels) in a random population sample at baseline
- Quantify the proportion of SARS-CoV-2–infected people (by serology assessment of anti–SARS-CoV-2 IgG levels) in a convenience sample (hospital staff) at baseline
- Quantify the proportion of participants with asymptomatic SARS-CoV-2 infection
- Quantify the proportion of mildly-to-moderately symptomatic (management at home) COVID-19 cases among all participants
- Quantify the proportion of severely symptomatic (management at hospital) COVID-19 cases among all participants
- Quantify the proportion of biochemically verified (by serum cotinine) current, former, and never smokers among all participants (random population sample + convenience sample)
- Quantify the proportion and analyze the association between smoking status (current, former, and never smokers) and:
  - SARS-CoV-2 infection (asymptomatic and symptomatic combined)
  - Asymptomatic SARS-CoV-2 infection
  - Mild-to-moderate COVID-19 (management at home)
  - Severe COVID-19 (hospitalization needed)
- Record relevant clinical confounders known to be associated with COVID-19 outcomes
- Compare anti–SARS-CoV-2 IgG levels at baseline among current, former, and never smokers
- Monitor and compare anti–SARS-CoV-2 IgG levels changes from baseline to 2 months and 6 months among current, former, and never smokers.

Study Design

This study will investigate the association between biochemically verified smoking status of the study population and serological data as well as COVID-19 outcomes (ie, clinical symptoms and hospitalization). The research design involves a 6-month prospective multiple cohort study with serial sampling of the same individuals each time. Sampling will be commenced in July and repeated at 8 weeks (Figure 1). A final follow-up visit will be carried out at 24 weeks.

Figure 1. The Troina Study: design.



Study Population and Setting

Within the geographic scope of the study, high incidence of positive cases was identified in the general population of Troina, a town of around 9000 inhabitants in the province of Enna, in the center of Sicily. This town was hit hardest in terms of COVID-19 cases during the first wave in Italy [2-4], with hundreds of cases registered in the first epidemic weeks in March 2020 [37,38], and was declared a *red zone* on March 29, 2020, with the enforcement of lockdown retractions in that area [38]. The study population will consist of a population-based, age-stratified cohort in Troina that will be sampled through random selection of town residents. Identification and recruitment of participants will expand over different age groups to determine and compare age-specific attack rates. For logistic reasons, specimen and data collection will be performed at a single location, asking participants to travel to that location to participate in the study. Targeted testing will also be extended to a convenience sample consisting of about 600 staff members of Troina's main health care establishment (high-risk individuals).

Eligibility Criteria

Any individual identified for recruitment, irrespective of age, can participate. Exclusion criteria will be refusal to provide informed consent or contraindication to venipuncture. Suspected or confirmed active/acute or prior SARS-CoV-2 infection should not be considered as an exclusion criterion for this investigation. Doing so would underestimate the extent of infection in the population. For individuals currently receiving medical care for COVID-19 infection, a family member or proxy may be used to complete the questionnaire on their behalf.

Smoking Status Definition

Current smokers will be defined as those who report that they smoke and have serum cotinine levels ≥20 ng/mL. Former smokers will be defined as those who report that they used to smoke in the past but not now and have serum cotinine levels <20 ng/mL. Never smokers will be defined as those who report that they never smoked in the past and have serum cotinine levels <20 ng/mL.

Data Collection

Each participant recruited into the study will be asked to complete a questionnaire that will record the following information: demographics, information about known COVID-19 and relevant clinical course, comorbidities, and smoking status.

Specimen Collection

A small amount of blood (10 mL) will be collected from each participant upon recruitment (T0) and at specified follow-up time points (T8wks, T24wks).

Specimen Transport and Biobanking

For each biological sample collected, the time of collection, the conditions for transportation, and the time of arrival at the study laboratory will be recorded. Specimens should reach the laboratory as soon as possible after collection. Serum should be separated from whole blood and stored at –20 °C or lower and shipped on dry ice. A biobanking facility will be established in Troina.

Sample Storage

Prior to testing, serum samples will be stored at –80 °C at the reference biobanking facility. It is recommended to aliquot samples prior to freezing to minimize freeze thaw cycles.

Serological Testing

Serologic assays of high sensitivity and specificity for SARS-CoV-2 have been recently validated and published. Serum samples will be screened for the presence of SARS-CoV-2–specific antibodies using a quantitative ELISA test for anti–SARS-CoV-2 IgG (Euroimmun, CND W0105040619) [39].

Serum samples will be stored at –80 °C until use, and the assay will be performed according to the manufacturer's protocol. The neutralization capability, specificity, and sensitivity of the test have been thoroughly investigated and published together with the assay validation [40]. Reagent wells of the assays are coated with recombinant structural protein (S1 domain) of SARS-CoV-2. The optical density (OD) will be detected at 450 nm, and a ratio of the reading of each sample to the reading of the calibrator, included in the kit, will be calculated for each sample (OD ratio). The cutoff value for IgG OD ratio is 0.3. Following blocking, diluted serum (1:100 or 2-fold serially diluted for titers) will be added and incubated at 37 °C for 1 hour in the 96-well microtiter ELISA plates. Antigen-specific antibodies will be detected using peroxidase-labeled rabbit antihuman IgG and TMB as a substrate. The absorbance of each sample will be measured at 450 nm. Laboratory procedures involving sample manipulation must be carried out in a biosafety cabinet.

Cotinine Assay

About 1mL of serum will be pipetted into 10 ml tubes and 100 ng/mL of Ortho-cotinine used as internal standard will be added. About 50 µL of 0.1 M aqueous sodium hydroxide solution will then be added to the culture tube followed by 325 µL of chloroform. The tube will be secured with cap and vortex mixed for ~3 minutes (using VX 2500 Multi Tube Vortex Mixer) and centrifuged for ~4 minutes (in Beckmann Allegra centrifuge) at 2500 rpm. Using a glass Pasteur Pipette, the top aqueous layer will be removed and discarded into the hazardous waste container and the organic layer will remain in the tube. About ~100 mg (0.1 g) of anhydrous sodium sulfate will be added to the organic layer and allowed to rest for ~3 minutes (which will allow the sodium sulfate to absorb any water that may be present in the organic layer). In the end, the clear organic layer (with no water) will be carefully removed (without disturbing the settled sodium sulfate), concentrated to ~100 µL vial insert and placed in a gas chromatography (GC) vial. The concentrated sample will be capped and arranged on to an auto sampler tray for GC injection. One microliter (µL) of each sample will be injected into HP-5 Capillary GC Column (0.32 mm ID, 25 m length, and 0.52 µm film thickness; bonded 5% phenyl; and 95% dimethylpolysiloxane) of GC–nitrogen phosphorous detector. The inlet temperature will be 250 ˚C at split-less mode. The initial oven temperature will be 70 ˚C with a 1-minute hold and then increased to 230 ˚C at the rate of 25 ˚C per minute. Every batch of samples will be run with 6 calibration levels (20, 50, 100, 200, 400, 600 ng/mL), 4 quality controls (20, 100, 400, 600 ng/mL), and 1 blank control for accurate quantification. The amount of cotinine will be reported in ng/mL. The limit of quantification of cotinine is 20 ng/mL.

Statistical Plan

Estimates of margin of error as a function of seroprevalence are low for 300 samples. We will be aiming for >1000 samples of a representative sample of the population by gender and age groups (0-17 years, 18-65 years, and 66 years and older).

For the enrollment of participants into the study, the following inclusion and exclusion criteria need to be fulfilled:

- Inclusion in population criteria:
  - Aged into the aforementioned groups
  - Living in the town of interest
  - Willing to participate in the baseline and to be recontacted for follow-up waves
- Exclusion from population criteria:
  - Persons belonging to the institutionalized population
- Exclusion from sample (censoring) criteria:
  - Moved to another village during the study period
  - Those stating explicitly their wish not to be recontacted for this study

To correctly represent the population involved, the age groups of interest have been assigned to three different categories by gender in terms of population size. A corresponding targeted sample size for this study is specified for each category.

In the entire population, we estimated several sample sizes depending on the margin of error equal to 0.03, 0.04, or 0.05 for estimate proportions of the sampled population, as shown in Table 1.

Table 1. The Troina Study: sample size calculation.

Age groups and gender	Participants, n	Margin of error 3%[a]	Margin of error 4%[b]	Margin of error 5%[c]
0-17 years				
Male	694	100	47	29
Female	648	93	44	27
Total	1342	193	90	57
18-65 years				
Male	2751	396	185	116
Female	2803	403	189	118
Total	5554	799	374	235
>65 years				
Male	961	138	65	41
Female	1237	178	83	52
Total	2198	316	148	93
Total				
Male	4406	634	297	186
Female	4688	674	316	198
Total	9094	1308	613	384

[a](N * 1308) / total (N=9094) = n.

[b](N * 613) / total (N=9094) = n.

[c](N * 384) / total (N=9094) = n.

We will draw a multilayered sample with a confidence level of 0.97% to minimize the margin of error to 3% and ensure the best reliability of the sample data. The planned total sample size comprises up to 1308 participants at the recruitment stage. The attrition rate is estimated at 10%.

Information will be collected in a standardized format according to the questionnaires and tools in the protocol. The data shared should include only the study identification number and not any personal identifiable information. We will report the following information:

- The number of households and the number of individuals included
- The age and sex of all individuals included
- The antibody levels in the sample of all individuals included
- The number of individuals with serologic evidence of COVID-19 virus infection (stratified by age)
- The number of individuals with serologic evidence of COVID-19 virus infection who have reported symptoms
- The number of individuals with known previous SARS-CoV-2 infection who were hospitalized or recovered at home
- The number of individuals with serologic evidence of COVID-19 virus infection who are current, former, and never smokers (biochemically verified by serum cotinine assay)

Sociodemographic and baseline characteristics will be summarized for the Troina population, for the convenience sample, and for the total sample recruited. Categorical variables will be reported as numbers and proportions with 95% CIs. Between-group comparisons will be carried out using chi-square testing or Fisher exact test, as appropriate. Continuous variables will be reported as means and SDs, and as medians and IQRs. Between-group comparisons will be carried out using tests like analysis of variance, Mann-Whitney *U* test, or Wilcoxon signed rank test, as appropriate. The proportions of patients developing a positive PCR test for SARS-CoV-2 result over the course of the study will be reported as numbers and proportions with 95% CIs, separated by subgroups identifying those with symptomatic or asymptomatic infection. Data on change in antibody levels from baseline to follow-up will be presented for the whole recruited population. Statistical significance of change will be estimated using repeated-measures *t* testing. Correlation between smoking status and the risk of COVID-19 infection will be tested using a 3 × 2 chi-square test of independence. A *P* value ≤.05 will be considered to represent the threshold of statistical significance for all comparisons.

Data Collection Procedures

To accomplish the specific aims of the project, data will be stored in a database system after each completed collection step and transferred to central data management for further data processing and merging. Each participant will be assigned a unique identification code consisting of a number identifier that will be used for data merging. After data collection, data validation checks will be performed as agreed in a data validation plan, and data cleaning procedures will be used as applicable to ensure the best achievable quality of data for analysis purposes. Only the study staff working with the fieldwork provider will be able to identify the participants based on the identification codes. Only deidentified data will be

transferred from the fieldwork provider to the central data management. All electronic data files will be kept on secure servers with backup processes in place. Personal data of participants must be strictly kept separately from study data and is accessed only by authorized staff for the purposes of the study conduct. Before starting data collection, the involved staff will receive training on the background and objectives of this study, on eligibility criteria, on the participant selection procedure, on ethical obligations, on completion and validation of the procedure, and on the data collection platform. Local fieldwork staff will be trained for each relevant data collection process and logistic-related procedure.

Eligible participants are informed about the study purpose, their requested tasks, time of involvement, data confidentiality, and data protection. Once they stated their willingness to participate, they will proceed with the screening and study enrollment. Enrolled participants have the right to stop their participation at any time without any penalty. Preferably, the reason for the premature end of participation will be recorded. Participants who drop out will not be replaced. Every effort will be made to protect participant confidentiality according to the General Data Protection Regulation.

Results

We expect to find a higher prevalence of antibodies in individuals at high risk for viral exposure (ie, health care personnel and other essential workers) according to previous evidence and to refine current estimates on the association between smoking status and SARS-CoV-2/COVID-19. A total of 1785 participants have been enrolled in the study. Data cleaning and analyses are ongoing.

Discussion

This project is the first population-based study that uses seroprevalence data and an objective assessment of the current smoking status to examine the association between smoking and SARS-CoV-2 infection susceptibility and severity. Additionally, the study will examine for the first time the magnitude of the seroconversion response in current smokers, compared to former and never smokers, and the changes in antibody titers over time according to the smoking status. Instead of focusing on hospitalized patients only, the study will also include participants who infected individuals who were either asymptomatic or had COVID-19 but were not hospitalized. It will also consider confounding factors in the association between smoking and SARS-CoV-2 that were not addressed in previous research. Finally, the results from this survey may serve as a reference to other contexts and provide an actionable metric to quantify and offer a clear overview of SARS-CoV-2 spread, and the methodology and findings can be exploited in public health research and policies to minimize the disease impact and implement the most appropriate prevention measures to protect susceptible populations.

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Authors' Contributions

RP conceived the study, contributed to its design, and drafted and finalized the manuscript. VT and GGC contributed to the design of the study, with particular input on analysis and interpretation of data. PF contributed to the design of the study and revised the manuscript. ACR contributed to the design of the study and will be involved in the project management to organize and coordinate the data collection process. SR contributed with input on analytical testing and will be involved in the project management to organize and coordinate the data collection process. DS contributed to the design of the study and will be involved in the project management and central coordination. F Caraci contributed to the design of the study and revised the manuscript. CR contributed to the design of the study and revised the manuscript. MT contributed with input on analytical testing. PZ contributed with input on analytical testing. JR contributed with input on analytical testing and revised the manuscript. MF contributed with input on analytical testing. JB contributed to the design of the study with particular input on analysis and interpretation of data. F Cibella contributed to the design of the study with particular input on analysis and interpretation of data. EI contributed to the design of

the study and will be involved in the project management to organize and coordinate the data collection process. RF contributed to the design of the study and revised the manuscript.

Conflicts of Interest

RP is a full tenured professor of Internal Medicine at the University of Catania (Italy) and Medical Director of the Institute for Internal Medicine and Clinical Immunology at the same University. In relation to his recent work in the area of respiratory diseases, clinical immunology, and tobacco control, RP has received lecture fees and research funding from Pfizer, GlaxoSmithKline, CV Therapeutics, NeuroSearch A/S, Sandoz, MSD, Boehringer Ingelheim, Novartis, Duska Therapeutics, and Forest Laboratories. Lecture fees from a number of European EC industry and trade associations (including FIVAPE in France and FIESEL in Italy) were directly donated to vaper advocacy no-profit organizations. RP has also received grants from European Commission initiatives (U-BIOPRED and AIRPROM) and from the Integral Rheumatology & Immunology Specialists Network initiative. He has also served as a consultant for Pfizer; Global Health Alliance for Treatment of Tobacco Dependence; CV Therapeutics; Boehringer Ingelheim; Novartis; Duska Therapeutics; Electronic Cigarette Industry Trade Association, in the UK; Arbi Group Srl; Health Diplomats; and Sermo Inc. RP has served on the Medical and Scientific Advisory Board of Cordex Pharma, Inc; CV Therapeutics; Duska Therapeutics Inc; Pfizer; and PharmaCielo. RP is also founder of the Center for Tobacco Prevention and Treatment at the University of Catania and of the Center of Excellence for the Acceleration of Harm Reduction at the same university, which has received support from the Foundation for a Smoke-Free World to conduct 8 independent investigator-initiated research projects on harm reduction. RP is currently involved in a patent application concerning an app tracker for smoking behavior developed for ECLAT SRL. RP is also currently involved in the following pro bono activities: scientific advisor for Lega Italiana Anti Fumo (Italian for Italian Anti-Smoking League), the Consumer Advocates for Smoke-Free Alternatives, and the International Network of Nicotine Consumers Organizations; Chair of the European Technical Committee for Standardization on “Requirements and test methods for emissions of electronic cigarettes” (CEN/TC 437; WG4). JR receives research support from the Foundation for a Smoke-Free World, Philip Morris International, Altria, and JUUL Labs; consults with Revive Pharmaceuticals; and consults and has patent purchase agreements with Philip Morris International. SR does consulting work for ECLAT SRL. All other authors have no relevant conflicts of interest to declare in relation to this study.

References

1. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard. URL: https://covid19.who.int [accessed 2021-04-18]
2. Istituto Superiore di Sanità. Sorveglianza integrata COVID-19: i principali dati nazionali. EpiCentro. URL: https://www.epicentro.iss.it/coronavirus/sars-cov-2-sorveglianza-dati [accessed 2021-04-18]
3. COVID-19 Italia Monitoraggio della situazione. Dipartimento Protezione Civile. URL: https://mappe.protezionecivile.gov.it/it/mappe-emergenze/mappe-coronavirus [accessed 2021-04-18]
4. Balasco N, D'Alessandro V, Ferrara P, Smaldone G, Vitagliano L. Analysis of the time evolution of COVID-19 lethality during the first epidemic wave in Italy. Acta Biomed 2021 May 12;92(2):e2021171 [FREE Full text] [doi: 10.23750/abm.v92i2.11149] [Medline: 33988144]
5. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. World Health Organization. URL: https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov [accessed 2020-04-18]
6. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020 Apr;8(4):420-422 [FREE Full text] [doi: 10.1016/S2213-2600(20)30076-X] [Medline: 32085846]
7. Guzik T, Mohiddin S, Dimarco A, Patel V, Savvatis K, Marelli-Berg FM, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res 2020 Aug 01;116(10):1666-1687 [FREE Full text] [doi: 10.1093/cvr/cvaa106] [Medline: 32352535]
8. Zhu J, Ji P, Pang J, Zhong Z, Li H, He C, et al. Clinical characteristics of 3062 COVID-19 patients: a meta-analysis. J Med Virol 2020 Oct;92(10):1902-1914 [FREE Full text] [doi: 10.1002/jmv.25884] [Medline: 32293716]
9. Roxby AC, Greninger AL, Hatfield KM, Lynch JB, Dellit TH, James A, et al. Detection of SARS-CoV-2 among residents and staff members of an independent and assisted living community for older adults - Seattle, Washington, 2020. MMWR Morb Mortal Wkly Rep 2020 Apr 10;69(14):416-418. [doi: 10.15585/mmwr.mm6914e2] [Medline: 32271726]
10. Hu Z, Song C, Xu C, Jin G, Chen Y, Xu X, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Sci China Life Sci 2020 May;63(5):706-711 [FREE Full text] [doi: 10.1007/s11427-020-1661-4] [Medline: 32146694]
11. Della Valle P, Fabbri M, Madotto F, Ferrara P, Cozzolino P, Calabretto E, The Mustang-Occupation-Covid-Study Group. Occupational exposure in the Lombardy Region (Italy) to SARS-CoV-2 infection: results from the MUSTANG-OCCUPATION-COVID-19 Study. Int J Environ Res Public Health 2021 Mar 04;18(5):2567 [FREE Full text] [doi: 10.3390/ijerph18052567] [Medline: 33806578]
12. Oran DP, Topol EJ. The proportion of SARS-CoV-2 infections that are asymptomatic: a systematic review. Ann Intern Med 2021 May;174(5):655-662 [FREE Full text] [doi: 10.7326/M20-6976] [Medline: 33481642]

13. Wang Y, He Y, Tong J, Qin Y, Xie T, Li J, et al. Characterization of an asymptomatic cohort of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected individuals outside of Wuhan, China. Clin Infect Dis 2020 Nov 19;71(16):2132-2138 [FREE Full text] [doi: 10.1093/cid/ciaa629] [Medline: 32442265]
14. Huang L, Zhang X, Zhang X, Wei Z, Zhang L, Xu J, et al. Rapid asymptomatic transmission of COVID-19 during the incubation period demonstrating strong infectivity in a cluster of youngsters aged 16-23 years outside Wuhan and characteristics of young patients with COVID-19: A prospective contact-tracing study. J Infect 2020 Jun;80(6):e1-e13 [FREE Full text] [doi: 10.1016/j.jinf.2020.03.006] [Medline: 32283156]
15. Sakurai A, Sasaki T, Kato S, Hayashi M, Tsuzuki S, Ishihara T, et al. Natural history of asymptomatic SARS-CoV-2 infection. N Engl J Med 2020 Aug 27;383(9):885-886 [FREE Full text] [doi: 10.1056/NEJMc2013020] [Medline: 32530584]
16. Hung IF, Cheng VC, Li X, Tam AR, Hung DL, Chiu KH, et al. SARS-CoV-2 shedding and seroconversion among passengers quarantined after disembarking a cruise ship: a case series. Lancet Infect Dis 2020 Sep;20(9):1051-1060 [FREE Full text] [doi: 10.1016/S1473-3099(20)30364-9] [Medline: 32539986]
17. Primi risultati dell'indagine di sieroprevalenza SARS-CoV-2. Istituto Nazionale di Statistica. URL: https://www.istat.it/it/files/2020/08/ReportPrimiRisultatiIndagineSiero.pdf [accessed 2021-04-18]
18. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020 Mar 28;395(10229):1054-1062 [FREE Full text] [doi: 10.1016/S0140-6736(20)30566-3] [Medline: 32171076]
19. Guan W, Liang W, Zhao Y, Liang H, Chen Z, Li Y, China Medical Treatment Expert Group for COVID-19. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020 May;55(5):2000547 [FREE Full text] [doi: 10.1183/13993003.00547-2020] [Medline: 32217650]
20. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med 2020 Jun 18;382(25):e102 [FREE Full text] [doi: 10.1056/NEJMoa2007621] [Medline: 32356626]
21. Caci G, Albini A, Malerba M, Noonan DM, Pochetti P, Polosa R. COVID-19 and obesity: dangerous liaisons. J Clin Med 2020 Aug 04;9(8):2511 [FREE Full text] [doi: 10.3390/jcm9082511] [Medline: 32759719]
22. Arcavi L, Benowitz NL. Cigarette smoking and infection. Arch Intern Med 2004 Nov 08;164(20):2206-2216. [doi: 10.1001/archinte.164.20.2206] [Medline: 15534156]
23. Stämpfli MR, Anderson GP. How cigarette smoke skews immune responses to promote infection, lung disease and cancer. Nat Rev Immunol 2009 May;9(5):377-384. [doi: 10.1038/nri2530] [Medline: 19330016]
24. Feldman C, Anderson R. Cigarette smoking and mechanisms of susceptibility to infections of the respiratory tract and other organ systems. J Infect 2013 Sep;67(3):169-184. [doi: 10.1016/j.jinf.2013.05.004] [Medline: 23707875]
25. Hiding in plain sight: treating tobacco dependency in the NHS. Royal College of Physicians. 2018. URL: https://www.rcplondon.ac.uk/projects/outputs/hiding-plain-sight-treating-tobacco-dependency-nhs [accessed 2021-04-18]
26. Vardavas C, Nikitara K. COVID-19 and smoking: a systematic review of the evidence. Tob Induc Dis 2020;18:20 [FREE Full text] [doi: 10.18332/tid/119324] [Medline: 32206052]
27. Simons D, Shahab L, Brown J, Perski O. The association of smoking status with SARS-CoV-2 infection hospitalization and mortality from COVID-19: a living rapid evidence review. Qeios. 2020. URL: https://www.qeios.com/read/article/582 [accessed 2021-04-18]
28. Liu W, Tao Z, Wang L, Yuan ML, Liu K, Zhou L, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J (Engl) 2020 May 05;133(9):1032-1038 [FREE Full text] [doi: 10.1097/CM9.0000000000000775] [Medline: 32118640]
29. Lippi G, Henry BM. Active smoking is not associated with severity of coronavirus disease 2019 (COVID-19). Eur J Intern Med 2020 May;75:107-108 [FREE Full text] [doi: 10.1016/j.ejim.2020.03.014] [Medline: 32192856]
30. Miyara M, Tubach F, Pourcher V, Morelot-Panzini C, Pernet J, Haroche J, et al. Low incidence of daily active tobacco smoking in patients with symptomatic COVID-19. Qeios. 2021. URL: https://www.qeios.com/read/article/574 [accessed 2021-04-18]
31. Farsalinos K, Barbouni A, Poulas K, Polosa R, Caponnetto P, Niaura R. Current smoking, former smoking, and adverse outcome among hospitalized COVID-19 patients: a systematic review and meta-analysis. Ther Adv Chronic Dis 2020;11:2040622320935765 [FREE Full text] [doi: 10.1177/2040622320935765] [Medline: 32637059]
32. CDC COVID-19 Response Team. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019 - United States, February 12-March 28, 2020. MMWR Morb Mortal Wkly Rep 2020 Apr 03;69(13):382-386. [doi: 10.15585/mmwr.mm6913e2] [Medline: 32240123]
33. Dreher M, Kersten A, Bickenbach J, Balfanz P, Hartmann B, Cornelissen C, et al. Charak- teristik von 50 hospitalisierten COVID-19-patienten mit und ohne ARDS. Dtsch Arztebl Int 2020:271-278. [doi: 10.3238/arztebl.2020.0271]
34. Gaibazzi N, Tuttolomondo D, Guidorossi G, Botti A, Tedeschi A, Martini C, et al. Smoking prevalence is low in symptomatic patients admitted for COVID-19. medRxiv Preprint posted online on June 13, 2020. [doi: 10.1101/2020.05.05.20092015]
35. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020 May 22;369:m1966 [FREE Full text] [doi: 10.1136/bmj.m1966] [Medline: 32444366]

36. Long Q, Tang X, Shi Q, Li Q, Deng H, Yuan J, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med 2020 Aug;26(8):1200-1204. [doi: 10.1038/s41591-020-0965-6] [Medline: 32555424]
37. Monitoraggio e mappatura dinamica dei contagi da COVID-19 in Sicilia. Regione Siciliana Dipartimento Protezione Civile. URL: https://www.protezionecivilesicilia.it/it/219-monitoraggio-e-mappatura-dinamica-dei-contagi-da-covid-19-nel-territorio-della-regione-sicilia.asp [accessed 2021-09-04]
38. Ordinanza contingibile e urgente n. 12 del 29-03-2020. Regione Siciliana. URL: https://www.regione.sicilia.it/sites/default/files/2020-12/Ordinanza_n12_del_29032020.pdf [accessed 2021-09-04]
39. Manufacturer protocol Anti-SARS-CoV-2 ELISA. EUROIMMUN Medizinische Labordiagnostika AG. URL: https://www.euroimmun.com [accessed 2021-09-04]
40. Okba NM, Müller MA, Li W, Wang C, GeurtsvanKessel CH, Corman VM, et al. Severe acute respiratory syndrome coronavirus 2-specific antibody responses in coronavirus disease patients. Emerg Infect Dis 2020 Jul;26(7):1478-1488. [doi: 10.3201/eid2607.200841] [Medline: 32267220]

Abbreviations

ELISA: enzyme-linked immunosorbent assay
GC: gas chromatography
ICU: intensive care unit
OD: optical density
PCR: polymerase chain reaction

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Protocol

Health-Related Quality of Life of Lebanese Women With Breast Cancer: Protocol for a Prospective Cohort Study

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Abstract

Background: In the past few decades, Lebanon has witnessed a significant increase in the incidence rates of women diagnosed with breast cancer. This increase, which is associated with the advancements in treatment modalities, emphasizes the need to evaluate the health-related quality of life (HRQoL) of women with breast cancer and to compare its patterns before and after breast-conserving surgery (BCS).

Objective: This study aims to describe changes in HRQoL according to body image pre- and post-BCS and just before initiation of adjuvant therapy in newly diagnosed patients with breast cancer in Lebanon.

Methods: A prospective cohort study targeting Lebanese women newly diagnosed with breast cancer and who have an indication for BCS will be conducted in 2 health care facilities. Baseline characteristics and clinical data will be collected. The European Organization for Research and Treatment of Cancer Quality-of-Life cancer-specific and breast cancer–specific questionnaires will be used to assess HRQoL. The outcomes will be measured at baseline and 1 day after breast surgery. The primary outcome will be the body image dimensions of the Quality-of-Life breast cancer–specific questionnaire. Statistical analyses will include descriptive statistics, paired 2-tailed *t* test, and stepwise multiple regression. A total of 120 patients will be required.

Results: A total of 120 patients were enrolled in the study. Future outcomes will be published in professional peer-reviewed health-related research journals.

Conclusions: This study is strengthened by its follow-up nature, allowing us to draw conclusions about causality. The results of this study will identify the most affected components of HRQoL, as well as the factors that could play a role in improving HRQoL among women undergoing BCS. The findings of this study will help decision makers, physicians, and social workers to design a comprehensive program with multidisciplinary components for the management and care of patients with breast cancer in Lebanon.

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KEYWORDS

breast cancer; cohort; health-related quality of life; Lebanese women; prospective

Introduction

Background

Approximately 2.1 million women were newly diagnosed with breast cancer in 2018 worldwide [1]. According to Global Cancer Observatory estimates, 684,996 breast cancer–related deaths occurred in 2020 [2]. In the Arab World, the incidence of breast cancer represents 14%-42% of all cancers in women [3]. This wide range is attributed to the capability of each country to detect, monitor, and treat patients with breast cancer [4]. For example, Kuwait, Bahrain, and Qatar can be classified as high-incidence areas with >40% of all female cancers [5]. Meanwhile, the United Arab Emirates, Saudi Arabia, and Oman are classified as low-incidence areas [6]. Lebanon, in particular, is a small Arabic middle-income country with a prominent breast cancer incidence [7]. A significant number of Lebanese women are diagnosed with an incidence rate that has been on the rise over the years, going from a reported 1451 cases in 2005 to 3219 cases in 2018 [8-10]. Approximately 920 (10%) breast cancer–related deaths occurred in 2018 [1].

Breast-conserving surgery (BCS) is one of the most recommended treatments for early-stage breast cancer [11,12]. According to El Saghir et al [4], BCS in Lebanon increased from 48% between 1997 and 2002 to 64% between 2002 and 2010, with a corresponding decrease in the total mastectomy rate from 51% to 36%.

Despite the increase in BCS, this treatment carries an array of side effects and uncomfortable physical symptoms as well as psychological disturbances, such as fear of recurrence, feelings of decreased femininity and attractiveness, and depression. The experience of breast cancer has a prevailing effect on female body image, which varies according to the clinical features and phases of the disease [13]. Unfortunate body image perceptions have the potential to negatively impact the physical and psychological functioning of patients with breast cancer and subsequently their health-related quality of life (HRQoL) [14].

Body image is defined as women's perception and feelings about their body and their self-observation, self-esteem, social interaction, and belief [15]. Han et al [16] found that patients with breast cancer who had better conceptualization of their body image better managed with cancer. Furthermore, fatigue is one of the most common and disabling HRQoL symptoms of cancer among women successfully treated for breast cancer [17]. Fatigue is defined as a general feeling of debilitating tiredness or loss of energy. Fatigue can be associated with several symptoms, such as pain, sleep disturbance, and depression [18,19]. Thus, the impact of body image and fatigue on HRQoL can be extensive, reducing the patient's engagement in work and personal and social activities [20]. With the intention of supporting patients who adapt to their illness and report positive mental health states, several studies have been performed to identify psychological resources that predict better outcomes. One of these resources is habitual or dispositional optimism, a personality trait that describes the degree to which a person generally expects positive outcomes [21,22]. Dispositional optimism is associated with HRQoL [23,24].

Robust scientific data on the HRQoL of patients with breast cancer postactive treatment in Lebanon, especially those who experienced BCS, are still scarce. Only 2 single-center studies with cross-sectional designs were conducted in Lebanon [25,26]. Data of the first study collected from 89 participants between 2009 and 2010 showed that younger, single, and better-educated participants who were diagnosed for <30 months, who had no metastasis, and who paid <US $450 per month on medical expenses had better HRQoL. The second study conducted among 150 female patients with breast cancer diagnosed between January 2009 and March 2014 showed that participants who were Iraqi, had stage 4 disease, had a monthly household income <US $1000, or had received chemotherapy exhibited significantly lower HRQoL. Impaired quality of life (QoL) was also reported in patients with worse psychological well-being [26]. The results of this study cannot be generalized because of the lack of a well-representative sample and the small sample size of patients [27-30]. In addition, this study did not compare the QoL of the same individuals at several time points but rather compared different participants with various times elapsed since diagnosis.

Objectives

This study aims to describe changes in the HRQoL according to body image pre- and post-BCS and just before initiation of adjuvant therapy in newly diagnosed patients with breast cancer in Lebanon. The secondary objectives are (1) to assess changes in the HRQoL according to fatigue and optimism and pessimism between pre- and post-BCS and (2) to identify sociodemographic and clinical factors associated with changes in the HRQoL.

Methods

Study Design

To meet the objectives of the study, a prospective study must be conducted.

Characteristics of Participants

Inclusion Criteria

Only the patients who met the inclusion criteria were invited to participate in this study.

Patient inclusion criteria are women aged ≥18 years; recently diagnosed with invasive early breast cancer of stages 1, 2a, and 2b who are scheduled to undergo breast surgery as primary treatment; without a history of another type of cancer or metastasis; with an absence of other medical or psychiatric conditions; with no previous chemotherapy or radiotherapy; able to read and write the Arabic language; and able to sign informed consent.

Exclusion Criteria

Patients were excluded if they met any of the following exclusion criteria: women who are pregnant or breastfeeding, women who were treated with neoadjuvant chemotherapy, women who had bilateral breast cancer, and women with an active infection or other underlying serious conditions that may prevent the patient from receiving surgery.

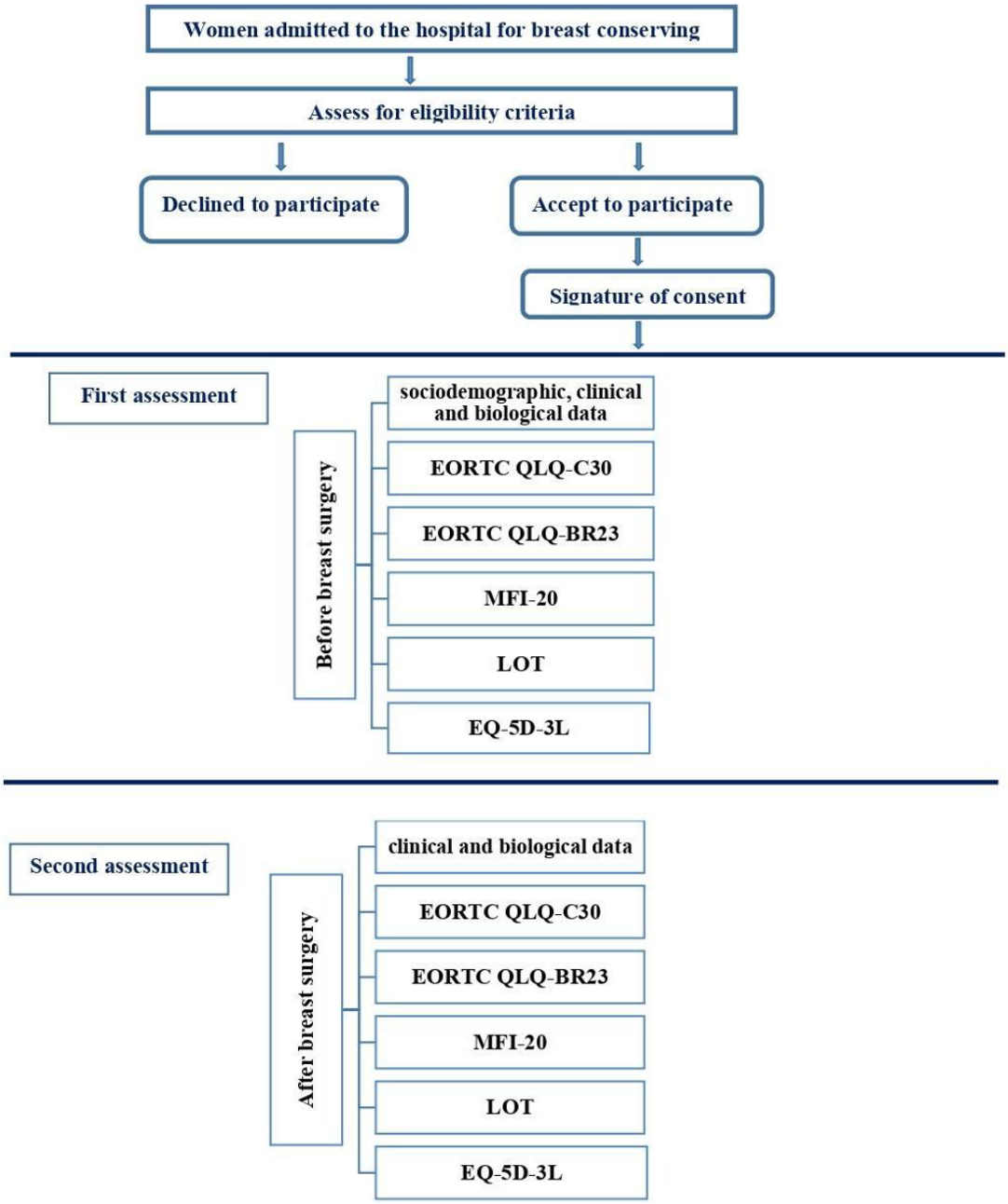
Proceedings

After an explanation of the study, the principal researcher will answer the participants' questions and present the consent form for signature. Patients will complete the questionnaires during 2 periods: the first assessment will be done on the admission day, and the second period is 1 day after the surgery (Figure 1). The estimated average time spent on assessment will be 30-45 minutes. The patients will complete the following questionnaires:

- The European Organization for Research and Treatment of Cancer Quality of Life cancer-specific questionnaire (EORTC QLQ-C30) to assess HRQoL [31]
- The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life breast cancer–specific questionnaire (QLQ-BR23) to assess HRQoL
- The Multidimensional Fatigue Inventory (MFI-20) to assess the multidimensional aspect of fatigue [32]
- The Life Orientation Test (LOT) to assess Optimism and Pessimism [24]
- The European Quality of Life group 5-Dimensional questionnaire–5 Level version (EQ-5D-5L) to assess HRQoL [33]

The study will be conducted in 2 hospitals located in Beirut, namely Rafik Hariri University Hospital and Sahel General Hospital. The duration of the study is estimated at approximately 34 months.

Figure 1. Study flowchart. EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life breast cancer–specific Questionnaire; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life cancer-specific Questionnaire; EQ-5D-5L: European Quality of Life group 5-Dimensional questionnaire–5 Level version; LOT: Life Orientation Test; MFI-20: Multidimensional Fatigue Inventory.



Ethical Statement

The proposal of the study was approved by the institutional review board of the Rafik Hariri University Hospital in Beirut (reference number: 18.007-Trans-CMO-[OM]) and the ethical committee of Sahel General Hospital. Informed consent was obtained from each participant. All necessary measures to safeguard participants' anonymity and confidentiality of information were respected.

Outcome Measures

The primary outcome measure will be a change in the body image dimension of HRQoL. The secondary outcome measures will be changes in the HRQoL, first according to fatigue and second according to optimism and pessimism; the EORTC QLQ-C30 dimension (physical, emotional, social, role, cognitive, pain, nausea or vomiting, constipation, diarrhea, insomnia, dyspnea, and appetite loss); and the EORTC QLQ-BR23 dimension (sexual functioning, sexual enjoyment, future perspective, systemic therapy side effects, breast symptoms, arm symptoms, and upset by hair loss), as summarized in Table 1.

Table 1. Outcome measures and source data.

Outcome and measure	Validation in Arabic language	Description	Source of data	Period of assessment	
				Before surgery	After surgery
HRQoL[a]					
EORTC QLQ-C30[b] [30]	✓[c]	A cancer HRQoL questionnaire that has been widely used in clinical trials and investigations for individual patient with cancer management • 30 items • Includes 5 function domains: physical, emotional, social, role, cognitive; and 9 symptoms: fatigue, pain, nausea or vomiting, constipation, diarrhea, insomnia, dyspnea and appetite loss and global health or quality-of-life and financial impact • Recall period: past week • Items 1-28 formed by Likert scale: 1-4 (very much) • Items 29-30 formed by Likert scale: 1-7 (excellent)	PRO[d]	✓	✓
EORTC QLQ-BR23[e] [40]	✓	A breast cancer–specific module of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire • 23 items • Includes 8 function domains: body image, sexual functioning, sexual enjoyment, future perspective, systemic therapy side effects, breast symptoms, arm symptoms, and upset by hair loss • Recall period: past week • Items 1-23 formed by Likert scale: 1-4 (very much)	PRO	✓	✓
EQ-5D-5L[f] [33,35,36]	✓	A measure of HRQoL that can be used in a wide range of health conditions and treatments • Includes 5 dimensions: mobility, self-care, usual activities, pain or discomfort, anxiety or depression • Includes a visual analog scale • Such dimensions are evaluated by 3 levels: no problems, some problems, extreme problems	PRO	✓	✓
Body image					
EORTC QLQ-BR23 [40]	✓	__[g]	PRO	✓	✓
Fatigue					
MFI-20[h] [39]	✓	A scale designed to evaluate the dimensions of fatigue • 20 items • Includes 5 dimensions: general fatigue, physical fatigue, reduced activity, reduced motivation, mental fatigue • Recall period: past 4 weeks • Items 1-20 formed by Likert scale: 1-5 (no, it's not true)	PRO	✓	✓
Optimism and pessimism					
LOT[i] [41]	✓	A scale was developed to assess individual differences in generalized optimism versus pessimism: • 10 items • Distinguishing between optimism and pessimism • 3 items measure the optimism, and 3 items measure the pessimism • Recall period: present • Items 2, 5, 6, and 8 are fillers • Items 1-10 formed by Likert scale: 1-4 (strongly disagree)	PRO	✓	✓

[a]HRQoL: health-related quality of life.

[b]EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life cancer-specific Questionnaire.

[c]Feature present.

[d]PRO: patient-reported outcome.

[e]EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life breast- cancer–specific Questionnaire.

[f]EQ-5D-5L: European Quality of Life group 5-Dimensional questionnaire–5 Level version.

[g]Not available.

[h]MFI-20: Multidimensional Fatigue Inventory.

[i]LOT: Life Orientation Test.

Body Image

Body image will be evaluated using the Arabic version of the EORTC QLQ-BR23 [30]. The breast cancer module is designed for patients with different disease stages and treatment modalities [34].

Functional and symptomatic items of the QLQ-BR23 questionnaire will be rated on a 4-level response system from *not at all* (score 1) to *very much* (score 4), whereas the global QoL (Q29 and Q30) will be rated on a 7-point response scale.

Health-Related Quality of Life

HRQoL will be evaluated using the Arabic versions of the EORTC QLQ-C30 and its QLQ-BR23 [30] and the Arabic version of the EQ-5D-5L [33,35,36].

The EORTC QLQ-C30 is a cancer-specific HRQoL questionnaire that has been widely used in clinical trials and investigations for individual cancer patient management [31]. It comprises 30 items. Items 1-28 are assessed on a 4-point Likert scale from 1, *not at all*, to 4, *very much*, and items 29 and 30 from 0 to 7. The EORTC QLQ-C30 incorporates 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), a global health status or QoL scale, and a number of single items assessing additional symptoms commonly reported by patients with cancer (dyspnea, loss of appetite, insomnia, constipation, and diarrhea), and the perceived financial impact of the disease.

For each scale, a score is generated from 0 to 100 according to the recommendations of the EORTC such that a high score will correspond to a high level of global health/QoL health, a high functional level, and a high symptomatic level.

The QLQ-BR23 incorporates 5 multi-item scales to assess systemic therapy side effects, arm symptoms, breast symptoms, body image, and sexual functioning. In addition, single items assess sexual enjoyment, hair loss, and future perspectives [31]. As with the EORTC QLQ-C30, a score is generated per dimension such that a high score will reflect a high functional level and a high symptomatic level [31].

The EQ-5D-5L was also used to assess the patients' HRQoL levels. The Arabic version was requested from the European Quality of Life group [33]. The EQ-5D-5L descriptive system comprises the same 5 dimensions as the EQ-5D-3L (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression); however, each dimension now has 5 response levels: no problems, slight problems, moderate problems, severe problems, and unable to or extreme problems. The respondent is asked to indicate his or her health state by checking the box next to the most appropriate response level for each of the 5 dimensions [32]. Furthermore, another part of EQ-5D-5L is a visual analog scale, which can be used to assess the self-rated health of respondents using a 100 mm scale with the score ranging from 0 (the worst health you can imagine) to 100 (the best health you can imagine). The Arabic version of EQ-5D-5L has been used and validated elsewhere, and it was requested from the European Quality of Life group [33,35,36].

Fatigue

The MFI-20 is a self-report tool that has been used to assess fatigue in patients with a variety of cancers [37,38]. The MFI-20 Arabic version will be used to evaluate the multidimensional aspects of fatigue [39]. The scale comprises items evaluating general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue during the past 4 weeks. Each item is scored on a 5-point Likert scale from 0 (yes, it's true) to 5 (no, it's not true) [32], which is a 20-item scale evaluating the dimensions of fatigue.

Optimism and Pessimism

The LOT is a 10-item self-report measure; 4 of the items are filler items that are included to disguise (somewhat) the underlying purpose of the test. Of the 6 scored items, 3 are phrased in an optimistic direction and 3 in a pessimistic direction. The respondents indicated the extent to which they agreed with each of the items on a 5-point scale from 0 (strongly disagree) to 4 (strongly agree). The recall period was the present. The total score was calculated by the addition of the optimism raw scores and the inverted pessimism raw scores. Scores range from 0 to 24; higher scores indicate greater optimism, and lower scores indicate lower optimism, often referred to as pessimism [24].

Statistical Considerations

Population Analysis

The primary population of analysis will be all included patients with both questionnaires completed pre- and postsurgery. Secondary analyses will be conducted on all included patients with at least the baseline questionnaire completed.

Sample Size

According to the International Agency for Research on Cancer, the number of new breast cancer cases in Lebanon in 2018 was estimated to be 3219, regardless of the stage of the disease [10]. To demonstrate a change of at least 5 points and considering a bilateral type 1 error rate of 5% and a statistical power of 80% as the minimal clinically important difference in the body image

score after surgery as compared with the baseline score, with an SD of 20 points, it will be required to include 120 patients (paired *t* test) with both baseline and postsurgery scores available. Indeed, to explore factors associated with change in the body image scale after surgery, a multiple linear regression model will be used. With a sample size of 95 patients, a bilateral type 1 error rate of 5%, and a statistical power of 80%, we will be able to introduce 5 explanatory variables in the model in addition to age as a control variable. To consider 5% of nonexploitable data, a total of 126 patients need to be included.

Statistical Analysis

Descriptive statistics will be calculated for all study variables at specified times. The qualitative variables will be expressed using frequencies and percentages, whereas quantitative data will be presented as means and SDs, and demographic and clinical characteristics of patients with breast cancer will be compared using the *t* test for continuous variables and chi-square tests for categorical variables. To determine potential predictors of HRQoL, bivariate associations among candidate predictor variables (demographic information, including age, marital status, family situation, education, employment status, habitation, and medical data, including the type of surgery, pathological tumor size, histological grade of tumor, menopausal status, and hormone receptor status) and HRQoL pre- and post-BCS scores were examined using Pearson correlation coefficients. Significant predictor variables for HRQoL will be included in the multiple regression analyses.

Variables with a P value ≤.20 in the univariate model were eligible for the multivariate model. The collinearity between variables will be tested using univariate analysis. Variables presenting collinearity will not be simultaneously included in the same multivariate model. A stepwise selection approach will be then used to select the final multivariate model. The 95% CI will be calculated, and R^2 values will be computed to determine how the data fit the regression model.

Repeated measures analysis of variance (ANOVA) will be used to determine surgery effects on the variables of interest. To evaluate the relationships between body image scores, fatigue scores, optimism and pessimism scores, and HRQoL scores, Spearman correlation coefficients will be calculated for all patients pre- and post-BCS.

The scale scores of the EORTC QLQ-C30 and QLQ-BR23 will be computed as recommended [31]. The minimal clinically important difference will be set at 5 points for each score of the EORTC QLQ-C30 and QLQ-BR23 questionnaires [31,42] and at 10 points for the MFI-20 questionnaire [43]. All the results will be interpreted within the meaning of this minimal clinically important difference, in addition to the statistical significance, to measure the clinical relevance of the results. The percentage of missing questionnaires and missing items for the HRQoL questionnaire will be provided. Only women who provide information pre and after operation could be included for the comparison.

Analysis of the Primary Outcome

Normally distributed continuous outcomes will be summarized as means and SDs. The rate of missing data at each HRQoL measurement time will be reported.

To compare the main scores of the EORTC QLQ-C30, QLQ-BR23, EQ-5D-5L, MFI-20, and LOT across pre- and postsurgery data, a paired *t* test will be used.

To compare possible differences between pre- and postsurgery outcomes, a one-way ANOVA will be used for quantitative variables.

The factors associated with the change in HRQoL according to body image before BCS will be identified using a multiple regression model. To determine the factors potentially predicting the change in HRQoL according to body image, Pearson correlation coefficients between all the numerical variables collected at inclusion and the body image scores at baseline and after surgery will be calculated.

Analysis of the Secondary Outcomes

Independent sample *t* tests and ANOVAs will be used to test differences in the mean scores of the main questionnaires used in this study and their subscales (EORTC QLQ-C30, QLQ-BR23, EQ-5D-5L, MFI-20, and LOT) and mean scores of demographic variables (age, residence, employment, and income) and clinical characteristics (comorbidities, BMI, and laboratory values). Pearson correlation between EORTC QLQ-C30 and EQ-5D-5L, MFI-20, and LOT scores and their subscales will be calculated to see which domain has the strongest relationship with QoL after surgery.

All analyses will be calculated with their 95% CIs; statistical significance will be set at P<.05. The collected data will be captured and analyzed using the SPSS software version 26 (IBM Corp).

Ethics Approval and Consent to Participate

The proposal of study is approved by the institutional review board of the Rafik Hariri University Hospital in Beirut (reference number: 18.007-Trans-CMO-[OM]) and the ethical committee of Sahel General Hospital.

Results

The study received ethics approval from the institutional review board. Recruitment and enrollment began in January 2018. A total of 120 patients were enrolled in this study. Future outcomes will be published in professional peer-reviewed health-related research journals.

Discussion

Principal Findings

Nowadays, Lebanese women in general reflect the importance of gender roles in the Lebanese culture and society; most women are still expected to be homemakers, taking care of their families' needs, although many of them work outside the house and are breadwinners as much as their male partners [30]. However, most studies show that patients with breast cancer

experience physical symptoms and psychosocial distress that adversely affect their HRQoL [44,45]. So far, according to limited data, there is a weakness in studies concerning the impact of HRQoL on Lebanese women with breast cancer [29]. This study will report an important gap in the literature by answering a crucial question regarding the patient-reported outcome of HRQoL after BCS. In this context, we designed a study to evaluate HRQoL changes between pre- and post-BCS and just before initiation of adjuvant therapy in newly diagnosed patients with invasive breast cancer, targeting the body image dimension as the primary outcome of interest.

This study is strengthened by its follow-up nature, allowing us to draw conclusions about causality. However, the questionnaires used were well-validated in Lebanese populations. However, some limitations must be acknowledged. As it is a sample of convenience and not population based, the generalizability of the results to the entire Lebanese population is not possible as data were collected from 2 hospitals only. However, our hospitals are a reference center in Beirut city for the treatment of breast cancer, and our population could be representative of this group of patients. On the other hand, considering the gap in the scientific literature on prospective studies focusing on HRQoL, body image, fatigue, and optimism and pessimism before and after BCS, this study is presented as the first prospective study on HRQoL of breast cancer in Lebanon.

Subgroup analysis will be performed to compare baseline characteristics and will be adjusted in the multivariable analysis considering those variables with significant differences.

Conclusions

In summary, the findings of this study will help decision makers, physicians, and social workers design a comprehensive program with multidisciplinary components for the management and care of patients with breast cancer in Lebanon.

Acknowledgments

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Authors' Contributions

REH, VN, AA, and LAA conceptualized the study; REH was responsible for writing the original draft, reviewing and editing; VN and AA were responsible for visualization; and VN, AA, and LAA supervised the study. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018 Nov;68(6):394-424 [FREE Full text] [doi: 10.3322/caac.21492] [Medline: 30207593]
2. Cancer today. International Agency for Research on Cancer. URL: http://gco.iarc.fr/today/home [accessed 2021-07-26]
3. Haddou Rahou B, El Rhazi K, Ouasmani F, Nejjari C, Bekkali R, Montazeri A, et al. Quality of life in Arab women with breast cancer: a review of the literature. Health Qual Life Outcomes 2016 Apr 27;14:64 [FREE Full text] [doi: 10.1186/s12955-016-0468-9] [Medline: 27117705]
4. El Saghir NS, Assi HA, Jaber SM, Khoury KE, Nachef Z, Mikdashi HF, et al. Outcome of breast cancer patients treated outside of clinical trials. J Cancer 2014;5(6):491-498 [FREE Full text] [doi: 10.7150/jca.9216] [Medline: 24959302]
5. Hashim MJ, Al-Shamsi FA, Al-Marzooqi NA, Al-Qasemi SS, Mokdad AH, Khan G. Burden of breast cancer in the Arab world: findings from Global Burden of Disease, 2016. J Epidemiol Glob Health 2018 Dec;8(1-2):54-58 [FREE Full text] [doi: 10.2991/j.jegh.2018.09.003] [Medline: 30859788]
6. Al-Othman S, Haoudi A, Alhomoud S, Alkhenizan A, Khoja T, Al-Zahrani A. Tackling cancer control in the Gulf Cooperation Council Countries. Lancet Oncol 2015 May;16(5):e246-e257. [doi: 10.1016/S1470-2045(15)70034-3] [Medline: 25943069]
7. Fares MY, Salhab HA, Khachfe HH, Khachfe HM. Breast cancer epidemiology among Lebanese women: an 11-year analysis. Medicina (Kaunas) 2019 Aug 10;55(8):463 [FREE Full text] [doi: 10.3390/medicina55080463] [Medline: 31405167]
8. Homepage. Ministry of Public Health. URL: http://www.moph.gov.lb [accessed 2021-11-01]
9. Breast cancer statistics. World Cancer Research Fund. URL: https://www.wcrf.org/dietandcancer/cancer-trends/breast-cancer-statistics [accessed 2020-05-28]
10. Howard MA, Sisco M, Yao K, Winchester DJ, Barrera E, Warner J, et al. Patient satisfaction with nipple-sparing mastectomy: a prospective study of patient reported outcomes using the BREAST-Q. J Surg Oncol 2016 Sep;114(4):416-422 [FREE Full text] [doi: 10.1002/jso.24364] [Medline: 27393183]

11. Breast Cancer Control in Canada. Canadian Partnership Against Cancer. 2012. URL: https://s22457.pcdn.co/wp-content/uploads/2019/01/Breast-cancer-control-EN.pdf [accessed 2021-10-19]
12. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002 Oct 17;347(16):1233-1241. [doi: 10.1056/NEJMoa022152] [Medline: 12393820]
13. Fazzino TL, Hunter RC, Sporn N, Christifano DN, Befort CA. Weight fluctuation during adulthood and weight gain since breast cancer diagnosis predict multiple dimensions of body image among rural breast cancer survivors. Psychooncology 2017 Mar;26(3):392-399 [FREE Full text] [doi: 10.1002/pon.4035] [Medline: 26564108]
14. Fobair P, Stewart SL, Chang S, D'Onofrio C, Banks PJ, Bloom JR. Body image and sexual problems in young women with breast cancer. Psychooncology 2006 Jul;15(7):579-594. [doi: 10.1002/pon.991] [Medline: 16287197]
15. Lehmann V, Hagedoorn M, Tuinman MA. Body image in cancer survivors: a systematic review of case-control studies. J Cancer Surviv 2015 Jun;9(2):339-348. [doi: 10.1007/s11764-014-0414-y] [Medline: 25446910]
16. Han J, Grothuesmann D, Neises M, Hille U, Hillemanns P. Quality of life and satisfaction after breast cancer operation. Arch Gynecol Obstet 2010 Jul;282(1):75-82. [doi: 10.1007/s00404-009-1302-y] [Medline: 19960349]
17. Bower JE, Ganz PA, Desmond KA, Rowland JH, Meyerowitz BE, Belin TR. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. J Clin Oncol 2000 Feb;18(4):743-753. [doi: 10.1200/JCO.2000.18.4.743] [Medline: 10673515]
18. Armstrong TS, Cohen MZ, Eriksen LR, Hickey JV. Symptom clusters in oncology patients and implications for symptom research in people with primary brain tumors. J Nurs Scholarsh 2004;36(3):197-206. [doi: 10.1111/j.1547-5069.2004.04038.x] [Medline: 15495487]
19. Dodd MJ, Miaskowski C, Lee KA. Occurrence of symptom clusters. J Natl Cancer Inst Monogr 2004(32):76-78. [doi: 10.1093/jncimonographs/lgh008] [Medline: 15263044]
20. Ancoli-Israel S, Liu L, Marler MR, Parker BA, Jones V, Sadler GR, et al. Fatigue, sleep, and circadian rhythms prior to chemotherapy for breast cancer. Support Care Cancer 2006 Mar;14(3):201-209 [FREE Full text] [doi: 10.1007/s00520-005-0861-0] [Medline: 16010529]
21. Carver CS, Scheier MF, Segerstrom SC. Optimism. Clin Psychol Rev 2010 Nov;30(7):879-889 [FREE Full text] [doi: 10.1016/j.cpr.2010.01.006] [Medline: 20170998]
22. Carver CS, Scheier MF. Dispositional optimism. Trends Cogn Sci 2014 Jun;18(6):293-299 [FREE Full text] [doi: 10.1016/j.tics.2014.02.003] [Medline: 24630971]
23. Colby DA, Shifren K. Optimism, mental health, and quality of life: a study among breast cancer patients. Psychol Health Med 2013;18(1):10-20. [doi: 10.1080/13548506.2012.686619] [Medline: 22690751]
24. Scheier MF, Carver CS, Bridges MW. Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. J Pers Soc Psychol 1994 Dec;67(6):1063-1078. [doi: 10.1037//0022-3514.67.6.1063] [Medline: 7815302]
25. Akel R, El Darsa H, Anouti B, Mukherji D, Temraz S, Raslan R, et al. Anxiety, depression and quality of life in breast cancer patients in the Levant. Asian Pac J Cancer Prev 2017 Oct 26;18(10):2809-2816 [FREE Full text] [doi: 10.22034/APJCP.2017.18.10.2809] [Medline: 29072421]
26. Abu-Saad Huijer H, Abboud S. Health-related quality of life among breast cancer patients in Lebanon. Eur J Oncol Nurs 2012 Dec;16(5):491-497. [doi: 10.1016/j.ejon.2011.11.003] [Medline: 22257429]
27. Naja F, Fadel RA, Alameddine M, Aridi Y, Zarif A, Hariri D, et al. Complementary and alternative medicine use and its association with quality of life among Lebanese breast cancer patients: a cross-sectional study. BMC Complement Altern Med 2015 Dec 22;15:444 [FREE Full text] [doi: 10.1186/s12906-015-0969-9] [Medline: 26692096]
28. Doumit MA, El Saghir N, Abu-Saad Huijer H, Kelley JH, Nassar N. Living with breast cancer, a Lebanese experience. Eur J Oncol Nurs 2010 Feb;14(1):42-48. [doi: 10.1016/j.ejon.2009.08.003] [Medline: 19815459]
29. Akel R, El Darsa H, Anouti B, Mukherji D, Temraz S, Raslan R, et al. Anxiety, depression and quality of life in breast cancer patients in the Levant. Asian Pac J Cancer Prev 2017 Oct 26;18(10):2809-2816 [FREE Full text] [doi: 10.22034/APJCP.2017.18.10.2809] [Medline: 29072421]
30. Huijer HA, Sagherian K, Tamim H. Validation of the Arabic version of the EORTC quality of life questionnaire among cancer patients in Lebanon. Qual Life Res 2013 Aug;22(6):1473-1481. [doi: 10.1007/s11136-012-0261-0] [Medline: 22961075]
31. EORTC QLQ-C30 Reference Values. EORTC Quality of Life Group. 2008. URL: https://www.eortc.org/app/uploads/sites/2/2018/02/reference_values_manual2008.pdf [accessed 2021-10-21]
32. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995 Apr;39(3):315-325. [doi: 10.1016/0022-3999(94)00125-o] [Medline: 7636775]
33. EQ-5D-5L - self-complete version on paper. EQ-5D. URL: https://euroqol.org/eq-5d-instruments/eq-5d-5l-available-modes-of-administration/self-complete-on-paper/ [accessed 2021-10-19]

34. Sprangers MA, Groenvold M, Arraras JI, Franklin J, te Velde A, Muller M, et al. The European Organization for research and treatment of cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol 1996 Oct;14(10):2756-2768. [doi: 10.1200/JCO.1996.14.10.2756] [Medline: 8874337]
35. Bekairy AM, Bustami RT, Almotairi M, Jarab A, Katheri AM, Aldebasi TM, et al. Validity and reliability of the Arabic version of the the EuroQOL (EQ-5D). A study from Saudi Arabia. Int J Health Sci (Qassim) 2018;12(2):16-20 [FREE Full text] [Medline: 29599689]
36. Aburuz S, Bulatova N, Twalbeh M, Gazawi M. The validity and reliability of the Arabic version of the EQ-5D: a study from Jordan. Ann Saudi Med 2009;29(4):304-308 [FREE Full text] [doi: 10.4103/0256-4947.55313] [Medline: 19584581]
37. Fürst CJ, Ahsberg E. Dimensions of fatigue during radiotherapy. An application of the multidimensional fatigue inventory. Support Care Cancer 2001 Jul;9(5):355-360. [doi: 10.1007/s005200100242] [Medline: 11497389]
38. Jean-Pierre P, Figueroa-Moseley CD, Kohli S, Fiscella K, Palesh OG, Morrow GR. Assessment of cancer-related fatigue: implications for clinical diagnosis and treatment. Oncologist 2007;12(1):11-21 [FREE Full text] [doi: 10.1634/theoncologist.12-S1-11] [Medline: 17573452]
39. Haggag W, Soliman H. The Arabic version of multidimensional fatigue inventory: reliability, validity and findings in three groups. Egypt J Psychiatry 1997 Feb 10;20:85-96 [FREE Full text]
40. Awad MA, Denic S, El Taji H. Validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaires for Arabic-speaking populations. Ann N Y Acad Sci 2008 Sep;1138:146-154. [doi: 10.1196/annals.1414.021] [Medline: 18837895]
41. Life orientation test. Sudan Forum. URL: https://psycho.sudanforums.net/t1479-topic [accessed 2021-10-19]
42. Cocks K, King MT, Velikova G, St-James MM, Fayers PM, Brown JM. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. J Clin Oncol 2011 Jan 01;29(1):89-96. [doi: 10.1200/JCO.2010.28.0107] [Medline: 21098316]
43. Chan A, Yo TE, Wang XJ, Ng T, Chae J, Yeo HL, et al. Minimal Clinically Important Difference of the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) for fatigue worsening in Asian breast cancer patients. J Pain Symptom Manage 2018 Mar;55(3):992-7.e2 [FREE Full text] [doi: 10.1016/j.jpainsymman.2017.10.014] [Medline: 29097274]
44. Paraskevi T. Quality of life outcomes in patients with breast cancer. Oncol Rev 2012 Mar 05;6(1):e2 [FREE Full text] [doi: 10.4081/oncol.2012.e2] [Medline: 25992204]
45. Perry S, Kowalski TL, Chang CH. Quality of life assessment in women with breast cancer: benefits, acceptability and utilization. Health Qual Life Outcomes 2007 May 02;5:24-25 [FREE Full text] [doi: 10.1186/1477-7525-5-24] [Medline: 17474993]

Abbreviations

ANOVA: analysis of variance
BCS: breast-conserving surgery
EORTC: European Organization for Research and Treatment of Cancer
EQ-5D-5L: European Quality of Life group 5-Dimensional questionnaire–5 Level version
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life cancer-specific Questionnaire
HRQoL: health-related quality of life
LOT: Life Orientation Test
MFI-20: Multidimensional Fatigue Inventory
QLQ-BR23: Quality of Life breast cancer–specific Questionnaire
QoL: quality of life

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Protocol

A Quality-of-Life Evaluation Study Assessing Health-Related Quality of Life in Patients Receiving Medicinal Cannabis (the QUEST Initiative): Protocol for a Longitudinal Observational Study

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Abstract

Background: Evidence supports several countries introducing legislation to allow cannabis-based medicine as an adjunctive treatment for the symptomatic relief of chronic pain, chemotherapy-induced nausea, spasticity in multiple sclerosis (MS), epileptic seizures, depression, and anxiety. However, clinical trial participants do not represent the entire spectrum of disease and health status seen in patients currently accessing medicinal cannabis in practice.

Objective: This study aims to collect real-world data to evaluate health-related quality of life in patients prescribed medicinal cannabis oil and describe any differences over time, from before starting therapy to after 3 and 12 months of therapy.

Methods: Adult patients newly prescribed medicinal cannabis oil by authorized prescribers and under the Special Access Schemes across Australia will be screened for eligibility and invited to participate. A sample size of 2142 is required, with a 3-month follow-up. All participants will complete the EuroQol 5-Dimension; European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-30; Depression, Anxiety, and Stress Scale-21; Patients' Global Impression of Change; Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form (SF) version 1.0: Sleep Disturbance 8b; and PROMIS SF Fatigue 13a questionnaires. Patients with chronic pain conditions will also complete the PROMIS SF version 1.0: Pain Intensity 3a and PROMIS SF version 1.0: Pain Interference 8a. Patients with movement disorders will also complete Quality of Life in Neurological Disorders (Neuro-QoL) SF version 1.0: Upper Extremity Function (Fine Motor and Activities of Daily Living) and if chorea is indicated, the Neuro-QoL SF version 2.0: Huntington's Disease health-related Quality of LIFE-Chorea 6a. All questionnaires will be administered at baseline, 2 weeks (titration), monthly up to 3 months, and then every 2 months up to 1 year.

Results: Recruitment commenced in November 2020. By June 2021, 1095 patients were screened for the study by 69 physicians in centers across 6 Australian states: Australian Capital Territory, New South Wales, Queensland, South Australia, Victoria, and Western Australia. Of the patients screened, 833 (39% of the target sample size) provided consent and completed baseline questionnaires. Results are expected to be published in 2022. Results of this study will show whether patient-reported outcomes improve in patients accessing prescribed medicinal cannabis from baseline to 3 months and whether any changes are maintained over a 12-month period. This study will also identify differences in improvements in patient-reported outcomes among patients with different chronic conditions (eg, chronic pain, MS, epilepsy, Parkinson disease, or cancer).

Conclusions: This protocol contains detailed methods that will be used across multiple sites in Australia. The findings from this study have the potential to be integral to treatment assessment and recommendations for patients with chronic pain and other health indicators for accessing medicinal cannabis.

Trial Registration: Australian New Zealand Clinical Trials Registry: ANZCTRN12621000063819; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=380807&isReview=true

International Registered Report Identifier (IRRID): DERR1-10.2196/32327

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KEYWORDS

medicinal cannabis; patient-reported outcomes; quality of life; chronic pain; pain management; mental health; depression; anxiety; cannabis oil

Introduction

Medicinal Cannabis

With the first accounts of cannabis being used as medicine dating back to China in 2600 BC, its use for medicinal purposes has been recorded on nearly every continent throughout history [1]. Many countries criminalized the consumption of cannabis in the 1900s, consequently limiting the potential therapeutic benefits and research into medicinal use. However, the identification of cannabinoids, cannabidiol, and Δ9-tetrahydrocannabinol as analgesics in 1940 refocused attention on using cannabis-based medicine as an adjunctive treatment for the symptomatic relief of chronic pain [1]. The last 2 decades have seen an increase in medicinal cannabis research, particularly in response to growing concerns about the misuse and adverse events associated with opioids [2], including increased risk of endocrinopathy, bowel dysfunction, cognitive decline, hospitalization, and death from overdose [3]. Research to date has provided sufficient evidence for several countries to introduce legislation allowing its use for medicinal purposes. These policies help to avoid the potential risk of cannabis abuse by self-medicating [4] and enable appropriate monitoring of possible adverse drug-drug interactions [5]. In 2020, there were approximately 400,000 medicinal cannabis patient registrations in Canada [6], more than 60,000 in Germany [7], and more than 25,000 in Australia [8].

Evidence from randomized controlled trials indicates that medicinal cannabis can reduce chronic pain [9-12], neuropathic pain [13], cancer pain [14], chemotherapy-induced nausea [15], spasticity in multiple sclerosis (MS) [16,17], epileptic seizures [18], depression [10,12], anxiety [12], improve sleep [19], and reduce opioid prescription numbers [20]. However, depression, anxiety, and sleep problems may be exasperated with formulations containing high ratios of Δ9-tetrahydrocannabinol [21], and for some health indications, using medicinal cannabis in a *real-world* setting may be confounded by drug-drug interactions [5]. This supports the need for oversight by health care professionals and further research collecting *real-world* evidence.

Why Patient-Reported Outcomes Are Important

A patient-reported outcome (PRO) is any report coming directly from patients without interpretation by physicians or others about how the patient feels in relation to a health condition and its therapy [22]. PROs can include symptoms, aspects of functioning, multidimensional constructs such as health-related quality of life (HRQL), and perceptions of treatment. PROs are regarded as the gold standard for assessing pain [23] and are particularly important end points to include when assessing patients with chronic conditions where the primary aim is to palliate symptoms [24]. These patient reports were captured and quantified by PRO measures (PROMs) using validated and reliable standardized questionnaires that allow comparisons between treatment groups and within groups over time. The wide acceptance of PROM-based evidence by regulatory bodies is reflected in the Australian Commission on Safety and Quality in Health Care's support of the use of PROMs to drive quality improvement [25] and the US Food and Drug Administration's approval of PROs to support product labeling claims [26].

Health Indications for Accessing Medicinal Cannabis

The Australian Therapeutic Goods Administration (TGA) currently approves Special Access Scheme (SAS) applications from health care providers who provide a clinical justification for prescribing medicinal cannabis where conventional therapies have failed [8]. There are no TGA-imposed restrictions on the types of health conditions; however, prescriptions are more commonly sought for chronic pain and spasticity from neurological conditions.

Chronic Pain

Chronic pain is a widespread health issue broadly defined as pain that lasts or recurs for more than 3 months [27] and is categorized as *chronic primary pain*—a disease in its own right such as nonspecific low-back pain—or as *chronic secondary pain* initiated as a symptom of an underlying disease, such as cancer-related pain or neuropathic pain [28]. In Australia, more than 15% of the adult population lives with persistent chronic pain or recurring pain lasting longer than 6 months [29]. In the United Kingdom, as many as 35% of adults experience some level of chronic pain lasting more than 3 months, with more than 10% reporting moderate to severely limiting chronic pain [30]. In 2016, the Centers for Disease Control and Prevention reported that 20% of US adults had chronic pain and 8% experienced chronic pain that severely interfered with daily functioning on most days or every day for a 6-month period [31].

Cancer-related pain is experienced by approximately one-third of patients with cancer at diagnosis and during treatment and by approximately three-fourths of patients with advanced-stage

cancer. However, 10%-15% of the patients are nonresponsive to conventional pain therapy [32]. Residual tissue damage from cancer and cancer treatment often results in chronic pain in cancer survivors, which lasts many years after treatment [33].

Neuropathic pain, which is caused by a lesion or disease of the somatosensory nervous system [34], is experienced by approximately 8% of the population [35] and approximately 86% of the patients with MS [36]. Neuropathic pain is associated with higher rates of unemployment [35], poor physical, psychological, and social functioning, significantly impaired overall HRQL and sleep, and higher depression and anxiety than those with other chronic pain and those without pain [37]. Less than 35% of the patients with neuropathic pain respond to conventional therapy [38], whereas others often receive incomplete pain relief along with conventional treatment-related side effects [39].

The prevalence of chronic pain increases dramatically in patients receiving palliative care [40,41]. A study of patients in palliative care clinics in the United States found that most of them were admitted with unrelieved pain and that chronic pain assessment and management were inadequate [42]. In addition, one-third of the patients receiving palliative care who experienced pain were significantly more likely to also suffer from depression [41], report insufficient sleep [43], and were at a higher risk of opioid misuse [40]. Effective pain and symptom management aimed at reducing suffering and improving overall HRQL are the primary goals of palliative care.

Neurological and Movement Disorders

MS is a chronic inflammatory and demyelinating neurodegenerative disorder that often involves symptoms such as spasms, tremors, pain, fatigue, bladder dysfunction, cognitive impairment, depression, and impairments in swallowing, speech, vision, and balance [44]. In 2018, MS Research Australia reported an estimated 24,600 Australians with MS, and, on average, their overall HRQL was 31% less than the Australian population norm (measured by the health state utility valuation) [45]. As a currently incurable and often progressive condition, treatment and management largely focus on improving the quality of everyday life by relieving symptoms [44]. A systematic review of reviews conducted in 2018 on the effects of cannabidiol, Δ9-tetrahydrocannabinol, or cannabidiol and Δ9-tetrahydrocannabinol formulations in treating MS symptoms found sufficient evidence supporting cannabinoids in relieving both pain and spasticity symptoms [46].

Epilepsy is a chronic neurological disease characterized by 2 or more unprovoked seizures and affects approximately 50 million people worldwide [47]. High-quality evidence from randomized clinical trials suggests that cannabidiol reduces seizure frequency; however, further examination of PROs is needed to assess whether cannabidiol interacts with other antiseizure medications to produce unwanted side effects [48].

Critical Gaps in Knowledge About HRQL in Patients Accessing Medicinal Cannabis

PRO assessment can assist health care professionals in monitoring treatment outcomes over time from patients' perspectives. In 2020, there were no published results from a centralized PRO data collection for a large sample of patients accessing prescribed medical cannabis within Australia that covers all approved health indications using a comprehensive battery of PROMs. Participants studied under controlled clinical trial environments have not always been representative of the entire spectrum of disease and health status seen in people currently accessing medicinal cannabis in practice [49]. Therefore, although clinical trials provide evidence of the efficacy of medicinal cannabis, the true gauge of how effective it is in practice comes from real-world evidence from patients across all health conditions receiving prescribed medicinal cannabis [49]. Real-world data are needed to develop a scientific evidence base to inform regulation and policy making [7].

A scoping review that we conducted identified the following limitations in the current evidence on PROs for medicinal cannabis:

1. Very few studies have collected PRO data longitudinally, including baseline, maintenance, and long-term use data [4].
2. A large proportion of cannabinoid research was focused on pharmacokinetic, animal, and preclinical studies.
3. Many cannabinoid clinical studies include case studies [4] or have small sample sizes [50].
4. Early studies did not use the currently recommended individualized dosing titration paradigm of starting low and gradually escalating to achieve optimal effects [50].
5. Formulations studied may not reflect current commercially available cannabinoid products [11].
6. Many PROMs used have limited validity in the health conditions assessed [12].
7. Very few clinical studies used comprehensive pain assessments.

Therefore, the real-world collection of a comprehensive suite of PROs in a large sample of people across all health conditions, as approved by the TGA, accessing current formulations of prescribed medicinal cannabis in Australia is needed to enable clinically relevant assessment and provide ongoing evidence for decision-making both in practice and at a policy level.

Objectives

The aim of this study is to evaluate PROs in patients who are prescribed medicinal cannabis by authorized prescribers and under the SAS across clinics within Australia. The findings from this study have the potential to be integral to treatment assessment and recommendations for chronic pain sufferers and other patients with health indicators for accessing medicinal cannabis.

Primary Objective

The primary objective of this study is to describe changes in the PROs (HRQL, pain, fatigue, sleep, anxiety, and depression) from baseline to 3 months for a large cohort receiving medicinal cannabis.

Secondary Objectives

The secondary objectives of this study are to describe changes in PROS (HRQL, pain, fatigue, sleep, anxiety, depression, and physical functioning) from baseline up to 12 months and to

describe differences between patients accessing medicinal cannabis with different chronic health conditions, including, but not limited to, chronic pain, MS, epilepsy, Parkinson disease, and cancer.

Exploratory Objectives

The exploratory objectives of this study are to explore (1) which individuals are more likely to have lower symptom burden and greater HRQL, (2) associations among PROs, with the hypothesis that a high symptom burden is associated with poorer HRQL, and (3) associations between PROs and resource and medication use over time, with the hypothesis that lower symptom burden is associated with reduced health care–resource use and reduced use of opioids and other prescribed medications for managing symptoms.

Hypotheses

The study includes 3 hypotheses: (1) PROs will improve from baseline to 3 months in patients accessing medicinal cannabis, (2) improvements in PROs at 3 months will be maintained over a 12-month period, and (3) no differences in PROs will be observed between patients being treated for different conditions (eg, chronic pain, MS, epilepsy, Parkinson disease, or cancer).

Methods

Overview of Project Research Design

This is a multicenter prospective longitudinal cohort study of patients newly prescribed with medicinal cannabis in Australia by authorized prescribers and under the SAS. The study is registered in the Australian New Zealand Clinical Trials Registry (ACTRN12621000063819).

Study Arrangements

To be eligible to participate in the study, participants must have already been identified as eligible to receive a medicinal cannabis product from an authorized prescriber or under the SAS category B pathway, with approval given by the Australian TGA. This means that a suitable health practitioner has seen and assessed their patient, adhering to relevant standards of good medical practice, and successfully applied to the TGA for access to the particular medicinal cannabis product for the patient. Little Green Pharma Ltd (LGP) is responsible for the manufacture and quality of the products following the TGA guidelines. The prescriber is responsible for the prescription of the product for the patient and seeking TGA approval either as an authorized prescriber or under the SAS-B scheme, including the patient's informed consent for the product.

The University of Sydney researchers are responsible for the design of the cohort study and the data collection and analysis, as outlined in this protocol.

LGP is responsible for arrangements for delivery of the product, any subsidization arrangements, and the arrangements entered into with the participating sites and the physicians at these sites.

The prescriber is responsible for identifying the patients suitable for the study and obtaining consent to email them an invitation to participate in the study.

Eligibility

The inclusion and exclusion criteria are provided in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Patient is an adult (aged ≥18 years).
- Patient has been identified as eligible to receive medicinal cannabis by a Therapeutic Goods Administration–approved authorized prescriber or through the Special Access Scheme (or equivalent in other countries and jurisdictions) and the physician has sought and obtained Therapeutic Goods Administration approval for the Little Green Pharma Ltd product for their patient.
- Patient is able to read and understand English.
- Patient is able to provide informed consent.
- Patient has not started any prescribed medicinal cannabis therapy in the last 4 weeks or started prescribed Little Green Pharma Ltd medicinal cannabis therapy within the last 2 days (we expect no therapeutic benefit within 2 days) and did not receive any prescribed medicinal cannabis therapy in the last 4 weeks.
- Patient has a life expectancy of >3 months.

Exclusion criteria

- Patient is unconscious or confused.
- Patient has cognitive impairment (eg, advanced Alzheimer disease).
- Patient is pregnant or breastfeeding.
- Patient is unable to read and write in English.
- Patient is denied access to medicinal cannabis under the relevant Special Access Scheme for their country of registration.

Sample Size

Sample Size Considerations

Our aim is to recruit a large, broad, and representative sample of medicinal cannabis users. Therefore, we will invite every eligible patient treated at each participating center during a 12-month recruitment period. This large real-world cohort will enable several important analyses exploring differences in PROs between disease groups commonly treated with medicinal cannabis, as discussed in the *Objectives* section.

Minimum Sample Required for Primary Objective (Change Over Time)

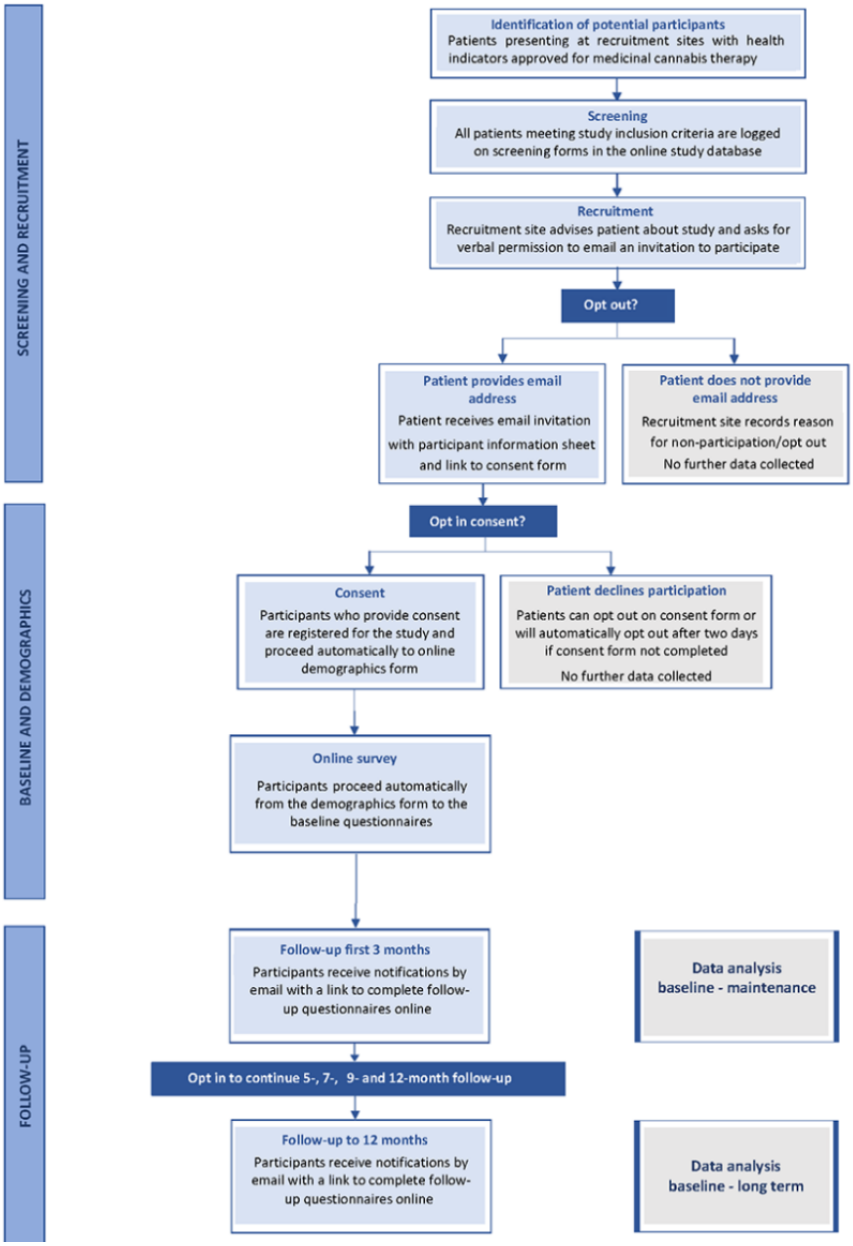
Following the guidelines [51] for the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-30 (EORTC QLQ-C30) [52] and allowing for a 20% loss to follow up, a baseline sample size of 2142 is required with a minimum follow-up of 3 months. This sample size provides 95% power to detect the smallest effect size threshold of 0.1 for the insomnia domain of the QLQ-C30, using a 2-tailed significance level of 1% [53].

Recruitment and Consent Procedures

Screening

Recruitment will take place between November 2020 and November 2021, with the aim of including all eligible patients receiving medicinal cannabis at participating sites during the recruitment period. Figure 1 provides an overview of the patient recruitment and data collection procedures.

Figure 1. Patient recruitment and data collection process.



LGP, following the World Health Organization Guidelines on Good Agricultural and Collection Practices for Medicinal Plants and European Union-Goods Manufacturing Practices standards, provides its medicinal cannabis products in Australia under the SAS. As part of this process, LGP engages with medical cannabis–focused clinics, authorized prescribers, and other

health care professionals prescribing LGP products and will be responsible for identifying recruitment sites for this study. Advertising and information relevant to the study will be disseminated via a dedicated study website and social media platforms. Content on the study website will inform potential participants and recruitment sites of the study objectives, terms, and conditions, including eligibility criteria, and who to contact for more information. Approved recruitment sites will receive study-specific training from the University of Sydney researchers regarding participant screening and recruitment.

Patients from participating centers who meet the eligibility criteria will be invited to participate in the study. Patients will be identified by physicians at recruitment sites and approached to participate by either the physician or site staff. A record of those identified as eligible and invited to participate will be logged in the web-based research database with the patient's verbal consent. Physicians at recruitment sites will use a generic link to access the study database to create a new record for each patient screened.

The physician or staff at recruitment sites will ask if the patient agrees to have the Participant Information Statement and invitation sent to them through email. Patients will be informed that the process involves recruitment site staff entering the information, as per the *Registration and Clinical Data* section, into the research database, which then sends an invitation to them automatically. Participants will be informed that email addresses are stored within the Research Electronic Data Capture (REDCap) system and used solely for sending reminders to complete questionnaires at scheduled time points. REDCap [54] is a secure web-based application developed by Vanderbilt University that runs on the servers of the University of Sydney, ensuring that the data stay within the Sydney University data center.

All patients who provide their email address to receive an invitation for the study will receive their medicinal cannabis product at a standardized cost. As medicinal cannabis is still an unregistered product, it has been difficult to control the cost of the product; consequently, there has been considerable variability in what people pay for the product. LGP has partnered with several pharmacies across Australia to ensure that all participants taking part in this study will be charged the same amount for their product, eliminating variability in out-of-pocket costs and enabling a health economic evaluation.

As soon as an email address is entered in the web-based database, the patient will receive an email invitation with a link to the web-based forms for their record. The email will include the Participant Information Statement (Multimedia Appendix 1) to be considered before giving consent on the web. The Participant Information Statement contains detailed information about the rationale, design, and personal implications of the study. Patients will then provide their consent to join the study by checking the consent box before being able to proceed to the data collection forms or they can opt out of study participation at this point. They have as much time as they need to consider their participation. The patient's right to refuse consent without giving reasons will be respected. If the patient does not respond to the invitation, 2 daily follow-up reminders will be sent via email, after which the system will automatically record the patient as having selected *opt out* without reason.

Participants will remain free to withdraw from the study at any time without giving reasons and without prejudicing any further treatment. Participants can withdraw responses from the study before the data have been analyzed; otherwise, they will be included.

Registration

When physicians at recruitment sites complete the web-based screening form, REDCap will automatically generate a number to be used as the participant's study ID number for study registration.

Data Collection and Assessment

Study data will be recorded by physicians at recruitment sites on case report forms and by participants in the questionnaire booklets. These will be completed on the web through the University of Sydney research data capture system, REDCap [54].

Screening and registration and clinical data will be completed by the physician at the recruitment sites. The REDCap database will collect information only identifiable by REDCap-assigned study record ID numbers. Physicians at recruitment sites will maintain a record of participants' study ID numbers for each screened and registered participant entered. Where required, data can be updated for individual participants by notifying the study project manager of the corresponding study ID numbers (eg, to record participant withdrawal). If 2 consecutive assessments are missed by participants, the study project manager will contact the physician at the recruitment site to determine the reasons for missed assessments, if known.

Registration and Clinical Data

The following patient screening details will be entered into the REDCap web-based registration form by physicians at recruitment sites: age, sex, country, email address, health indications for accessing medicinal cannabis, neuropathic pain screening using the short-form Douleur Neuropathique en 4 Questions [55,56] (if pain is selected as a health indication), duration of pain (if pain is recorded as a health indication), comorbidities, medicinal cannabis type and dosage, date and dose of any previously prescribed medicinal cannabis, recruitment physician ID, and reasons for declining study participation (if applicable).

Patient Consent and Demographics

Patients who provide email addresses will receive an email with a link to the patient consent and demographic form corresponding to their study record ID. Patient consent and demographic questions include the following: consent to participate (or opt out), reasons for declining study participation (if applicable), ethnicity and cultural background, education, living arrangements, marital status, height, weight, gender identity, work status, access to health services, any medication other than medicinal cannabis taken during the last 4 weeks for health indication, and previous history of cannabis use.

PROM Administration

Administration

Baseline PROMs will be presented to participants on the web automatically after completing the demographic questions. Participants self-complete the questionnaires through the web-based platform at home, accessible on a computer or other device with an internet connection, depending on their preference. All the questionnaires will be administered in the same order. It is anticipated that completion of baseline questionnaires may take up to 30 minutes. Follow-up questionnaires may take approximately 25 minutes. We have estimated the time to complete the questionnaires (including demographic questions) based on 10-12 seconds per item [57].

Patient-Reported Outcome Measures

All participants will complete the following PROMs.

Generic HRQL

Generic HRQL will be assessed in all participants using the EuroQol 5-Dimension questionnaire (EQ-5D-5L). The EQ-5D-5L is a standardized measure of health status developed by the EuroQol Group to provide a simple, generic measure of health for clinical and economic appraisals [58]. EQ-5D-5L is designed for self-completion by respondents and consists of 5 items covering the dimensions of mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Ratings for each item range from 1 (no problem) to 5 (extreme problem), with a recall period of *today*. In addition to the 5 items, there is a visual numeric scale of global health rated on a scale of 0-100. The questionnaire has validated language translations suitable for use in Australia.

To make the EQ-5D-5L suitable for use in economic evaluations, health states were valued using a preference-elicitation method in the general population. Australian national values have been collected and subsequently modeled and will be used for economic analysis [59].

All participants will receive the EORTC QLQ-C30 core quality of life cancer questionnaire [52], which includes core domains of functioning, cancer-specific symptoms, fatigue, and general pain. The QLQ-C30 core questionnaire was designed to be used by any patient participating in a cancer clinical trial; however, it has also been used to evaluate HRQL in other health conditions [60-64], as well as in large general population samples in Europe, the United States, and Australia [65]. It is a 30-item questionnaire with a recall period of 1 week and contains 9 multi-item subscales and 6 single items. It incorporates 5 functional scales (physical, role, cognitive, emotional, and social functioning), 3 symptom scales (fatigue, pain, and nausea or vomiting), and a global health status and HRQL scale. The single items assess dyspnea, appetite loss, sleep disturbance, constipation, diarrhea, and perceived financial impact of disease and treatment. The ratings for each item range from 1 (not at all) to 4 (very much). The QLQ-C30 also produces a summary score of HRQL based on 13 scales [66].

The QLQ-C30 can be used for economic evaluation through the QLU-C10D [67], a health state classification system derived from the QLQ-C30 for which Australian utility weights have been established [68].

Overall Change in Health Status

Patients' subjective rating of overall change in health status related to their primary health condition will be assessed using the Patients' Global Impression of Change [69]. The Patients' Global Impression of Change contains 1 item rated from 1 (very much improved) to 7 (very much worse). The recall period is *since beginning medicinal cannabis treatment*.

Anxiety and Depression

Anxiety, depression, and stress will be assessed in all participants with the validated 21-item short version of the Depression, Anxiety, and Stress Scale [70]. The Depression, Anxiety, and Stress Scale-21 includes 3 scales, each containing 7 items, assessing depression, anxiety, and stress. The depression scale assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest or involvement, anhedonia, and inertia. The anxiety scale assesses autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect. The stress scale assesses difficulty relaxing, nervous arousal, and being easily upset or agitated, irritable or overreactive, and impatient. Ratings for each item range from 0 (not at all) to 3 (very much or most of the time) with a recall period of 1 week [71].

Sleep and Fatigue

Sleep quality will be assessed in all participants using the Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form version 1.0: Sleep Disturbance 8b [72]. This measurement system is a universal, rather than disease-specific, 8 item assessment of sleep quality, sleep depth, and restoration associated with sleep. Items are rated from 1 (not at all) to 5 (very much so), with a recall period of 1 week.

Fatigue will be assessed in all participants using the PROMIS Fatigue 13a or the Functional Assessment of Chronic Illness Therapy Fatigue Scale [73]. The 13-item measure has been validated in the general population as well as in patients with cancer, anemia, and arthritis [74,75]. The scale consists of 2 domains: 5 items covering fatigue experience and 8 items assessing the impact of fatigue on daily activities. Ratings for each item range from 0 (not at all) to 4 (very much so), with a recall period of 1 week.

Conditional PROMs

The following questionnaires will only be administered to patients with identified conditions or health status.

Palliative Care

To reduce the burden on patients with a primary health indication of palliative care for advanced, symptomatic, incurable cancer with a life expectancy of a few months, they will receive the EORTC QLQ-C15-PAL instead of the QLQ-C30. It is a shorter, 15-item questionnaire that assesses the same outcomes as the QLQ-C30 questionnaire and is used extensively in the palliative care setting [76]. Palliative care participants will only complete the EQ-5D and QLQ-C15 questionnaires.

Pain

Participants with pain as a health indication in their baseline clinical data will complete additional pain-specific questionnaires (excluding those in palliative care):

Pain intensity will be assessed using the PROMIS Scale version 1.0: Pain Intensity 3a (PS-PI) [77]. The scale includes 3 items assessing pain intensity: 2 items cover pain at its worst, on average, over the last 1 week and 1 item about current pain. All items are rated from 1 (no pain) to 5 (very severe).

Pain interference will be assessed using the PROMIS Short Form version 1.0: Pain Interference 8a [78]. This measurement system contains 8 items measuring the degree to which pain interferes with physical, emotional, and social activities. Items are rated from 1 (not at all) to 5 (very much so), with a recall period of 1 week.

Motor Function

Participants with movement disorder, chorea, as a health indication will be assessed with the Quality of Life in Neurological Disorders Short Form version 2.0–Huntington's Disease health-related Quality of LIFE-Chorea 6a [79]. This 6-item scale producing 1 score was developed for patients with Huntington disease and is appropriate for patients experiencing irregular, random, involuntary movements of varying amplitude affecting the face, trunk, and limbs. The domains cover the impact of movement disorders on physical activity and participation, with each item rated from 1 (never or not at all) to 5 (always or very much), with a recall period of 1 week.

Participants with movement disorders affecting the upper body as a health indication will be assessed using the Quality of Life in Neurological Disorders version 1.0: Upper Extremity Function (Fine Motor and Activities of Daily Living) Short Form [80]. This 8-item scale assesses the ability to perform various activities involving digital, manual, and reach-related functions, ranging from fine motor to self-care (activities of daily living) for patients with stroke, MS, amyotrophic lateral sclerosis, Parkinson disease, epilepsy, and muscular dystrophy. Items are rated from 1 (unable to do) to 5 (without any difficulty) and emphasize current capabilities; therefore, they do not use a recall period.

Work Status

For participants who indicate that they are working or would normally be working (ie, not retired or only studying), the impact of health on work performance will be assessed using the absenteeism and presenteeism questions of the World Health Organization's Health and Work Performance Questionnaire [81]. The questionnaire contains 2 items covering absenteeism in the last 1 week and 2 items covering absenteeism in the last 4 weeks, rated in number of days. Presenteeism is covered by 3 items rated from 0 (worst performance) to 10 (top performance).

Follow-Up Data Collection

Participants will receive automatic reminders from the REDCap system to their email addresses at scheduled follow-up assessment time points (Table 1). Follow-up questionnaires can be completed using computers or mobile devices depending on their preference. Up to 2 email reminders to complete the follow-up questionnaires will be sent within the assessment time windows (Table 1). The following questions will be added to the front page of the follow-up questionnaires: current cannabis product and dose, any reduction in other medications taken for health indication because of using medicinal cannabis (including brand, strength, and dose), and work status.

Table 1. Patient-reported outcome assessment schedule.

PRO[a] measure	Baseline	Titration[b]	1-month follow-up	2-month follow-up	3-month follow-up	5-month follow-up	7-month follow-up	9-month follow-up	12-month follow-up
		14-21 days after T0	4 weeks (and 3 days) after T1	8 weeks (and 7 days) after T1	13 weeks (and 7 days) after T1	21 weeks (and 7 days) after T1	30 weeks (and 7 days) after T1	39 weeks (and 7 days) after T1	52 weeks (and 14 days) after T1
	T0	T1	T2	T3	T4	T5	T6	T7	T8
EQ-5D[c] questionnaire for measuring generic health status	✓	✓	✓	✓	✓	✓	✓	✓	✓
QLQ-C30[d]	✓	✓	✓	✓	✓	✓	✓	✓	✓
Depression, Anxiety, and Stress Scale-21	✓	✓	✓	✓	✓	✓	✓	✓	✓
PROMIS[e] Short Form for Sleep Disturbance	✓	✓	✓	✓	✓	✓	✓	✓	✓
PROMIS Short Form for Fatigue-Fat	✓	✓	✓	✓	✓	✓	✓	✓	✓
Patients' Global Impression of Change		✓	✓	✓	✓	✓	✓	✓	✓
World Health Organization Health and Work Performance Questionnaire: Absenteeism and Presenteeism questions	✓		✓		✓		✓		✓
PROMIS Scale for Pain Intensity[f]	✓	✓	✓	✓	✓	✓	✓	✓	✓
PROMIS Short Form for Pain Interference[f]	✓	✓	✓	✓	✓	✓	✓	✓	✓
Neuro-QoL[g] Short Form for chorea[h]	✓	✓	✓	✓	✓	✓	✓	✓	✓
Neuro-QoL Upper Extremity Function Short Form[h]	✓	✓	✓	✓	✓	✓	✓	✓	✓
15-item version of QLQ-C30 for Palliative Care patients receiving palliative care[i]	✓	✓	✓	✓	✓				

[a]PRO: patient-reported outcome.

[b]The titration period is of approximately 2 weeks. As the EQ-5D assesses the current state (today), whereas the other patient-reported outcome questionnaires have a recall period of the past week, the time period is within 2-3 weeks to capture the end of titration across the questionnaires.

[c]EQ-5D: EuroQol 5-Dimension.

[d]QLQ-C30: Quality of Life Questionnaire, 30 items.

[e]PROMIS: Patient-Reported Outcomes Measurement Information System.

[f]Pain questionnaires will be only administered to participants with a health indication of pain.

[g]Neuro-QoL: Quality of Life in Neurological Disorders.

[h]Impact on Motor Function Questionnaire will be only administered to patients with a health indication of movement disorder.

[i]Participants in palliative care with life expectancy of a few months will only complete the EuroQol 5-Dimension and Quality of Life Questionnaire, 15 items.

PRO Assessment Time Points

Prospective assessment of newly prescribed patients before and after treatment is required to assess changes in PROs over time. PROs will be completed at baseline before starting medicinal cannabis, at 2-3 weeks after starting medicinal cannabis (end of titration period), and then at 1, 2, 3, 5, 7, 9, and 12 months after the titration period.

The acceptable PRO assessment time windows are indicated in Table 1.

Analyses and Statistical Considerations

Analysis Set

All analyses will be performed using SPSS software (version 26.0; IBM Corp). Baseline demographic and clinical data will be summarized descriptively for all patients registered for the study. Categorical data will be presented as frequencies and percentages. For continuous scale data, mean, SD, median, 25th and 75th percentiles, and minimum and maximum scores will be presented.

PRO analyses will explore changes over time using mixed linear models. Subgroup analyses will compare differences in PROs between underlying conditions, dose, and duration of pain and over time using linear mixed models.

Statistical Considerations

A comprehensive PRO-specific statistical analysis plan will be produced by the study statistician. The key considerations include the following:

1. PRO questionnaire responses will be scored into PRO scales for outcome analysis according to standard scoring algorithms provided by the questionnaire developers and custodians.
2. Rates and reasons for missed PRO assessments will be summarized to assess likely missing data mechanisms against missing data assumptions of statistical modeling.
3. For each PRO, all participants with a score for that PRO at baseline and at least one time point after starting medicinal cannabis will be analyzed.
4. Linear mixed models will be used to compare groups in their PRO scores, adjusted for their PRO levels at baseline and with additional covariates such as duration of pain, previous cannabis use, use of other medications, and overall and prespecified subgroups.
5. If the scores are highly skewed, a suitable transformation will be sought to achieve normality.
6. As there are several PRO scales and time points and correlation among them is anticipated, statistical significance levels will be adjusted using an appropriate method [82].
7. The clinical significance of differences in the PRO questionnaires will be interpreted using existing guidelines (eg, QLQ-C30) [83], maintaining the overall type 1 error at 5% or less.

Missing items within the PRO questionnaires are not expected. This is because of the web-based administration platform alerting participants of missed items and the requirement to complete those items before progressing to the next page. Only those participants who complete at least 2 questionnaires (baseline and one other) will be included in the analysis. Single missed assessments will be imputed using the last value carried forward technique, that is, no change from that individual's last assessment. Pattern mixture models will be used to impute scores for missed assessments based on recorded reasons [84].

Economic Evaluation

The economic evaluation will use collected data around pharmaceutical and other medical costs to explore the drivers of patient-level costs. As this study is not a comparative randomized trial, we are not proposing to conduct a formal economic evaluation, resulting in a cost per quality-adjusted life year. We will instead use baseline resource use as an indicator of typical care and contrast resource use throughout the study with baseline data. We will explore the relationship between HRQL and resource use across the cohort, which is potentially important information for future economic evaluation of medicinal cannabis.

Results

Participant recruitment in Australia commenced on November 27, 2020. By June 4, 2021, 1095 patients were screened for the study by 69 physicians in centers across 6 Australian states: Australian Capital Territory, New South Wales, Queensland, South Australia, Victoria, and Western Australia. Of the 1095 patients screened, 833 (76.07%) participants provided consent, completed baseline questionnaires, and remained on the study. Baseline recruitment is expected to end in March 2022 when the target sample size of participants has completed the baseline questionnaires and a 3-month follow-up. The final results for the primary objective are expected to be published in 2022.

Discussion

Principal Findings

The results of this study will show whether PROs improve in patients accessing prescribed medicinal cannabis from baseline to 3 months and whether any changes are maintained over a 12-month period. This study will also identify whether there are differences in improvements in PROs among patients being treated for different conditions (eg, chronic pain, MS, epilepsy, Parkinson disease, or cancer).

Conclusions

The findings from this study have the potential to be integral to treatment assessment and recommendations for chronic pain sufferers and other patients with health indicators for accessing medicinal cannabis.

Acknowledgments

The authors thank Little Green Pharma Ltd (LGP) for standardizing the cost of their medicinal cannabis formulations to Aus $150 (US $112.26) per unit (bottle) for study participants and funding direct research costs to conduct this study. The authors thank Dr Leon Warne at LGP for providing technical advice on LGP medicinal cannabis products. The authors thank all the study participants and the physicians who identified patients eligible to receive a study invitation.

Authors' Contributions

MT wrote the manuscript and managed data collection. All authors provided critical feedback on study design and reviewed the final manuscript.

Conflicts of Interest

The University of Sydney received funding from Little Green Pharma Ltd to support CR and MT to conduct this study.

Multimedia Appendix 1
QUEST participant information statement.
[PDF File (Adobe PDF File), 279 KB - resprot_v10i11e32327_app1.pdf]

References

1. Robson P. Human studies of cannabinoids and medicinal cannabis. In: Pertwee RG, editor. Cannabinoids - Handbook of Experimental Pharmacology. Berlin, Heidelburg: Springer; 2005:719-756.
2. Gautam CS, Pandey A, Tahlan A, Gautam SS. Opioid use in palliative care/chronic pain: ethical and legal perspectives in India. Biomedicine (India). 2017. URL: https://www.researchgate.net/publication/319456746_Opioid_use_in_palliative_carechronic_pain_Ethical_legal_perspectives_in_India [accessed 2020-04-29]
3. Haroutounian S, Ratz Y, Ginosar Y, Furmanov K, Saifi F, Meidan R, et al. The effect of medicinal cannabis on pain and quality-of-life outcomes in chronic pain: a prospective open-label study. Clin J Pain 2016 Dec;32(12):1036-1043. [doi: 10.1097/AJP.0000000000000364] [Medline: 26889611]
4. Zhang MW, Ho RC. The cannabis dilemma: a review of its associated risks and clinical efficacy. J Addict 2015;2015:707596 [FREE Full text] [doi: 10.1155/2015/707596] [Medline: 26539302]
5. Rong C, Carmona NE, Lee YL, Ragguett R, Pan Z, Rosenblat JD, et al. Drug-drug interactions as a result of co-administering Δ-THC and CBD with other psychotropic agents. Expert Opin Drug Saf 2018 Jan;17(1):51-54. [doi: 10.1080/14740338.2017.1397128] [Medline: 29082802]
6. Medical client registrations and applications. Government of Canada. 2019. URL: https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/research-data/medical-purpose.html#a1 [accessed 2021-05-11]
7. Schlag A. An evaluation of regulatory regimes of medical cannabis: what lessons can be learned for the UK? Med Cannabis Cannabinoids 2020 Jan 15;3(1):76-83. [doi: 10.1159/000505028]
8. Access to medicinal cannabis products. Therapeutic Goods Administration, Australian Government. 2020. URL: https://www.tga.gov.au/access-medicinal-cannabis-products-1 [accessed 2021-05-11]
9. Petzke F, Enax-Krumova E, Häuser W. [Efficacy, tolerability and safety of cannabinoids for chronic neuropathic pain: a systematic review of randomized controlled studies]. Schmerz 2016 Feb;30(1):62-88. [doi: 10.1007/s00482-015-0089-y] [Medline: 26830780]
10. Arboleda MF, Dam V, Prosk E, Dworkind M, Vigano A. Abstracts of the MASCC/ISOO Annual Meeting 2018. Support Care Cancer 2018 Apr 23:39-364 S108 [FREE Full text] [doi: 10.1007/s00520-018-4193-2] [Medline: 29682691]
11. Nugent SM, Morasco BJ, O'Neil ME, Freeman M, Low A, Kondo K, et al. The effects of cannabis among adults with chronic pain and an overview of general harms. Ann Intern Med 2017 Aug 15;167(5):319. [doi: 10.7326/m17-0155]
12. Bruce D, Foster E, Shattell M. Perceived efficacy of medical cannabis in the treatment of co-occurring health-related quality of life symptoms. Behav Med 2021 Nov 06;47(2):170-174. [doi: 10.1080/08964289.2019.1683712] [Medline: 31693457]
13. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. J Pain 2013 Feb;14(2):136-148 [FREE Full text] [doi: 10.1016/j.jpain.2012.10.009] [Medline: 23237736]
14. Johnson JR, Lossignol D, Burnell-Nugent M, Fallon MT. An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. J Pain Symptom Manage 2013 Aug;46(2):207-218 [FREE Full text] [doi: 10.1016/j.jpainsymman.2012.07.014] [Medline: 23141881]
15. Badowski ME. A review of oral cannabinoids and medical marijuana for the treatment of chemotherapy-induced nausea and vomiting: a focus on pharmacokinetic variability and pharmacodynamics. Cancer Chemother Pharmacol 2017 Sep;80(3):441-449 [FREE Full text] [doi: 10.1007/s00280-017-3387-5] [Medline: 28780725]
16. Collin C, Davies P, Mutiboko IK, Ratcliffe S, Sativex Spasticity in MS Study Group. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. Eur J Neurol 2007 Mar;14(3):290-296. [doi: 10.1111/j.1468-1331.2006.01639.x] [Medline: 17355549]
17. Zettl UK, Rommer P, Hipp P, Patejdl R. Evidence for the efficacy and effectiveness of THC-CBD oromucosal spray in symptom management of patients with spasticity due to multiple sclerosis. Ther Adv Neurol Disord 2016 Jan 06;9(1):9-30 [FREE Full text] [doi: 10.1177/1756285615612659] [Medline: 26788128]
18. Sulak D, Saneto R, Goldstein B. The current status of artisanal cannabis for the treatment of epilepsy in the United States. Epilepsy Behav 2017 May;70(Pt B):328-333. [doi: 10.1016/j.yebeh.2016.12.032] [Medline: 28254350]

19. Lee K, MacDiarmid P, Shalansky S, Wilcox P. The use of self-administered medicinal cannabis for cystic fibrosis symptom management: patient-reported experiences. Pediatr Pulmonol 2012:214 [FREE Full text]
20. Reiman A, Welty M, Solomon P. Cannabis as a substitute for opioid-based pain medication: patient self-report. Cannabis Cannabinoid Res 2017;2(1):160-166. [doi: 10.1089/can.2017.0012] [Medline: 28861516]
21. Rong C, Lee Y, Carmona NE, Cha DS, Ragguett R, Rosenblat JD, et al. Cannabidiol in medical marijuana: research vistas and potential opportunities. Pharmacol Res 2017 Jul;121:213-218. [doi: 10.1016/j.phrs.2017.05.005] [Medline: 28501518]
22. Patient-reported outcome measures: use in medical product development to support labeling claims - guidance for industry. US Department of Health & Human Support Food & Drug Administration. 2009. URL: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims [accessed 2020-06-30]
23. Dansie EJ, Turk DC. Assessment of patients with chronic pain. Br J Anaesth 2013 Jul;111(1):19-25 [FREE Full text] [doi: 10.1093/bja/aet124] [Medline: 23794641]
24. Lipscomb J, Gotay CC, Snyder CF. Patient-reported outcomes in cancer: a review of recent research and policy initiatives. CA Cancer J Clin 2007;57(5):278-300 [FREE Full text] [doi: 10.3322/CA.57.5.278] [Medline: 17855485]
25. About PROMs. Australian Commission on Safety and Quality in Health Care (ACSQHC), Sydney. 2019. URL: https://www.safetyandquality.gov.au/our-work/indicators-measurement-and-reporting/patient-reported-outcomes/about-proms [accessed 2021-10-19]
26. Patrick DL, Burke LB, Powers JH, Scott JA, Rock EP, Dawisha S, et al. Patient-reported outcomes to support medical product labeling claims: FDA perspective. Value Health 2007 Nov;10 Suppl 2:125-137 [FREE Full text] [doi: 10.1111/j.1524-4733.2007.00275.x] [Medline: 17995471]
27. Treede R, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. A classification of chronic pain for ICD-11. Pain 2015 Jun;156(6):1003-1007 [FREE Full text] [doi: 10.1097/j.pain.0000000000000160] [Medline: 25844555]
28. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain 2019 Jan;160(1):19-27. [doi: 10.1097/j.pain.0000000000001384] [Medline: 30586067]
29. Miller A, Sanderson K, Bruno R, Breslin M, Neil AL. The prevalence of pain and analgesia use in the Australian population: findings from the 2011 to 2012 Australian National Health Survey. Pharmacoepidemiol Drug Saf 2017 Nov 12;26(11):1403-1410. [doi: 10.1002/pds.4301] [Medline: 28895247]
30. Todd A, Akhter N, Cairns J, Kasim A, Walton N, Ellison A, et al. The Pain Divide: a cross-sectional analysis of chronic pain prevalence, pain intensity and opioid utilisation in England. BMJ Open 2018 Sep 11;8(7):e023391 [FREE Full text] [doi: 10.1136/bmjopen-2018-023391] [Medline: 30206064]
31. Dahlhamer J, Lucas J, Zelaya C, Nahin R, Mackey S, DeBar L, et al. Prevalence of chronic pain and high-impact chronic pain among adults - United States, 2016. MMWR Morb Mortal Wkly Rep 2018 Sep 14;67(36):1001-1006 [FREE Full text] [doi: 10.15585/mmwr.mm6736a2] [Medline: 30212442]
32. Gordin V, Weaver MA, Hahn MB. Acute and chronic pain management in palliative care. Best Pract Res Clin Obstet Gynaecol 2001 Apr 20;15(2):203-234. [doi: 10.1053/beog.2001.0164] [Medline: 11358398]
33. Levy M, Chwistek M, Mehta R. Management of chronic pain in cancer survivors. Cancer J 2008;14(6):401-409. [doi: 10.1097/PPO.0b013e31818f5aa7] [Medline: 19060605]
34. Jensen TS, Baron R, Haanpää M, Kalso E, Loeser JD, Rice AS, et al. A new definition of neuropathic pain. Pain 2011 Oct;152(10):2204-2205. [doi: 10.1016/j.pain.2011.06.017] [Medline: 21764514]
35. Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. J Pain 2006 Apr;7(4):281-289. [doi: 10.1016/j.jpain.2005.11.008] [Medline: 16618472]
36. Urits I, Adamian L, Fiocchi J, Hoyt D, Ernst C, Kaye AD, et al. Advances in the understanding and management of chronic pain in multiple sclerosis: a comprehensive review. Curr Pain Headache Rep 2019 Jul 25;23(8):59. [doi: 10.1007/s11916-019-0800-2] [Medline: 31342191]
37. Attal N, Lanteri-Minet M, Laurent B, Fermanian J, Bouhassira D. The specific disease burden of neuropathic pain: results of a French nationwide survey. Pain 2011 Dec;152(12):2836-2843. [doi: 10.1016/j.pain.2011.09.014] [Medline: 22019149]
38. Burgess G, Williams D. The discovery and development of analgesics: new mechanisms, new modalities. J Clin Invest 2010 Nov;120(11):3753-3759 [FREE Full text] [doi: 10.1172/JCI43195] [Medline: 21041957]
39. Gilron I, Dickenson AH. Emerging drugs for neuropathic pain. Expert Opin Emerg Drugs 2014 Sep 03;19(3):329-341. [doi: 10.1517/14728214.2014.915025] [Medline: 24793304]
40. Childers JW, King LA, Arnold RM. Chronic pain and risk factors for opioid misuse in a palliative care clinic. Am J Hosp Palliat Care 2015 Sep 16;32(6):654-659. [doi: 10.1177/1049909114531445] [Medline: 24744398]
41. Maltoni B, Forti P, Zoli M, Maltoni M, Ricci M. Prevalence of chronic cancer and no-cancer pain in elderly hospitalized patients: elements for the early assessment of palliative care needs. Int J Gerontol 2018 Sep;12(3):180-185. [doi: 10.1016/j.ijge.2017.11.005]
42. Ninashvili N, Shavdia M. Chronic pain management in palliative patients. J Glob Oncol 2018 Oct 01;4(Supplement 2):86. [doi: 10.1200/jgo.18.72000]

43. Yamada K, Kubota Y, Shimizu Y, Shibata M, Morotomi N. Association of sleep sufficiency and duration with chronic pain prevalence: a population-based cross-sectional study. J Psychosom Res 2019 May;120:74-80. [doi: 10.1016/j.jpsychores.2019.03.005] [Medline: 30929711]
44. Compston A, Coles A. Multiple sclerosis. Lancet 2008 Oct;372(9648):1502-1517 [FREE Full text] [doi: 10.1016/s0140-6736(08)61620-7]
45. Ahmad H, Taylor BV, van der Mei I, Colman S, O'Leary BA, Breslin M, et al. The impact of multiple sclerosis severity on health state utility values: evidence from Australia. Mult Scler 2016 Oct 03;23(8):1157-1166 [FREE Full text] [doi: 10.1177/1352458516672014] [Medline: 34418738]
46. Nielsen S, Germanos R, Weier M, Pollard J, Degenhardt L, Hall W, et al. The use of cannabis and cannabinoids in treating symptoms of multiple sclerosis: a systematic review of reviews. Curr Neurol Neurosci Rep 2018 Feb 13;18(2):8. [doi: 10.1007/s11910-018-0814-x] [Medline: 29442178]
47. Epilepsy. World Health Organization. 2019. URL: https://www.who.int/en/news-room/fact-sheets/detail/epilepsy [accessed 2021-11-08]
48. Morano A, Fanella M, Albini M, Cifelli P, Palma E, Giallonardo AT, et al. Cannabinoids in the treatment of epilepsy: current status and future prospects. Neuropsychiatric Dis Treat 2020 Feb;Volume 16:381-396. [doi: 10.2147/ndt.s203782]
49. Monti S, Grosso V, Todoerti M, Caporali R. Randomized controlled trials and real-world data: differences and similarities to untangle literature data. Rheumatology (Oxford) 2018 Oct 01;57(57 Suppl 7):vii54-vvii8. [doi: 10.1093/rheumatology/key109] [Medline: 30289534]
50. Rahn EJ, Hohmann AG. Cannabinoids as pharmacotherapies for neuropathic pain: from the bench to the bedside. Neurotherapeutics 2009 Oct;6(4):713-737 [FREE Full text] [doi: 10.1016/j.nurt.2009.08.002] [Medline: 19789075]
51. Cocks K, King MT, Velikova G, Martyn SM, Fayers PM, Brown JM. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. J Clin Oncol 2011 Jan 1;29(1):89-96. [doi: 10.1200/JCO.2010.28.0107] [Medline: 21098316]
52. Aaronson N, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez N. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-376. [doi: 10.1037/t01822-000]
53. Fayers P, Machin D. Sample sizes. In: Fayers P, Machin D, editors. Quality of Life: Assessment, Analysis and Interpretation. Hoboken, New Jersey, United States: John Wiley & Sons Ltd; 2016:283-307.
54. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 Apr;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
55. Spallone V, Morganti R, D'Amato C, Greco C, Cacciotti L, Marfia G. Validation of DN4 as a screening tool for neuropathic pain in painful diabetic polyneuropathy. Diabet Med 2012 May;29(5):578-585 [FREE Full text] [doi: 10.1111/j.1464-5491.2011.03500.x] [Medline: 22023377]
56. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005 Mar;114(1-2):29-36. [doi: 10.1016/j.pain.2004.12.010] [Medline: 15733628]
57. Stockler MR, Heritier S, Nowak AK, Goldstein D, Turner J, Jefford M, et al. The time taken to complete quality of life questionnaires in an advanced cancer trial. J Clin Oncol 2006 Jun 20;24(18_suppl):8592. [doi: 10.1200/jco.2006.24.18_suppl.8592]
58. EuroQoL Group. EuroQol - a new facility for the measurement of health-related quality of life. Health Policy 1990 Dec;16(3):199-208. [doi: 10.1016/0168-8510(90)90421-9]
59. Norman R, Cronin P, Viney R. Deriving utility weights for the EQ-5D-5L using a discrete choice experiment. CHERE Working Paper 2012/01. Working Papers 2012/01, CHERE, University of Technology, Sydney. 2012. URL: https://ideas.repec.org/p/her/chewps/2012-01.html [accessed 2020-05-14]
60. Ueda Y, Obara N, Yonemura Y, Noji H, Masuko M, Seki Y, et al. Effects of eculizumab treatment on quality of life in patients with paroxysmal nocturnal hemoglobinuria in Japan. Int J Hematol 2018 Jun;107(6):656-665. [doi: 10.1007/s12185-018-2409-3] [Medline: 29383624]
61. Stellingwerf ME, Sahami S, Winter DC, Martin ST, D'Haens GR, Cullen G, et al. Prospective cohort study of appendicectomy for treatment of therapy-refractory ulcerative colitis. Br J Surg 2019 Nov;106(12):1697-1704. [doi: 10.1002/bjs.11259] [Medline: 31393608]
62. Robinson SM, Rasch S, Beer S, Valantiene I, Mickevicius A, Schlaipfer E, et al. Systemic inflammation contributes to impairment of quality of life in chronic pancreatitis. Sci Rep 2019 May 13;9(1):7318 [FREE Full text] [doi: 10.1038/s41598-019-43846-8] [Medline: 31086257]
63. Proust F, Bracard S, Thines L, Pelissou-Guyotat I, Leclerc X, Penchet G, FASHE investigators. Functional outcome 1 year after aneurysmal subarachnoid hemorrhage due to ruptured intracranial aneurysm in elderly patients. Neurochirurgie 2020 Feb;66(1):1-8. [doi: 10.1016/j.neuchi.2019.11.002] [Medline: 31863744]
64. Friedrich M, Karoff J, Hinz A. Response shift effects in patients' assessments of their quality of life after cardiac rehabilitation. Qual Life Res 2019 Sep;28(9):2609-2620. [doi: 10.1007/s11136-019-02195-9] [Medline: 31069601]

65. Mercieca-Bebber R, Costa DS, Norman R, Janda M, Smith DP, Grimison P, et al. The EORTC Quality of Life Questionnaire for cancer patients (QLQ-C30): Australian general population reference values. Med J Aust 2019 Jun;210(11):499-506. [doi: 10.5694/mja2.50207] [Medline: 31155722]
66. Giesinger JM, Kieffer JM, Fayers PM, Groenvold M, Petersen MA, Scott NW, et al. Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. J Clin Epidemiol 2016 Jan;69:79-88 [FREE Full text] [doi: 10.1016/j.jclinepi.2015.08.007] [Medline: 26327487]
67. King MT, Costa DSJ, Aaronson NK, Brazier JE, Cella DF, Fayers PM, et al. QLU-C10D: a health state classification system for a multi-attribute utility measure based on the EORTC QLQ-C30. Qual Life Res 2016 Mar;25(3):625-636. [doi: 10.1007/s11136-015-1217-y] [Medline: 26790428]
68. King MT, Viney R, Pickard AS, Rowen D, Aaronson NK, Brazier JE, MAUCa Consortium. Australian utility weights for the EORTC QLU-C10D, a multi-attribute utility instrument derived from the cancer-specific Quality of Life Questionnaire, EORTC QLQ-C30. Pharmacoeconomics 2018 Feb;36(2):225-238 [FREE Full text] [doi: 10.1007/s40273-017-0582-5] [Medline: 29270835]
69. Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manipulative Physiol Ther 2004 Jan;27(1):26-35. [doi: 10.1016/j.jmpt.2003.11.003] [Medline: 14739871]
70. Ng F, Trauer T, Dodd S, Callaly T, Campbell S, Berk M. The validity of the 21-item version of the Depression Anxiety Stress Scales as a routine clinical outcome measure. Acta Neuropsychiatr 2007 Oct 24;19(5):304-310. [doi: 10.1111/j.1601-5215.2007.00217.x] [Medline: 26952943]
71. Lovibond S, Lovibond P. Manual for the Depression Anxiety Stress Scales. 2nd Ed. Sydney: Psychology Foundation; 1995.
72. Yu L, Buysse DJ, Germain A, Moul DE, Stover A, Dodds NE, et al. Development of short forms from the PROMIS™ sleep disturbance and sleep-related impairment item banks. Behav Sleep Med 2011 Dec 28;10(1):6-24 [FREE Full text] [doi: 10.1080/15402002.2012.636266] [Medline: 22250775]
73. Cella D, Lai J, Stone A. Self-reported fatigue: one dimension or more? Lessons from the Functional Assessment of Chronic Illness Therapy--Fatigue (FACIT-F) questionnaire. Support Care Cancer 2011 Sep 13;19(9):1441-1450. [doi: 10.1007/s00520-010-0971-1] [Medline: 20706850]
74. Acaster S, Dickerhoof R, DeBusk K, Bernard K, Strauss W, Allen LF. Qualitative and quantitative validation of the FACIT-fatigue scale in iron deficiency anemia. Health Qual Life Outcomes 2015 May 17;13:60 [FREE Full text] [doi: 10.1186/s12955-015-0257-x] [Medline: 25980742]
75. Chandran V, Bhella S, Schentag C, Gladman DD. Functional assessment of chronic illness therapy-fatigue scale is valid in patients with psoriatic arthritis. Ann Rheum Dis 2007 Jul;66(7):936-939 [FREE Full text] [doi: 10.1136/ard.2006.065763] [Medline: 17324972]
76. Groenvold M, Petersen MA, Aaronson NK, Arraras JI, Blazeby JM, Bottomley A, EORTC Quality of Life Group. The development of the EORTC QLQ-C15-PAL: a shortened questionnaire for cancer patients in palliative care. Eur J Cancer 2006 Jan;42(1):55-64. [doi: 10.1016/j.ejca.2005.06.022] [Medline: 16162404]
77. Cella D, Yount S, Rothrock N, Gershon R, Cook K, Reeve B, PROMIS Cooperative Group. The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH Roadmap cooperative group during its first two years. Med Care 2007 May;45(5 Suppl 1):3-11 [FREE Full text] [doi: 10.1097/01.mlr.0000258615.42478.55] [Medline: 17443116]
78. Chen CX, Kroenke K, Stump T, Kean J, Krebs EE, Bair MJ, et al. Comparative responsiveness of the PROMIS pain interference short forms with legacy pain measures: results from three randomized clinical trials. J Pain 2019 Jun;20(6):664-675 [FREE Full text] [doi: 10.1016/j.jpain.2018.11.010] [Medline: 30529442]
79. Carlozzi NE, Schilling SG, Lai J, Paulsen JS, Hahn EA, Perlmutter JS, et al. HDQLIFE: development and assessment of health-related quality of life in Huntington disease (HD). Qual Life Res 2016 Oct;25(10):2441-2455 [FREE Full text] [doi: 10.1007/s11136-016-1386-3] [Medline: 27522213]
80. Cella D, Lai J, Nowinski CJ, Victorson D, Peterman A, Miller D, et al. Neuro-QOL: brief measures of health-related quality of life for clinical research in neurology. Neurology 2012 Jun 05;78(23):1860-1867 [FREE Full text] [doi: 10.1212/WNL.0b013e318258f744] [Medline: 22573626]
81. Kessler RC, Barber C, Beck A, Berglund P, Cleary PD, McKenas D, et al. The World Health Organization Health and Work Performance Questionnaire (HPQ). J Occup Environ Med 2003 Feb;45(2):156-174. [doi: 10.1097/01.jom.0000052967.43131.51] [Medline: 12625231]
82. Blakesley RE, Mazumdar S, Dew MA, Houck PR, Tang G, Reynolds CF, et al. Comparisons of methods for multiple hypothesis testing in neuropsychological research. Neuropsychology 2009 Mar;23(2):255-264 [FREE Full text] [doi: 10.1037/a0012850] [Medline: 19254098]
83. Cocks K, King MT, Velikova G, de Castro G, Martyn St-James M, Fayers PM, et al. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. Eur J Cancer 2012 Jul;48(11):1713-1721. [doi: 10.1016/j.ejca.2012.02.059] [Medline: 22418017]
84. Fayers P, Machin D. Missing data. In: Fayers P, Machin D, editors. Quality of Life: Assessment, Analysis and Interpretation. Third Ed. Hoboken, New Jersey, United States: John Wiley & Sons Ltd; 2016:393-427.

Abbreviations

EORTC: European Organization for the Research and Treatment of Cancer
EQ-5D: EuroQol 5-Dimension
HRQL: health-related quality of life
LGP: Little Green Pharma Ltd
MS: multiple sclerosis
Neuro-QoL: Quality of Life in Neurological Disorders
PRO: patient-reported outcome
PROM: patient-reported outcome measure
PROMIS: Patient-Reported Outcomes Measurement Information System
QLQ-C15: Quality of Life Questionnaire, 15 items
QLQ-C30: Quality of Life Questionnaire, 30 items
REDCap: Research Electronic Data Capture
SAS: Special Access Scheme
TGA: Therapeutic Goods Administration

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Protocol

Assessing Values and Preferences Toward SARS-CoV-2 Self-testing Among the General Population and Their Representatives, Health Care Personnel, and Decision-Makers: Protocol for a Multicountry Mixed Methods Study

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Abstract

Background: Accessible, safe, and client-centered SARS-CoV-2 testing services are an effective way to halt its transmission. Testing enables infected individuals to isolate or quarantine to prevent further transmission. In countries with limited health systems and laboratory capacity, it can be challenging to provide accessible and safe screening for COVID-19. Self-testing provides a convenient, private, and safe testing option; however, it also raises important concerns about lack of counseling and ensuring timely reporting of self-test results to national surveillance systems. Investigating community members' views and perceptions regarding SARS-CoV-2 self-testing is crucial to inform the most effective and safe strategies for implementing said testing.

Objective: We aimed to determine whether SARS-CoV-2 self-testing was useful to diagnose and prevent the spread of SARS-CoV-2 for populations in low-resource settings and under which circumstances it would be acceptable.

Methods: This multisite, mixed methods, observational study will be conducted in 9 countries—Brazil, India, Indonesia, Kenya, Malawi, Nigeria, Peru, the Philippines, and South Africa—and will consists of 2 components: cross-sectional surveys and interviews (semistructured and group) among 4 respondent groupings: the general population, general population representatives, health care workers, and decision-makers. General population and health care worker survey responses will be analyzed separately from each other, using bivariate and multivariate inferential analysis and descriptive statistics. Semistructured interviews and group interviews will be audiorecorded, transcribed, and coded for thematic comparative analysis.

Results: As of November 19, 2021, participant enrollment is ongoing; 4364 participants have been enrolled in the general population survey, and 2233 participants have been enrolled in the health care workers survey. In the qualitative inquiry, 298 participants have been enrolled. We plan to complete data collection by December 31, 2021 and publish results in 2022 via publications, presentations at conferences, and dissemination events specifically targeted at local decision-makers, civil society, and patient groups.

Conclusions: The views and perceptions of local populations are crucial in the discussion of the safest strategies for implementing SARS-CoV-2 self-testing. We intend to identify sociocultural specificities that may hinder or accelerate the widespread utilization of SARS-CoV-2 self-testing.

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KEYWORDS

COVID-19; SARS-CoV-2; diagnostic; self-testing; mixed methods; testing; protocol; preference; testing; population; health care worker; decision-making; accessibility; transmission; screening

Introduction

COVID-19 is caused by a novel coronavirus, SARS-CoV-2, which was first identified in December 2019 [1]. COVID-19 is mainly transmitted through the air, as virus particles are expelled when an infected individual coughs, sneezes, or speaks [2]. In older adults and individuals with chronic diseases (such as hypertension, diabetes, and malignant tumors), COVID-19 may be fatal [3]. While there are several vaccines and treatments available, there is currently no cure for COVID-19.

On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a global pandemic [4]. As of October 12, 2021, there have been more than 237 million confirmed COVID-19 cases worldwide, with more than 4.8 million deaths due to COVID-19 reported [5].

Providing accessible, safe, and client-centered SARS-CoV-2 testing services is an effective way to halt transmission of the virus. Testing allows the health system and individuals to conduct contact-tracing, to accelerate access to treatment, and to isolate affected individuals [6,7].

In countries with limited laboratory capacity, the provision of accessible and safe SARS-CoV-2 screening is challenging [3]. The use of SARS-CoV-2 self-tests that have acceptable performance in terms of diagnostic accuracy in low- and middle-income countries could help reduce COVID-19 transmission by enabling the rapid identification of those infected. Because SARS-CoV-2 self-testing can be conducted by individuals in their home, it enables people to regularly check their infection status without needing to attend a health care facility. Self-testing has particular benefits in settings where human resources and laboratory capacity for molecular SARS-CoV-2 testing is limited.

Similar to that seen for other diseases—such as HIV, and recently, hepatitis C—self-testing can provide a convenient, private, and safe approach to scale-up testing [8-10]. However, as with HIV and hepatitis C self-testing, with SARS-CoV-2 self-testing, there are important concerns about lack of counseling for test results, potential for psychosocial harm, and ensuring timely reporting of test results to national surveillance systems [11]. The risk of potential social harms and incorrect action based on test results must be investigated to ensure safe implementation of any self-testing program for COVID-19 [12].

To date, there have been no studies on the values and preferences of individuals in low- and middle-income countries regarding SARS-CoV-2 self-testing. To the best of our knowledge, there have been just 3 studies published on the usability and acceptability of self-testing for SARS-CoV-2—2 from England [13,14] and one from Ireland [15]. These studies [13-15] reported that SARS-CoV-2 self-testing appears to be feasible for and acceptable to untrained users.

We are only aware of 3 ongoing studies in low- and middle-income countries: (1) an ongoing SARS-CoV-2 self-testing acceptability study in Lesotho and Zambia led by the London School of Hygiene & Tropical Medicine; (2) a study exploring the feasibility of self-sampling and self-testing for SARS-CoV-2, which is ongoing in Malawi and Zimbabwe under the leadership of FIND, the global alliance for diagnostics, in collaboration with the Center for Sexual Health and HIV/AIDS Research Zimbabwe; and (3) an ongoing usability and clinical evaluation study of self-testing for SARS-CoV-2 in South Africa, led by Ezintsha, Wits Health Consortium, University of the Witwatersrand [16].

Prior to issuing recommendations for SARS-CoV-2 self-testing in low- and middle-income countries, it is imperative to conduct a thorough assessment of values and preferences regarding the innovation [17]. The views of local populations are crucial in the discussion of the safest strategies for implementing SARS-CoV-2 self-testing. Evidence is also needed on sociocultural specificities that may hinder widespread utilization of SARS-CoV-2 self-testing, for example, familiarity of the target population with self-testing devices for infectious diseases such as HIV or for non-communicable diseases such as diabetes. We propose to address the evidence gap by conducting a multicountry research study on local population's values and preferences for SARS-CoV-2 self-testing. This global protocol details the harmonized objectives, methodologies, and ethics principles that will guide the implementation of this research in all participating countries to address the question: How acceptable would SARS-CoV-2 self-testing be, to diagnose and prevent the spread of SARS-CoV-2, for populations in low-resource settings, and under which circumstances?

Methods

Overview

This multisite, mixed methods, observational study will consist of 2 components: cross-sectional surveys and a qualitative inquiry. We will employ a similar approach to that used in providing supporting evidence for WHO 2021 recommendations and guidance on hepatitis C virus self-testing [18].

This study will be conducted in 9 countries: Brazil, India, Indonesia, Kenya, Malawi, Nigeria, Peru, the Philippines, and South Africa. The surveys will be conducted in all countries except Malawi. The qualitative inquiry will be conducted in all countries.

These countries were selected by considering (1) the need to obtain the perspectives of inhabitants from different WHO regions; (2) availability of local partners to conduct research activities in areas not subject to movement and social gathering restrictions; (3) potential for dissemination of findings at local diagnostic development institutions, manufacturers, and distributors; and (4) previous experience from research on self-testing devices of the sponsor (FIND) in selected countries.

Cross-sectional Survey: General Population

Design

The cross-sectional survey for the general population (Multimedia Appendix 1) is designed to answer specific objectives 2 and 4 (Textbox 1). To participate in this survey component, individuals must be aged 18 years old or older and willing to provide informed consent.

Textbox 1. Specific objectives of the research.

Objectives

- Measure the perceptions of the utility of different scenarios for SARS-CoV-2 self-testing delivery to halt the transmission of SARS-CoV-2 and to fast-track access to COVID-19 treatment.
- Understand the perceptions of and experience with current COVID-19 diagnostic modalities.
- Explore and map the factors that may foster or hinder acceptability of SARS-CoV-2 self-testing among a population.
- Understand the types of actions, under a variety of circumstances, that members of the general population would take after receiving a reactive SARS-CoV-2 self-test result.
- Analyze various culturally congruent, safe, and effective strategies for the implementation of SARS CoV-2 self-testing in resource-constrained settings.

Respondents are asked to reply based on their own experiences of current SARS-CoV-2 testing and their perceptions regarding SARS-CoV-2 self-testing. The survey is divided into 5 sections: sociodemographic characteristics, experience with COVID-19 and SARS-CoV-2 testing, values toward SARS-CoV-2 self-testing, actions the participant thinks they would take after testing positive using a SARS-CoV-2 self-test, and actions they think they would take after testing negative with a SARS-CoV-2 self-test. Not all survey respondents may be aware of SARS-CoV-2 self-testing; therefore, the surveyors, after probing them about other self-tests with which they might be acquainted, will briefly show an explanatory diagram and explain the concept of SARS-CoV-2 self-testing.

In all countries except for Brazil, the partner organizations with whom we work in each country to conduct the study identified an urban and a rural area to conduct the survey. Urban areas are defined as the capital of the country or state or main city in which the partner organization operates. Rural areas are defined as areas outside the defined urban areas. For rural areas, partner organizations identified areas (1) where it would be safe to have surveyors in the field without putting surveyors and respondents at an increased risk of catching SARS-CoV; (2) without access difficulties due to curfews, confinement perimeters, or lack of administrative permissions to operate; and (3) where it would be possible to obtain the perspectives of participants who may lack the level of COVID-19 diagnostic, prevention, and treatment resources that are available to people living in urban areas. In Brazil and India, the survey will only be conducted in urban areas only, because at the time of study planning, there were no rural areas that met these 3 characteristics where the partners in Brazil and India has license to operate.

Sample Size

To calculate sample size, we made a conservative assumption that at least 50% of the general population would accept SARS-CoV-2 self-testing as a decentralized SARS-CoV-2 screening strategy. We estimated that ≥196 respondents from both the urban and rural areas would be needed to give a confidence level of 95% for the real value (acceptability of SARS-CoV-2 self-testing) to be within ±7% of the measured value.

In each of Brazil, Indonesia, Kenya, Peru, the Philippines, and South Africa, 392 respondents will be necessary (Table 1). In India and Nigeria, where there is a need for regional representation to inform national decision-making given the federal or quasi-federal government structure, the study will be conducted in 4 and 5 states, respectively; therefore, 392 respondents per state will be required (ie, 1568 and 1960 participants, respectively) (Table 1).

Table 1. Countries, locations, and sample sizes.

Country and state	Urban		Rural	
	Area	n	Area	n
Brazil	São Paulo	392	N/A[a]	N/A
Indonesia	Jakarta	196	Banten	196
			North Sulawesi	196
Kenya	Mombasa	196	Taita Taveta County	196
Peru	City of Lima	196	Jauja-Huancayo	196
Philippines	Manila metropolitan area	196	El Nido (on the island of Palawan)	196
South Africa	Durban (KwaZulu-Natal)	196	King Sabata Dalindyebo (Eastern Cape)	196
Nigeria				
Akwa Ibom State	Uyo LGA[b]	196	Ibiono Ibom LGA	196
Anambra State	Awka South LGA	196	Dunukofia LGA	196
Benue State	Makurdi LGA	196	Ikpayongo LGA	196
Kaduna State	Kaduna South LGA	196	Kudan LGA	196
Lagos State	Ikeja LGA	196	Ikorodu LGA	196
India				
Uttar Pradesh State	Lucknow	392	N/A	N/A
Assam State	Guwahati	392	N/A	N/A
Maharashtra State	Thane	392	N/A	N/A
Tamil Nadu State	Chennai	392	N/A	N/A

[a]N/A: not applicable.

[b]LGA: local government area.

Sampling Method

A multistage sampling approach will be used to select clusters of households or street points in the study locations in each country, where respondents will be approached and invited to participate in the survey.

In each country, satellite-generated maps will be divided into 40 areas of similar geographic extension for both the urban and rural settings. A random list generator (Random.org, Randomness and Integrity Services Ltd) will be used to select 14 areas of the 40 areas.

The 14 urban areas and 14 rural areas that are selected will be randomly arranged to produce an urban calendar and a rural calendar that each cover a single week (ie, from Monday to Sunday, with morning and afternoon shifts). The expected sample size will be indicated in each calendar slot and will be equal for each area (15 respondents per shift for all areas, except for São Paulo, where sample size would be 29 respondents per shift). For each area, clusters of 21 households or street points will be selected, marked, and numbered. In the map of São Paulo, each area will have 30 selected street points.

To recruit respondents, a pair of surveyors, with a printed map of the area showing the 21 recruiting spots (households or street points), will walk to the first recruiting spot on their assigned shift and will seek survey respondents (1 per spot). While the first surveyor recruits their first respondent, obtains their signed informed consent, and administers the survey, the second surveyor will walk to the next preselected location and l repeat the process. The surveyors will continue this process at subsequent recruitment spots until the expected size per shift is reached.

In Nigeria and Kenya, the recruiting spots will be households, and the surveyors will randomly recruit household members who are present at the time they knock on their doors. In Peru, Brazil, India, Indonesia, and the Philippines, the recruiting spots will be street points, and the surveyors will recruit passers-by as participants. In South Africa, the recruiting spots will be community gathering venues (eg, schools, shopping malls, and post offices), and the surveyors will recruit respondents among the public at these venues. To decide whether the recruiting spots were to be households, street points, or community gathering venues, we considered, for each country, where it would be safest to conduct survey activities, and where it would be more acceptable for potential respondents to consent to participate in the survey.

Cross-sectional Survey: Health Care Workers

Design

The cross-sectional survey of health care workers (Multimedia Appendix 2) is designed to answer specific objectives 1, 2, and 4 (Textbox 1). The survey explores the same 5 themes as those explored in the general population survey; however, health care

workers will be asked to answer from their perspective as a health care worker how they think people in their catchment area would interact with SARS-CoV-2 self-testing and the potential impacts that such testing might have on the health system.

Sample Size

We estimate that 384 participants per country will be necessary to demonstrate that 50% of the health care workforce would accept SARS-CoV-2 self-testing as a decentralized SARS-CoV-2 infection screening strategy, with a 95% confidence level and a confidence interval of 5. This calculation was made for a finite population using a web-based calculator (Survey System, Creative Research Systems). As this component will be web-based and given the current level of engagement of health care workers with COVID-19 pandemic response, we anticipate a nonresponse rate of up to 50%. Hence, we estimate that 768 health care workers will need to be recruited to achieve the required sample size of 384.

Sampling Method

The survey targeting health care workers will be conducted by internet or by phone, with the aim of achieving national coverage. Partner organizations will sample potential respondents in collaboration with national and regional health authorities, and national councils of laboratory, nursing, and medical professionals. These stakeholders will be requested to assist with sampling. Possible sampling options are

1. Stakeholders provide a list of email addresses (no names or other identifiers needed) for 764 randomly selected health care workers. An email will be sent from the partner organization to these health care workers (all email addresses in blind carbon copy) inviting them to participate in the web-based survey.
2. The stakeholders provide a list of all health care workers' email addresses (no names or other identifiers needed), and the partner organizations will randomly select 764 of these, using a random list generator. The partner organizations will send an email to these health care workers (all email addresses in blind carbon copy), inviting them to participate in the web-based survey.
3. The stakeholders will use their own communications channels to send an official email inviting 764 randomly selected health care workers to participate in the survey.
4. The partner organizations will advertise the survey on social media (eg, Facebook, Instagram, Twitter), and using established social messaging groups of local networks of health care workers (eg, in WhatsApp and Telegram groups), and then wait for interested health care workers to click the link and complete the survey questionnaire. This additional sampling approach will help the partner organizations reach health care workers that only work in the private sector and those who work for the public health system but do not have an institutional email. A limitation of this option is the possibility that only health care workers with previous knowledge or interest in SARS-CoV-2 self-testing will pay attention to the adverts and click the link.

Prior to accessing the survey, all health care workers will have to read an information sheet that includes an explanation of the study's aim, the institutions involved, the purpose of the survey, and an invitation to participate in the study as a respondent. The link to access a web-based questionnaire (Multimedia Appendix 2) will be included in the invitation.

General Population and Health Care Worker Survey Instrument Development

All partners involved in this study collaboratively designed and piloted 2 survey instruments in English to target the general population and health care workers. These questionnaires were piloted by partners in various rounds through item-by-item discussions. During this pilot, any questionnaire item considered to be misleading, unclear, or nonspecific was reworded. Feedback from this pilot stage was used to further refine the questionnaires (Multimedia Appendix 1 and Multimedia Appendix 2).

The questionnaires will be translated into the local languages of each setting and uploaded to web-based survey software (Intel, IPSOS, in India due to the need to use different alphabets; KoBoToolbox, Harvard Humanitarian Initiative, for all other countries) with apps for data collection that work on most devices with Android operating systems.

Once the translated instruments have been uploaded, they will be piloted again with 10 randomly chosen individuals (5 women and 5 men) from a location outside the boundaries of the study settings, chosen by the local investigators. These pilot participants will meet the same inclusion criteria for respondents in the general population survey. This pilot will be helpful to further refine the wording of the questionnaire and to assess the feasibility and usability of the KoBo mobile app (Harvard Humanitarian Initiative) at different study sites. The responses obtained from these participants will not be used in the statistical analyses.

Survey Data Analysis Plan

The general population and health care worker survey responses will be analyzed separately. For both surveys, bivariate and multivariate inferential analysis will be performed, and descriptive statistics will be generated. The primary endpoint of the analysis will be likelihood of using a SARS-CoV-2 self-test (for the general population), and likelihood of recommending SARS-CoV-2 self-testing to the general population (for health care workers). Drivers and hinderers of likelihood of acceptance and willingness to recommend SARS-CoV-2 self-testing will be investigated. Specifically, significant associations between respondents' sociodemographic variables and aspects of interest that may advance the study objectives will be examined, such as previous experiences of conventional SARS-CoV-2 testing, barriers to access and use of SARS-CoV-2 self-testing, perceptions of the advantages of SARS-CoV-2 self-testing, willingness-to-pay and to use SARS-CoV-2 self-testing, preferences for reporting SARS-CoV-2 self-testing results, and anticipated actions and social harm that could occur after a positive SARS-CoV-2 self-test.

Qualitative Inquiry

In qualitative research, sample size is determined by the richness of interviewees' narratives. What matters is depth, not breadth, and that the narratives are helpful in achieving the research objectives. Hence, sample size is usually considered to be achieved when, during a contemporaneous and iterative data collection and analysis process, researchers consider the properties of the analysis categories to be saturated or fully understood [19]. In pursuing saturation, this research aims to conduct a minimum of 30 individual interviews (10 with each targeted group) and 6 group interviews (2 with each targeted group) per country. We will aim to ensure balanced representation of sex and location (Table 2).

Table 2. Qualitative interviews.

Description	Semistructured interviewees, n	Group[a] interview participants, n
Total	30	30
Community representatives		
Rural		
Women	2	3
Men	3	2
Urban		
Women	3	2
Men	2	3
Health care workers		
Rural		
Women	3	2
Men	2	3
Urban		
Women	2	3
Men	3	2
Potential SARS-CoV-2 self-testing implementers		
Rural		
Women	2	3
Men	3	2
Urban		
Women	3	2
Men	2	3

[a]A total of 6 group interview sessions will take place, with the 3 rural and 3 urban groups shown.

Sampling Method

At the outset, all organizations involved will jointly prepare a list of potential interviewees per study setting. A purposive sampling technique will be used to identify health care workers, community representatives, and potential SARS-CoV-2 self-testing implementers that meet the inclusion criteria and could be approached as potential participants.

Identification of potential interviewees will be achieved by (1) consulting the websites and social media of local firms, civil society organizations, humanitarian aid organizations, diagnostic manufacturers, health care institutions, and other relevant organizations; (2) reviewing government and nongovernment reports, and other grey literature; and (3) seeking advice from experts in local academia, public health institutes, laboratories, and pharmaceutical product manufacturers about who to reach out to for the study.

This stakeholder mapping exercise will result in a list of purposively identified potential interviewees. To ensure that sampling is not done by convenience or proximity to the interviewees, the list will be randomly rearranged so that a team of trained interviewers will contact potential interviewees in the established order by phone or email (depending on the contact details available on websites, social media profiles, or literature reviewed). The purpose and methods of the study will be explained to the potential interviewees, who will then be invited to participate in either an individual or a group interview, but not both.

Data Collection

Individual and group interview methodologies are suitable approaches to explore the study topic and enable investigation of questions about acceptability, willingness-to-pay or to-use, or potential harm that may derive from SARS-CoV-2 self-testing

with key stakeholders beyond what is possible with a structured survey. The combination of both methodologies is useful to compare if there are differences between how people express their views when they are alone and when they are in a group.

Individual interviews will be conducted by a trained interviewer and are expected to last 60 minutes. Group interviews will be conducted by a trained interviewer accompanied by a note-taker and are expected to last 90 to 120 minutes. Where local gender norms advise that data collection be led by interviewers of the same gender as the interviewees, interviews will be scheduled accordingly by gender.

All individual and group interviews will be guided using the same semistructured guide (Multimedia Appendix 3). This guide includes items from interview guides previously used in other FIND-supported assessments of people's values and preferences about HIV and hepatitis C self-testing [9]. The guide does not have any items that are considered overly sensitive. Nevertheless, the guide will be translated into the local languages of study settings. If any rewording of content is recommended during the training of interviewers on the guide, this will be carried out in accordance with their suggestions.

Data collection will be conducted either by videoconference or in a private location chosen by partner organizations. At the start of audiorecording, the interviewers will first ask the interviewees to verbally reconfirm that they have agreed to participate in the study and that they consent to the conversation being audiorecorded. They will then be asked to respond to the questions in the guide, which will be posed in consecutive order by the interviewers. The interviewers will collect interviewees' sociodemographic data (ie, age, gender identity, education, and profession) at the start of the interview.

Data Analysis

Audiorecordings will be transcribed verbatim into a text document (Word, Microsoft Inc). Personal identifiers (ie, names, addresses, and employers) mentioned during the interviews will not be transcribed. The countries' respective principal investigators will be responsible for the accuracy, integrity, and completeness of all transcriptions.

Audiorecordings and finalized transcripts will be stored on a password-protected computer. These materials will only be accessible by the sites' principal investigators, the sponsor, and the lead social scientist. The lead social scientist will verify that the transcriptions are fully anonymized and then upload the transcripts to computer-assisted qualitative data analysis software (Quirkos Software).

Thematic analysis will be used to analyze individual and group interview transcripts. We consider this approach to be the most suitable to explore how the interviewees' narratives may inform future implementation of SARS-CoV-2 self-testing. Transcripts will be coded using a predefined set of labels that correspond with the semistructured guide's themes and topics of interest. Coded areas will initially be read, re-read, and reflected upon in a code-by-code manner and in a theme-by-theme manner. While reading through the coded areas, specific reflexive memos will be written about each theme of interest. Each memo will include the main findings and characteristic excerpts of each preidentified core theme of interest. These memos will form the basis for report preparation. During this process, attention will be paid to how narratives may differ between rural and urban participants, and based on gender (female, male) and group (health care worker, representative of the public, decision-maker), with attention to the intersectionality of gender and profession with other social variables of interest. Attention will also be given to identifying deviating or exceptional voices (ie, isolated or divergent opinions on aspects of interest regarding the implementation of SARS-CoV-2 self-testing).

Recordings will be fully erased at the end of the data analysis phase. The transcripts will be stored on password-protected computers for 5 years after completion of the study. The recordings and transcripts will never be shared with any individuals outside the research team.

Integration of Qualitative and Quantitative Data

This is a convergent mixed methods study in design [20,21], whereby qualitative and quantitative data will be collected contemporaneously, analyzed separately, and then merged for further interpretation. At the outset of study proposal preparation, thoughtful consideration was given to how qualitative and quantitative methodologies could be helpful in collecting and analyzing data to address the main research question and meet the study objectives. The definition of the study populations and the design of the different components' data collection instruments and sampling and recruitment procedures were done with the aim to ensure qualitative and quantitative data could be examined together. During the implementation phase, thematic and statistical analysis and reporting of each set of data will take place separately. Subsequently, the main results will be merged in a theme-oriented mixed analysis matrix that will allow critical comparison of findings, as well as the detection of divergences, similarities, inconsistencies, or emerging areas that may merit further inquiry in future research. Conclusions of the cross-comparison of merged qualitative and quantitative results will be discussed in specific continent- and global-level dissemination outputs combining all methodologies.

Ethics Approval and Consent to Participate

This study has been approved by the following ethics committees: Universitas Katolik Indonesia Atma Jaya (o674A/III/LPPM-PM.10.05/06/2021); Institute of Public Health, Obafemi Awolowo University (IPH/OAU/12/1739); Durban University of Technology (IREC165/21); Amref Health Africa (AMRED-ESRC P1011/2021); Kamuzu University of Health Sciences, College of Medicine Research Ethics Committee (P.07/21/3357); Universidad Peruana Cayetano Heredia (205954); and the Philippine Social Science Council (CE-21-19). The ethical approval process is ongoing in Brazil and India.

Availability of Data and Materials

The quantitative data set will be made available upon reasonable request to the corresponding author. The qualitative data set of interview transcripts will not be made available.

Results

As of November 19, 2021, data collection is ongoing; 4364 participants have been enrolled in the general population survey, and 2233 participants have been enrolled in the health care workers survey. In the qualitative inquiry, 298 participants have been enrolled. We expect to complete data collection by December 31, 2021 and publish results in 2022.

Discussion

This study will be conducted in accordance with the Declaration of Helsinki [22] and the Belmont Report [23] principles of respect for persons, justice, and beneficence. In applying these principles, care was taken to design informed consent processes to ensure that no vulnerable groups carry the burden of the research, that the findings of the research will be disseminated in such a way that they may benefit the most disadvantaged groups in society, and to plan how to mitigate or eliminate all risks of social and physical harm (eg, SARS-CoV-2 infection) that may derive from participation in the study.

Ethics approval will be obtained at the country level prior to the start of participant recruitment. All participants will be asked to provide informed consent prior to participating in the survey or qualitative inquiry. No incentives other than a bag of face masks and hand sanitizers will be offered to study participants, unless local Ethics Review Boards appraising the country-specific protocols advise on other type of acceptable incentives.

This study is considered minimal risk; however, due to the ongoing COVID-19 pandemic extra measures will be taken to minimize exposure to SARS-CoV-2 for respondents and study staff. This will include providing personal protective equipment to study staff and participants and ensuring that social distancing measures are maintained during the in-person surveys and interviews. All local regulations regarding movement restrictions will be followed, and if necessary, interviews will be conducted remotely by videoconferences.

We aim to promote positive social change, one aspect of which is improving the conditions under which the most vulnerable in society access and use infectious disease diagnostics, by disseminating the findings. The research team will produce dissemination outputs for internal meetings, regional and international conferences, and peer-reviewed journals. A variety of methods will be used to disseminate the results of the study at industry and policy decision-making levels.

We anticipate that partner organizations will take part in development of scientific outputs and organize consultations with decision-makers involved in SARS-CoV-2 testing to incorporate their opinions on the study findings.

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Authors' Contributions

SS and EIR conceptualized the study. GZMP designed the protocol. GZMP and SS finalized the protocol. SS wrote the first draft of the manuscript. ARA, EIR, and GZMP reviewed the manuscript. All authors have read and approved the manuscript.

Conflicts of Interest

SS and EIR are employees of FIND, the global alliance for diagnostics, and GZMP has been engaged by FIND to work on this study.

Multimedia Appendix 1
Survey questionnaire—general population.
[DOCX File , 49 KB - resprot_v10i11e33088_app1.docx]

Multimedia Appendix 2
Survey questionnaire—health care workers.
[DOCX File , 24 KB - resprot_v10i11e33088_app2.docx]

Multimedia Appendix 3
Qualitative interview guide.

[DOCX File , 21 KB - resprot_v10i11e33088_app3.docx]

References

1. Coronavirus disease (COVID-19). World Health Organization. 2021. URL: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/coronavirus-disease-covid-19 [accessed 2021-07-16]
2. Scientific brief: SARS-CoV-2 transmission. Centers for Disease Control and Prevention. URL: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/sars-cov-2-transmission.html [accessed 2021-07-16]
3. Giri A, Rana D. Charting the challenges behind the testing of COVID-19 in developing countries: Nepal as a case study. Biosaf Health 2020 Jun;2(2):53-56 [FREE Full text] [doi: 10.1016/j.bsheal.2020.05.002]
4. WHO Director-General's opening remarks at the media briefing on COVID-19. World Health Organization. 2020 Mar 11. URL: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 [accessed 2021-07-16]
5. WHO Coronavirus (COVID-19) dashboard. World Health Organization. 2021. URL: https://covid19.who.int/ [accessed 2021-07-16]
6. Mercer TR, Salit M. Testing at scale during the COVID-19 pandemic. Nat Rev Genet 2021 Jul;22(7):415-426 [FREE Full text] [doi: 10.1038/s41576-021-00360-w] [Medline: 33948037]
7. Tripathi SC, Deshmukh V, Patil A, Tripathy JP. COVID 19 diagnostic multiplicity and its role in community surveillance and control. Infez Med 2020 Jun 01;28(suppl 1):18-28 [FREE Full text] [Medline: 32532934]
8. Ingold H, Mwerinde O, Ross A, Leach R, Corbett E, Hatzold K, et al. The Self-Testing AfRica (STAR) Initiative: accelerating global access and scale-up of HIV self-testing. J Int AIDS Soc 2019 Mar;22 Suppl 1:e25249 [FREE Full text] [doi: 10.1002/jia2.25249] [Medline: 30907517]
9. Martínez-Pérez GZ, Nikitin DS, Bessonova A, Fajardo E, Bessonov S, Shilton S. Values and preferences for hepatitis C self-testing among people who inject drugs in Kyrgyzstan. BMC Infect Dis 2021 Jun 26;21(1):609 [FREE Full text] [doi: 10.1186/s12879-021-06332-z] [Medline: 34171990]
10. Serumondo J, Shilton S, Nshimiyimana L, Karame P, Dushimiyimana D, Fajardo E, et al. Values and preferences for hepatitis C self-testing among the general population and healthcare workers in Rwanda. BMC Infect Dis 2021 Oct 14;21(1):1064 [FREE Full text] [doi: 10.1186/s12879-021-06773-6] [Medline: 34649503]
11. Gagnon M, French M, Hébert Y. The HIV self-testing debate: where do we stand? BMC Int Health Hum Rights 2018 Jan 18;18(1):5 [FREE Full text] [doi: 10.1186/s12914-018-0146-6] [Medline: 29347929]
12. Conserve DF, Mathews A, Choko AT, Nelson LE. Preparing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) self-testing implementation: lessons learned from HIV self-testing. Front Med (Lausanne) 2020;7:599521 [FREE Full text] [doi: 10.3389/fmed.2020.599521] [Medline: 33365320]
13. Atchison C, Pristerà P, Cooper E, Papageorgiou V, Redd R, Piggin M, et al. Usability and acceptability of home-based self-testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies for population surveillance. Clin Infect Dis 2021 May 04;72(9):e384-e393 [FREE Full text] [doi: 10.1093/cid/ciaa1178] [Medline: 32785665]
14. Davies B, Araghi M, Moshe M, Gao H, Bennet K, Jenkins J. Acceptability, usability and performance of lateral flow immunoassay tests for SARS-CoV-2 antibodies: REACT-2 study of self-testing in non-healthcare key workers. medRxiv. Preprint published online on June 27, 2021. [doi: 10.1101/2021.06.21.21259254]
15. Jing M, Bond R, Robertson LJ, Moore J, Kowalczyk A, Price R, et al. User experience analysis of AbC-19 Rapid Test via lateral flow immunoassays for self-administrated SARS-CoV-2 antibody testing. Sci Rep 2021 Jul 07;11(1):14026 [FREE Full text] [doi: 10.1038/s41598-021-93262-0] [Medline: 34234188]
16. Majam M, Msolomba V, Scott L, Stevens W, Marange F, Kahamba T, et al. Self-sampling for SARS-CoV-2 diagnostic testing by using nasal and saliva specimens: protocol for usability and clinical evaluation. JMIR Res Protoc 2021 May 28;10(5):e24811 [FREE Full text] [doi: 10.2196/24811] [Medline: 33882023]
17. Zhang Y, Coello PA, Brożek J, Wiercioch W, Etxeandia-Ikobaltzeta I, Akl EA, et al. Using patient values and preferences to inform the importance of health outcomes in practice guideline development following the GRADE approach. Health Qual Life Outcomes 2017 May 02;15(1):52 [FREE Full text] [doi: 10.1186/s12955-017-0621-0] [Medline: 28460638]
18. Web Annex D. Values and preferences on hepatitis C virus self-testing. Recommendations and Guidance on Hepatitis C Virus Self-Testing. Geneva: World Health Organization; 2021. URL: https://www.who.int/publications/i/item/9789240031128 [accessed 2021-11-22]
19. Sandelowski M. Sample size in qualitative research. Res Nurs Health 1995 Apr;18(2):179-183 [FREE Full text] [doi: 10.1002/nur.4770180211] [Medline: 7899572]
20. Onwuegbuzie A, Slate J, Leech N, Collins K. Mixed data analysis: advanced integration techniques. Int J Mult Res Approaches 2014 Dec 17;3(1):13-33 [FREE Full text] [doi: 10.5172/mra.455.3.1.13]
21. Onwuegbuzie A, Slate J, Leech N, Collins K. Conducting mixed analyses: a general typology. Int J Mult Res Approaches 2014 Dec 17;1(1):4-17 [FREE Full text] [doi: 10.5172/mra.455.1.1.4]
22. Ethical principles for medical research involving human subjects. World Health Organization. URL: https://www.who.int/bulletin/archives/79(4)373.pdf [accessed 2021-11-22]

23. The Belmont Report: ethical principles and guidelines for the protection of human subjects of research. U.S. Department of Health, Education, and Welfare. URL: https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html [accessed 2021-11-22]

Abbreviations

HIV: human immunodeficiency virus
WHO: World Health Organization

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Protocol

A Deep Learning Approach to Refine the Identification of High-Quality Clinical Research Articles From the Biomedical Literature: Protocol for Algorithm Development and Validation

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Abstract

Background: A barrier to practicing evidence-based medicine is the rapidly increasing body of biomedical literature. Use of method terms to limit the search can help reduce the burden of screening articles for clinical relevance; however, such terms are limited by their partial dependence on indexing terms and usually produce low precision, especially when high sensitivity is required. Machine learning has been applied to the identification of high-quality literature with the potential to achieve high precision without sacrificing sensitivity. The use of artificial intelligence has shown promise to improve the efficiency of identifying sound evidence.

Objective: The primary objective of this research is to derive and validate deep learning machine models using iterations of Bidirectional Encoder Representations from Transformers (BERT) to retrieve high-quality, high-relevance evidence for clinical consideration from the biomedical literature.

Methods: Using the HuggingFace Transformers library, we will experiment with variations of BERT models, including BERT, BioBERT, BlueBERT, and PubMedBERT, to determine which have the best performance in article identification based on quality criteria. Our experiments will utilize a large data set of over 150,000 PubMed citations from 2012 to 2020 that have been manually labeled based on their methodological rigor for clinical use. We will evaluate and report on the performance of the classifiers in categorizing articles based on their likelihood of meeting quality criteria. We will report fine-tuning hyperparameters for each model, as well as their performance metrics, including recall (sensitivity), specificity, precision, accuracy, F-score, the number of articles that need to be read before finding one that is positive (meets criteria), and classification probability scores.

Results: Initial model development is underway, with further development planned for early 2022. Performance testing is expected to star in February 2022. Results will be published in 2022.

Conclusions: The experiments will aim to improve the precision of retrieving high-quality articles by applying a machine learning classifier to PubMed searching.

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KEYWORDS

bioinformatics; machine learning; evidence-based medicine; literature retrieval; medical informatics; natural language processing; NLP; biomedical; literature; literature surveillance; model development

Introduction

Background

The biomedical literature grows exponentially every year. According to the latest National Library of Medicine statistical report, more than 1.5 million new citations were indexed in PubMed in 2020 alone [1]. This high volume of literature is fed by the publication of at least 1 new article every 26 seconds [2] and 95 clinical trials per day [3]. Nevertheless, only 1% of published clinical studies meet the criteria for high scientific quality for use in health care decisions [4], driving the need for efficient and accurate approaches to identify clinical studies that have been conducted with methodological rigor.

Methodological search filters like PubMed Clinical Queries [5] are considered the cornerstone for information retrieval in evidence-based practice [6]. These and other search filters have been developed using a diagnostic testing procedure [7] to optimize sensitivity or specificity, or the best balance between the two, for such clinical study categories as treatment, diagnosis, prognosis, etiology, and clinical prediction guides [8]. Some search filters are limited by their partial reliance on MeSH (Medical Subject Headings) indexing terms, as it can take up to a year for articles to be indexed in MEDLINE [9]. Despite having highly sensitive search filters, with an aim to optimize specificity—essentially returning the most likely relevant articles while reducing the need to assess off-target articles—they also return large numbers of articles that are not on target.

Most search filters have been developed using databases of articles that have been tagged for clinical category and methodological rigor and using a diagnostic test approach to detect true and false, positive (on-target) and negative (off-target) articles [10]. The development of such a gold standard is costly and time-consuming, requiring highly trained staff. The Clinical Hedges database, developed at McMaster University, has been used as the gold standard for new search strategy development [11-14].

Machine learning is a subset of artificial intelligence referring to the application of computational methods to improve performance or achieve precise predictions via experience. Experience, in this context, is the information given to the machine for analysis [15]. Machine learning applications in the biomedical literature have been explored by many researchers over the years. In 2007, Yoo and colleagues [16] applied a novel machine learning approach for document clustering and text summarization, producing a textual summary of the information by automatically extracting the most relevant text content from a document cluster. Machine learning has also been applied to the ranking of biomedical publications. In 2009, the MedlineRanker webserver ranked citations in a data set based on their relevance to a given topic [17]. Other applications of machine learning include accurately predicting the citation count of a given article at the time of its publication to determine its scientific impact using a support vector machine (SVM) context–based classifier [18] and automating the systematic review screening process to decrease the screening workload [19]. For example, Miwa and colleagues [20] used an SVM pool–based active machine learning model to classify articles as relevant for inclusion in a systematic review. Miwa et al's [20] experiment used “certainty” as a criterion for article selection, which is effective in dealing with imbalanced data sets. An improvement in topic detection was proposed by Hashimoto et al [21] as they used a neural network model based on paragraph vectors capturing semantic similarities between words and documents. Paragraph vectors can accurately determine semantic relatedness between textual units of varying lengths, that is, words, phrases, and longer sequences (eg, sentences, paragraphs, and documents). Methods that consider factors such as word order within the text yield superior performance [21].

Recent advancement in natural language processing (NLP) is attributed to the development of pretrained language models (PTLMs) [22]. PTLMs transfer learning from training on one data set to the performance of different NLP functions on a new data set [22,23]. PTLMs provide more stable predictions and better model generalization [24]. PTLMs are applied using one of two main strategies: feature-based or fine-tuning models [23]. Feature-based approaches use task-specific architectures that include the pretrained representations as additional features, such as Embedding from Language Models (ELMo) [22,25]. Fine-tuning approaches attempt to pretrain the language model using general-domain text, then fine-tune the model on the target data and target task [22]. Fine-tuning language models are considered the mainstream for PTLM adaption [22]. Examples of fine-tuning approaches are Universal Language Model Fine-Tuning [26] and Bidirectional Encoder Representations from Transformers (BERT) [23]. The bidirectional approach used in BERT improves its performance in understanding text context over other PTLMs, making it the state-of-the-art model. BERT can be used for multiple NLP tasks, including text summarization, retrieval, question answers, named entity recognition, and document classification [27].

Over the past two decades, machine learning has been applied to classify the biomedical literature based on methodological rigor and evidence quality. For such classification tasks, supervised machine learning approaches in which the training data is labeled based on a selected high-quality standard are most commonly used [3,28-32]. The first reported experiments to classify biomedical literature based on quality by Aphinyanaphongs and colleagues relied on the American College of Physicians Journal Club as their high-quality training standard and used a supervised SVM as a classifier [28-30]. The most recent study to classify high-quality articles was conducted by Afzal and colleagues [31] and applied an artificial neural network using data gathered from the Cochrane Library as their high-quality standard. By using supervised approaches,

the model development was informed by decisions made by the researchers.

Objectives

The primary objective of this research is to derive and validate deep learning models using variations of BERT to retrieve high-quality, high-relevance evidence for clinical consideration from the biomedical literature; models will be trained using a large, tagged database of high-quality, high-relevance clinical articles.

Methods

Quality Standard Derivation

At McMaster University, the Health Information Research Unit (HiRU) has an established reputation for retrieval, appraisal, classification, organization, and dissemination of health-related research. Through the Knowledge Refinery, the unit daily screens research studies from over 120 clinical journals and identifies those that meet methodological rigor for original studies, systematic reviews, pooled original studies, and evidence-based guidelines within the categories of treatment, primary prevention, diagnosis, harm from medical interventions, economics, prognosis, clinical prediction, and quality improvement [33]. The steps in the process include the initial filtering of all journal articles using highly sensitive search filters (>99%) developed by HiRU to identify articles that fit the categories named above. This filtered subset is then manually reviewed by skilled research associates and a clinical editor. In this project, "rigor" is defined as meeting all the methodological criteria explicitly described on the HiRU website and in Multimedia Appendix 1 [34]. The process of selecting clinically relevant articles is further described by Haynes et al [35], and the high reliability of the critical appraisal step has been documented with a kappa value of over 80% for all categories of articles [36].

The Premium Literature Service (PLUS) process is based on scientific principles for critical appraisal of the medical literature to support evidence-based medicine, combined with multiple ratings of clinical relevance by a worldwide network of practicing health care professionals. Segments of the database have been used many times to test various machine learning approaches, including deep learning [3]. A vast community of >4000 clinicians then rate methodologically rigorous articles for clinical relevance and newsworthiness [37]. The resulting PLUS database contains a distillation of the most reliable and relevant published clinical research [38].

Data Set

The data used is the Critical Appraisal Process (CAP) data set, which consists of the titles and abstracts of 155,679 articles published between 2012 to 2020, identified by means of their PubMed identifier and manually labeled by research associates as those that "fulfilled" methodological rigor criteria (n=30,035) or "failed" to meet methodological rigor criteria (n=125,644). The data set will be randomly split into 80% for training, 10% for validation, and 10% for testing. Along with being unbalanced, the CAP data set is large and computationally challenging for deep learning model development. To overcome this limitation, we will first convert the data set into multiple balanced subsets, then independently train one model per each of the balanced subsets and use ensembling techniques [39-42] to combine the independently trained models into a better model with more robust performance.

Machine Learning Experiment

Using Python (Python Software Foundation), we will build our models using the HuggingFace Transformers library [43]. HuggingFace is an open-source NLP and artificial intelligence model hub that provides accessible and implementable state-of-the-art models to the community [44]. Using PTLMs available within the HuggingFace Transformers library, we will experiment with variations of BERT models to determine which have the best performance in article classification. These will include BERT [23], BioBERT [45], BlueBERT [46], and PubMedBERT [47]. These models differ in the pretraining text domain. Pretraining a biomedical BERT model follows a mixed-domain pretraining that initializes with standard BERT pretraining using text data from BookCorpus [48] and English Wikipedia (Wikimedia Foundation) [23], followed by continuous pretraining using biomedical text. BioBERT is pretrained using PubMed abstracts and PubMed Central full-text articles [45], while BlueBERT is pretrained using PubMed text and clinical notes from MIMIC-III (Medical Information Mart for Intensive Care) [46]. PubMedBERT is pretrained using domain-specific text data from a collection of 14 million PubMed abstracts, which were downloaded in February 2020, with abstracts under 128 words removed [47]. Our selection of these models was guided by their availability within the HuggingFace repository and their reported performance in the Biomedical Language Understanding and Reasoning Benchmark leaderboard [47,49].

For the top-performing model that maintains sensitivity >98%, we plan to prospectively validate its real-world performance in the McMaster PLUS reading process. A random sample of incoming articles that are classified as failed articles will be allocated to research staff blinded to the model determination.

To evaluate the performance of machine learning models, we will report the sensitivity (recall), specificity, accuracy, precision, the number of articles that need to be read before finding one that is positive, and F-score (harmonic mean of recall and precision metrics [50]) (Table 1). We will report the probability score threshold, with corresponding 95% CIs, for each model. The machine learning models return a probability score for each article that represents the probability that the article is of high quality, and ranges from 0 (does not meet criteria) to 1 (meets criteria). For a given article, the probability will vary depending on the composition of the model. To prospectively validate the performance of the best model, we will report the same diagnostic characteristics for prospective validation of the model. Fine-tuning hyperparameter settings (number of epochs, learning rate, batch size, and number of random seeds) of the selected models for validation will be reported.

Table 1. Definitions and formulas pertaining to performance metrics.

Measure	Definition	Formula
Recall (sensitivity)	The proportion of correctly identified positive articles fulfilling criteria among those predicted to be positive	TP[a]/(TP+FN[b])
Specificity	The proportion of articles correctly identified as not meeting criteria among those predicted as negative	TN[c]/(TN+FP[d])
Precision	The proportion of correctly identified positives among all classified positives	TP/(TP+FP)
F-measure	Harmonic mean of precision and recall	2 × ([precision × recall]/[precision + recall])
Accuracy	The number of correctly predicted documents out of all classified documents	(TP+TN)/(TP+FP+FN+TN)
Number needed to read	The number of articles that need to be read before finding one that is positive (meets criteria)	1/precision

[a]TP: true positive.

[b]FN: false negative.

[c]TN: true negative.

[d]FP: false positive.

Results

Initial model development is underway, with further development planned for early 2022. Performance testing is expected to start in February 2022. Results will be published in 2022.

Discussion

BERT is considered the state-of-the-art model for NLP. To our knowledge, this is the first experiment to investigate the use of PTLMs in the identification of high-quality articles from the biomedical literature [51]. Our study leverages a large data set of over 150,000 citations that have been manually tagged by experienced research associates, making it one of the few reliable sources for training machine learning models to identify high-quality clinical literature [50]. Our application and analysis of BERT models may provide a better performing automation model suitable for incorporation in literature surveillance processes at HiRU and elsewhere.

Artificial intelligence and machine learning applications are complex and known for their black-box nature, providing predictions without enough explanation [52]. Besides the accurate prediction and the decrease in workload, trust in algorithmic decisions is essential, especially in medicine and health care research [53]. To overcome the lack of transparency, interpreting machine learning models and their decision-making process has become a growing focus among academic and industrial machine learning experts [54]. Next steps include interpreting the decisions made by the model. This would allow us to understand the justification behind model decision-making [55].

Conflicts of Interest

None declared.

Multimedia Appendix 1
Inclusion criteria for articles meeting methodological rigor.
[DOCX File , 24 KB - resprot_v10i11e29398_app1.docx]

References

1. MEDLINE PubMed Production Statistics. National Library of Medicine. 2020. URL: https://www.nlm.nih.gov/bsd/medline_pubmed_production_stats.html [accessed 2021-07-31]
2. Garba S, Ahmed A, Mai A, Makama G, Odigie V. Proliferations of scientific medical journals: a burden or a blessing. Oman Med J 2010 Oct;25(4):311-314 [FREE Full text] [doi: 10.5001/omj.2010.89] [Medline: 22043365]
3. Del Fiol G, Michelson M, Iorio A, Cotoi C, Haynes RB. A Deep Learning Method to Automatically Identify Reports of Scientifically Rigorous Clinical Research from the Biomedical Literature: Comparative Analytic Study. J Med Internet Res 2018 Jun 25;20(6):e10281 [FREE Full text] [doi: 10.2196/10281] [Medline: 29941415]
4. Haynes R. Where's the meat in clinical journals? ACP Journal Club 1993;119(3):A22. [doi: 10.7326/ACPJC-1993-119-3-A22]
5. Wilczynski NL, McKibbon KA, Walter SD, Garg AX, Haynes RB. MEDLINE clinical queries are robust when searching in recent publishing years. J Am Med Inform Assoc 2013;20(2):363-368 [FREE Full text] [doi: 10.1136/amiajnl-2012-001075] [Medline: 23019242]

6. Bachmann LM, Coray R, Estermann P, Ter Riet G. Identifying diagnostic studies in MEDLINE: reducing the number needed to read. J Am Med Inform Assoc 2002;9(6):653-658 [FREE Full text] [doi: 10.1197/jamia.m1124] [Medline: 12386115]
7. Wilczynski NL, Morgan D, Haynes RB, Hedges Team. An overview of the design and methods for retrieving high-quality studies for clinical care. BMC Med Inform Decis Mak 2005 Jun 21;5:20 [FREE Full text] [doi: 10.1186/1472-6947-5-20] [Medline: 15969765]
8. Hedges. Health Information Research Unit - McMaster University. 2016. URL: https://hiru.mcmaster.ca/hiru/HIRU_Hedges_home.aspx [accessed 2021-11-18]
9. Irwin AN, Rackham D. Comparison of the time-to-indexing in PubMed between biomedical journals according to impact factor, discipline, and focus. Res Social Adm Pharm 2017;13(2):389-393. [doi: 10.1016/j.sapharm.2016.04.006] [Medline: 27215603]
10. Wong SS, Wilczynski NL, Haynes RB, Ramkissoonsingh R, Hedges Team. Developing optimal search strategies for detecting sound clinical prediction studies in MEDLINE. AMIA Annu Symp Proc 2003:728-732 [FREE Full text] [Medline: 14728269]
11. Geersing G, Bouwmeester W, Zuithoff P, Spijker R, Leeflang M, Moons KGM, et al. Search filters for finding prognostic and diagnostic prediction studies in Medline to enhance systematic reviews. PLoS One 2012;7(2):e32844 [FREE Full text] [doi: 10.1371/journal.pone.0032844] [Medline: 22393453]
12. Frazier JJ, Stein CD, Tseytlin E, Bekhuis T. Building a gold standard to construct search filters: a case study with biomarkers for oral cancer. J Med Libr Assoc 2015 Jan;103(1):22-30 [FREE Full text] [doi: 10.3163/1536-5050.103.1.005] [Medline: 25552941]
13. Keogh C, Wallace E, O'Brien KK, Murphy PJ, Teljeur C, McGrath B, et al. Optimized retrieval of primary care clinical prediction rules from MEDLINE to establish a Web-based register. J Clin Epidemiol 2011 Aug;64(8):848-860. [doi: 10.1016/j.jclinepi.2010.11.011] [Medline: 21411285]
14. Lee E, Dobbins M, Decorby K, McRae L, Tirilis D, Husson H. An optimal search filter for retrieving systematic reviews and meta-analyses. BMC Med Res Methodol 2012 Apr 18;12:51 [FREE Full text] [doi: 10.1186/1471-2288-12-51] [Medline: 22512835]
15. Mohri M, Rostamizadeh A, Talwalkar A. Foundations of Machine Learning, 2nd ed. Cambridge, MA: MIT Press; 2018.
16. Yoo I, Hu X, Song I. A coherent graph-based semantic clustering and summarization approach for biomedical literature and a new summarization evaluation method. BMC Bioinformatics 2007 Nov 27;8 Suppl 9:S4 [FREE Full text] [doi: 10.1186/1471-2105-8-S9-S4] [Medline: 18047705]
17. Fontaine J, Barbosa-Silva A, Schaefer M, Huska M, Muro E, Andrade-Navarro M. MedlineRanker: flexible ranking of biomedical literature. Nucleic Acids Res 2009 Jul;37(Web Server issue):W141-W146 [FREE Full text] [doi: 10.1093/nar/gkp353] [Medline: 19429696]
18. Fu LD, Aliferis CF. Using content-based and bibliometric features for machine learning models to predict citation counts in the biomedical literature. Scientometrics 2010 Feb 3;85(1):257-270. [doi: 10.1007/s11192-010-0160-5]
19. O'Mara-Eves A, Thomas J, McNaught J, Miwa M, Ananiadou S. Using text mining for study identification in systematic reviews: a systematic review of current approaches. Syst Rev 2015 Jan 14;4(1):5 [FREE Full text] [doi: 10.1186/2046-4053-4-5] [Medline: 25588314]
20. Miwa M, Thomas J, O'Mara-Eves A, Ananiadou S. Reducing systematic review workload through certainty-based screening. J Biomed Inform 2014 Oct;51:242-253 [FREE Full text] [doi: 10.1016/j.jbi.2014.06.005] [Medline: 24954015]
21. Hashimoto K, Kontonatsios G, Miwa M, Ananiadou S. Topic detection using paragraph vectors to support active learning in systematic reviews. J Biomed Inform 2016 Aug;62:59-65 [FREE Full text] [doi: 10.1016/j.jbi.2016.06.001] [Medline: 27293211]
22. Qiu X, Sun T, Xu Y, Shao Y, Dai N, Huang X. Pre-trained models for natural language processing: A survey. Sci China Technol Sci 2020 Sep 15;63(10):1872-1897. [doi: 10.1007/s11431-020-1647-3]
23. Devlin J, Chang MW, Lee K, Toutanova K. BERT: Pre-training of deep bidirectional transformers for language understanding. arXiv Preprint posted online Oct 1, 2018 [FREE Full text]
24. Dai AM, Le QV. Semi-supervised Sequence Learning. arXiv Preprint posted online Nov 4, 2015 [FREE Full text]
25. Peters M, Neumann M, Iyyer M, Gardner M, Clark C, Lee K, et al. Deep contextualized word representations. arXiv Preprint posted online Feb 14, 2018 [FREE Full text] [doi: 10.18653/v1/n18-1202]
26. Howard J, Ruder S. Universal Language Model Fine-tuning for Text Classification. arXiv Preprint posted online Jan 18, 2018 [FREE Full text] [doi: 10.18653/v1/p18-1031]
27. Adhikari A, Ram A, Tang R, Lin J. DocBERT: BERT for Document Classification. arXiv Preprint posted online Apr 17, 2019 [FREE Full text]
28. Aphinyanaphongs Y, Aliferis CF. Text categorization models for retrieval of high quality articles in internal medicine. AMIA Annu Symp Proc 2003:31-35 [FREE Full text] [Medline: 14728128]
29. Aphinyanaphongs Y, Aliferis C. Prospective validation of text categorization filters for identifying high-quality, content-specific articles in MEDLINE. AMIA Annu Symp Proc 2006:6-10 [FREE Full text] [Medline: 17238292]

30. Aphinyanaphongs Y, Tsamardinos I, Statnikov A, Hardin D, Aliferis C. Text categorization models for high-quality article retrieval in internal medicine. J Am Med Inform Assoc 2005;12(2):207-216 [FREE Full text] [doi: 10.1197/jamia.M1641] [Medline: 15561789]
31. Afzal M, Park BJ, Hussain M, Lee S. Deep Learning Based Biomedical Literature Classification Using Criteria of Scientific Rigor. Electronics 2020 Aug 05;9(8):1253. [doi: 10.3390/electronics9081253]
32. Kilicoglu H, Demner-Fushman D, Rindflesch TC, Wilczynski NL, Haynes RB. Towards automatic recognition of scientifically rigorous clinical research evidence. J Am Med Inform Assoc 2009;16(1):25-31 [FREE Full text] [doi: 10.1197/jamia.M2996] [Medline: 18952929]
33. McMaster Health Knowledge Refinery. Health Information Research Unit - McMaster University. 2016. URL: https://hiru.mcmaster.ca/hiru/HIRU_McMaster_HKR.aspx [accessed 2021-05-31]
34. Inclusion Criteria. Health Information Research Unit - McMaster University. 2019. URL: https://hiru.mcmaster.ca/hiru/InclusionCriteria.html [accessed 2021-05-31]
35. Haynes RB, Cotoi C, Holland J, Walters L, Wilczynski N, Jedraszewski D, McMaster Premium Literature Service (PLUS) Project. Second-order peer review of the medical literature for clinical practitioners. JAMA 2006 Apr 19;295(15):1801-1808. [doi: 10.1001/jama.295.15.1801] [Medline: 16622142]
36. Wilczynski NL, Walker CJ, McKibbon KA, Haynes RB. Assessment of methodologic search filters in MEDLINE. Proc Annu Symp Comput Appl Med Care 1993:601-605 [FREE Full text] [Medline: 8130545]
37. McMaster Online Rating of Evidence (MORETM). McMaster Premium Literature Service (PLUS) Project, McMaster University. 2018. URL: http://hiru.mcmaster.ca/more/ [accessed 2021-05-31]
38. McMaster Premium LiteratUre Service (PLUS). Health Information Research Unit - McMaster University. 2016. URL: https://hiru.mcmaster.ca/hiru/HIRU_McMaster_PLUS_projects.aspx [accessed 2021-05-31]
39. Ganaie M, Hu M, Tanveer M, Suganthan P. Ensemble deep learning: A review. arXiv Preprint posted online Apr 6, 2021 [FREE Full text]
40. Araque O, Corcuera-Platas I, Sánchez-Rada JF, Iglesias CA. Enhancing deep learning sentiment analysis with ensemble techniques in social applications. Expert Systems with Applications 2017 Jul;77:236-246. [doi: 10.1016/j.eswa.2017.02.002]
41. Xu Y, Qiu X, Zhou L, Huang X. Improving BERT Fine-Tuning via Self-Ensemble and Self-Distillation. arXiv Preprint posted online Feb 24, 2020 [FREE Full text]
42. Xu C, Barth S, Solis Z. Applying Ensembling Methods to BERT to Boost Model Performance. Stanford University. URL: https://web.stanford.edu/class/archive/cs/cs224n/cs224n.1194/reports/default/15775971.pdf [accessed 2021-11-18]
43. Wolf T, Debut L, Sanh V, Chaumond J, Delangue C, Moi A, et al. Transformers: State-of-the-Art Natural Language Processing. 2020 Presented at: Proceedings of the 2020 Conference on Empirical Methods in Natural Language Processing: System Demonstrations; Oct 2020; Online p. 38-45 URL: https://huggingface.co/transformers/ [doi: 10.18653/v1/2020.emnlp-demos.6]
44. HuggingFace. URL: https://huggingface.co/ [accessed 2021-11-16]
45. Lee J, Yoon W, Kim S, Kim D, Kim S, So C, et al. BioBERT: a pre-trained biomedical language representation model for biomedical text mining. Bioinformatics 2020 Feb 15;36(4):1234-1240 [FREE Full text] [doi: 10.1093/bioinformatics/btz682] [Medline: 31501885]
46. Peng Y, Yan S, Lu Z. Transfer Learning in Biomedical Natural Language Processing: An Evaluation of BERT and ELMo on Ten Benchmarking Datasets. arXiv Preprint posted online Jun 13, 2019 [FREE Full text] [doi: 10.18653/v1/w19-5006]
47. Gu Y, Tinn R, Cheng H, Lucas M, Usuyama N, Liu X, et al. Domain-Specific Language Model Pretraining for Biomedical Natural Language Processing. arXiv Preprint posted online Jul 30, 2020 [FREE Full text] [doi: 10.1145/3458754]
48. Zhu Y, Kiros R, Zemel R, Salakhutdinov R, Urtasun R, Torralba A, et al. Aligning books and movies: Towards story-like visual explanations by watching movies and reading book. 2015 Presented at: 2015 IEEE International Conference on Computer Vision (ICCV); December 7-13, 2015; Santiago, Chile p. 19-27 URL: https://www.computer.org/csdl/proceedings-article/iccv/2015/8391a019/12OmNro0HYa [doi: 10.1109/ICCV.2015.11]
49. BLURB Leaderboard. Microsoft. 2020. URL: https://microsoft.github.io/BLURB/index.html#page-top [accessed 2021-11-16]
50. Bekkar M, Djema H, Alitouche T. Evaluation measures for models assessment over imbalanced data sets. J Info Eng Appl 2013;3(10):27-38 [FREE Full text]
51. Abdelkader W, Navarro T, Parrish R, Cotoi C, Germini F, Iorio A, et al. Machine Learning Approaches to Retrieve High-Quality, Clinically Relevant Evidence From the Biomedical Literature: Systematic Review. JMIR Med Inform 2021 Sep 09;9(9):e30401 [FREE Full text] [doi: 10.2196/30401] [Medline: 34499041]
52. Watson DS, Krutzinna J, Bruce IN, Griffiths CE, McInnes IB, Barnes MR, et al. Clinical applications of machine learning algorithms: beyond the black box. BMJ 2019 Mar 12;364:l886. [doi: 10.1136/bmj.l886] [Medline: 30862612]
53. Hoeren T, Niehoff M. Artificial Intelligence in Medical Diagnoses and the Right to Explanation. European Data Protection Law Review 2018;4(3):308-319. [doi: 10.21552/edpl/2018/3/9]
54. Du M, Liu N, Hu X. Techniques for Interpretable Machine Learning. arXiv Preprint posted online Jul 31, 2018 [FREE Full text] [doi: 10.1145/3359786]
55. Chakraborty S, Tomsett R, Raghavendra R, Harborne D, Alzantot M, Cerutti F, et al. Interpretability of deep learning models: A survey of results. 2017 Presented at: IEEE SmartWorld, Ubiquitous Intelligence & Computing, Advanced &

Trusted Computed, Scalable Computing & Communications, Cloud & Big Data Computing, Internet of People and Smart City Innovation (SmartWorld/SCALCOM/UIC/ATC/CBDCom/IOP/SCI); Aug 4-7, 2017; San Francisco, CA. [doi: 10.1109/uic-atc.2017.8397411]

Abbreviations

BERT: Bidirectional Encoder Representations from Transformers
CAP: Critical Appraisal Process
HiRU: Health Information Research Unit
MeSH: Medical Subject Headings
MIMIC-III: Medical Information Mart for Intensive Care
NLP: natural language processing
PLUS: Premium Literature Service
PTLM: pretrained language model
SVM: support vector machine

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Protocol

Developing Core Outcome Sets (COS) and Core Outcome Measures Sets (COMS) in Cosmetic Gynecological Interventions: Protocol for a Development and Usability Study

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Abstract

Background: Studies evaluating cosmetic gynecological interventions have followed variable methodology and reported a diversity of outcomes. Such variations limit the comparability of studies and the value of research-based evidence. The development of core outcome sets (COS) and core outcome measures sets (COMS) would help address these issues, ensuring a minimum of outcomes important to all stakeholders, primarily women requesting or having experienced cosmetic gynecological interventions.

Objective: This protocol describes the methods used in developing a COS and COMS for cosmetic gynecological interventions.

Methods: An international steering group within CHORUS, including health care professionals, researchers, and women with experience in cosmetic gynecological interventions from 4 continents, will guide the development of COS and COMS. Potential outcome measures and outcomes will be identified through comprehensive literature reviews. These potential COS and COMS will be entered into an international, multi-perspective web-based Delphi survey where Delphi participants judge which domains will be core. A priori thresholds for consensus will get established before each Delphi round. The Delphi survey results will be evaluated quantitatively and qualitatively in subsequent stakeholder group consensus meetings in the process of establishing "core" outcomes.

Results: Dissemination and implementation of the resulting COS and COMS within an international context will be promoted and reviewed.

Conclusions: This protocol presents the steps in developing a COS and COMS for cosmetic gynecological interventions. Embedding the COS and COMS for cosmetic gynecological interventions within future clinical trials, systematic reviews, and practice guidelines could contribute to enhancing the value of research and improving overall patient care.

Trial Registration: Core Outcome Measures in Effectiveness Trials (COMET) 1592; https://tinyurl.com/n8faysuh

International Registered Report Identifier (IRRID): PRR1-10.2196/28032

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KEYWORDS

core outcome sets; core outcome measures sets; cosmetic gynecological surgery; intervention; labiaplasty; vulva; gynecology; cosmetic surgery; surgery; framework; outcome; effective; implementation

Introduction

Cosmetic gynecology is a rapidly developing area of gynecology, often closely linked to the clinical practice on the lower genital tract and relevant to the scope of practice of pelvic floor medicine and surgery, urogynecology, or plastic surgery [1].

Cosmetic gynecological interventions are elective surgical procedures aiming to "enhance the aesthetic appearance of the female external genitalia, modify genital organs, or functional vaginal procedures (in the absence of anatomic pathology), to help improve a woman's quality of life" [2].

According to the Cosmetic Surgery National Data Bank, cosmetic female genital surgery is the second fastest growing surgical procedure domain, with an increase of over 50% in 5 years [3].

Different approaches include surgical, nonsurgical, regenerative, and energy-based techniques. Increases in labiaplasty and other labial and vulvar procedures in recent years in different parts of the world, both for reconstructive as well as for cosmetic indications, may be partly due to an increasing popularity, lifestyle, and media interest [4,5]. When the outcomes of these interventions are suboptimal or even catastrophic, lifelong implications on women's anatomy, pelvic floor function, psychosexual function, and overall quality of life may require additional and long-term health care resources and support. On the other hand, associations between body dysmorphic disorders and requests for cosmetic procedures are well documented [6], and patient treatment pathways require robust scientific justification.

The combination of cultural shifting on body stereotypes and the patient's specific view about vulvar anatomy that intervenes in the sexual sphere up to associations with body dysmorphic disorders makes the management and fulfilling of patient expectations in cosmetic gynecological interventions delicate and critical [6-9].

In studies on cosmetic gynecological interventions, several issues around quality of evidence are obvious [10]: research evidence is limited, and the few published studies are mainly retrospective and observational, with small numbers of patients and short-term follow up [11,12]. Validated measurement instruments are of paramount importance in this type of research as well as clinical practice, in order to support our understanding of the role and appropriateness of cosmetic gynecological interventions. However, recent research has shown that measurement instruments in published studies are highly variable, ranging from only 2 validated questionnaires for cosmetic gynecological appearance and surgery (Genital Appearance Satisfaction scale and the Cosmetic Procedure Screening Scale-Labiaplasty) to mostly no outcome measures that fulfil actual subjective or objective standards [2,13].

Cosmetic procedures can be requested by patients with functional or psychological or psychiatric disorders [4], and underlying pathologies should be assessed and managed prior to considering embarking on surgery. The analysis by Crouch et al [14] revealed that women seeking surgery had the same normal-sized labia minora similar to women in the control group not desiring cosmetic gynecological surgery. A combination of shared decision-making and questionnaires evaluating patient expectations might be a favorable approach [15].

Furthermore, psychological well-being and disorders are very difficult to assess and may greatly change with time, so that regret and revisions surgery rates should be reviewed and evaluated over sufficiently long-term follow-up periods [9,16].

The collection and reporting of outcomes and the selection of outcome measures not only in this field but also in various other areas of pelvic floor research has been largely overlooked. The consequence of this is a variety of differing outcomes that make analysis and conclusion drawing across groups of studies through systematic reviews and meta-analyses difficult, and sometimes, impossible.

A COS might increase reporting of important outcomes, reduce the risk of selective outcome–reporting, and increase the feasibility of conducting systematic reviews and meta-analyses [17].

We have developed CHORUS, an International Collaboration for Harmonising Outcomes, Research, and Standards in Urogynecology and Women's Health (https://i-chorus.org/) with representatives from different geographical areas and academic institutions. Specific projects undertaken by CHORUS aim to tackle such limitations in research evidence and current standards. Among other initiatives, a number of systematic reviews on surgical interventions for anterior compartment vaginal prolapse, synthetic mesh procedures for the surgical

treatment of pelvic organ prolapse, childbirth trauma, posterior and apical prolapse surgery, stress incontinence, and chronic pelvic pain have already been completed and published [18-25].

Addressing the variation in treatment protocols, outcome selection, and reporting represents a priority. Aiming to work on the basis of the paradigm of the Outcome Measures in Rheumatology (OMERACT) initiative could help address these issues [26,27].

This project has been prospectively registered with the Core Outcome Measures in Effectiveness Trials (COMET) initiative [28-30] (registration number 1592, Protocol version 1, registration date July 2020) [31]. The Core Outcomes in Women's Health (CROWN) initiative will support the dissemination and implementation of a COS and COMS for cosmetic gynecological interventions to increase the value of primary research, by encouraging future POP trials to report core outcomes and thus contribute high-quality data to future meta-analyses [32].

Guidance for clinicians on how best to care for the healthy woman seeking cosmetic surgery is highly needed. The development of a COS and COMS by a multi-stakeholder group, would help address and guide patient expectations around various treatments and encourage physical and psychological long-term follow-up. COSs are minimum data sets of well-defined, discriminatory, and feasible outcomes that can be measured in a standardized manner and consistently reported [32].

Methods

Methods Overview

Our methodology for the development of the COS and COMS in cosmetic gynecological interventions will be based on the standards set out by the COS-STAD (Core Outcome Set-Standards for Development) recommendations [33-35]. The COS-STAD recommendations suggest that the development of a protocol at the start of the COS development process is advisable, as it increases transparency of the process.

The protocol is also in line with the COMET Initiative Handbook guidelines and other COS development research relevant to women's health, including preeclampsia, endometriosis, stress incontinence, and childbirth trauma [34-37].

Identifying Potential Outcomes

Selection of appropriate outcomes is an essential step of the study design. Clinical studies that evaluate cosmetic gynecological interventions must select outcomes of relevance to key stakeholders and measure them using appropriate instruments.

Mapping all outcomes reported in clinical studies evaluating cosmetic gynecological interventions in women will provide the basis for initializing the process of development of COS. This process is in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement, supported by funders of health research [38]. Data from a new systematic review that is under preparation will be the main basis of our report as none are available on patient outcomes.

In line with our previous work, a list of potential core domains on the variation in outcomes and outcome measures in cosmetic gynecological interventions from randomized trials [18,19,21] and other published research, in order to create a comprehensive inventory of potential outcomes on the basis of literature reviews and group discussions will be drafted. These inventories will form the basis for consideration of potentially eligible outcomes, and outcome measures and will be enriched during focus group consultations and the Delphi process and feedback. The COS will also comprise adverse events (AEs) and contextual factors that are reported in surgical trials. As cosmetic gynecological interventions are not attributable to a recognizable pathology (eg. genital malformation, dermatoses, or acquired disease), the identification of potential outcomes is of utmost importance. The International Society of Aesthetic Plastic Surgery (ISAPS) and the International Urogynecological Association (IUGA) are not prescriptive for the reporting of core outcomes in clinical trials on cosmetic gynecological interventions.

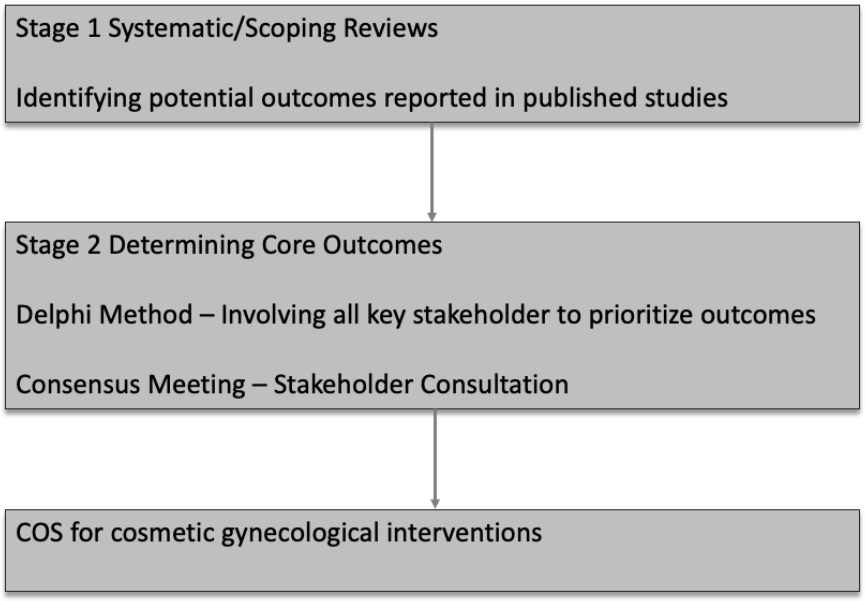
In the second line, data from expert guidelines (EG) and stakeholder opinions (SO) will be included and described in the *Creating an International Group for the Development of a COS for Cosmetic Gynecological Interventions* subsection.

All outcomes and outcome measures reported within the reports will be identified and categorized. Following the steering group's agreement, the outcomes and definitions will be entered into a modified Delphi method.

The first step will be to group different definitions together under the same outcome name. The next step will be to group these outcomes into outcome domains to classify broad aspects of the effects of interventions. Categorization of each outcome definition to an outcome name and of each outcome to an outcome domain will be performed independently by 2 researchers with diverse multi-professional backgrounds.

One way to overcome inconsistent selection, measurement, and divergent reporting of outcomes, is a process (Figure 1) recommended by the COMET Initiative [39]. This process has been successfully applied in several disciplines to develop, disseminate, and implement COS in cosmetic gynecology.

Figure 1. The stages of developing a core outcome set for cosmetic gynecological interventions. COS: core outcome set.



Outcome Inventory

A comprehensive inventory of outcomes, identified by the systematic reviews and analyses of qualitative interviews, as described above, will be developed on the basis of standard methodology we followed in other areas of pelvic floor disorders [40]. Outcome domains will be listed in a database and coded in accordance with the taxonomy proposed by the COMET Initiative.

If there is uncertainty regarding how to classify or present an outcome, consensus of the steering group will be sought. Following the steering group's agreement, the outcome inventory will be entered into the modified Delphi method.

Creating an International Group for the Development of a COS for Cosmetic Gynecological Interventions

An international steering group within CHORUS, including health care professionals from different geographical areas and disciplines; key opinion leaders such as plastic surgeons, urogynecologists, gynecologists, colorectal surgeons, urologists, general practitioners, researchers, policy makers, industry representatives, and professional societies' representatives; and most importantly women with experience of cosmetic gynecological interventions will lead the development of these COS and COMS [41]. In line with methods developed and endorsed by COMET (reference COMET Handbook), key stakeholders performing vulval surgery (self-declaration) or publishing on cosmetic gynecological interventions (randomized clinical trials or systematic reviews that are published in internationally peer-reviewed journals) will be identified, approached, and selected for representativeness via professional societies (ISAPS and IUGA) and the CHORUS website (i-chorus.org and social media). There are no clear recommendations for calculating the required sample [42]; based on previous studies, we will aim to include a minimum of 20 participants from each stakeholder group.

Generation of a List of Potential Core Domains

Potential core outcome domains to be selected and evaluated will comprise patient satisfaction and surgical outcomes and may further include morbidity, quality of life and life impact, resource use and economic impact, pathophysiological and psychological manifestations, choices influence by context, long-term impact, and adverse events [43]. A specific health framework on definitions and domains in cosmetic gynecological medicine is not available yet. The collated COS will not be categorized into primary or secondary outcomes as the prioritization will be designated by future studies. A COS will not preclude measurement of additional outcomes if relevant to a specific trial. Recommendations about the weighting of COS domains, however, will be proposed depending on the data from systematic reviews (SR), EGs, and SO. The category of recommendation will be declared (SR, EG, and SO). These COS and COMS will be applicable to clinical studies evaluating therapeutic interventions for women with cosmetic gynecological procedures.

This group will address the need for the development of effective interventions to improve the outcomes of cosmetic gynecological procedures and the effect these procedures may have on women's quality of life, considering the flaws and weaknesses of current evidence. Updates will be provided on a biyearly basis.

Study Management

The project for developing a COS and COMS for cosmetic gynecological interventions will be supervised by a management team and a steering committee. The management team will meet monthly and organize day-to-day tasks and overall work progress. The management team will include research partners. The steering committee will meet at 6-month intervals and will include an independent chairperson and 2 other independent expert members who can provide advice on methodology and cosmetic gynecology–related issues. There will also be representatives from the management team. The role of the steering committee will be to provide support and guidance.

The designed CHORUS members, from different geographical locations, will directly identify patients or will be helped to contact patients by other health care providers who could have direct contact to patients. Women with experience in cosmetic gynecological interventions will be invited to participate in the study management and oversight process after sending them an informative document.

The question regarding ethics has been considered and addressed in a number of previous COS development projects. It has been suggested that these projects are considered a service evaluation not directly influencing patient care or safety [26,34,35,37,44]. Consent will be sought from all participants involved before their participation in either stakeholder interviews or the Delphi survey. All procedures will be conducted in accordance with the tenets of the Declaration of Helsinki. A "no-response" option will be allowed both for the survey and interactive parts of the study, to ensure responders' right to withhold information. A specific timeframe of the Delphi process will be provided and information concerning the interval of data storage and handling will be made available to all participants.

Modified Delphi Method

The core outcomes will be determined using a modified Delphi method [45], where several surveys are delivered over a series of rounds. The Delphi method consists of sequential web-based surveys that constitute consecutive rounds in an anonymous way. After each round, the group responses are fed back to the respondents who can reconsider their views on the basis of the report of the group views [43]. The modified Delphi method has advantages over less structured consensus methods. Web-based Delphi surveys facilitate international participation and are considered feasible, efficient, and acceptable to the user [46,47].

Round 1

Participants will be asked to register on the internet, provide demographic details, and commit to all 3 rounds. They will be allocated a unique identifier, which will anonymize their responses.

Delphi survey round 1 will contain a list of outcomes to be scored, ordered alphabetically by domains. The list of outcomes will include the option to display a more detailed plain-language description. Participants will be asked to score individual outcomes, using a 7-point Likert Scale, anchored between 1 (not important) and 7 (critical). This scale was created by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group, and it has been widely adopted by COS developers [48]. There will be provision for an option for participants to suggest additional outcomes.

For each outcome, the median (IQR) values of scores will be calculated and summarized graphically for the whole and individual stakeholder group responses, using GraphPad Prism (GraphPad Software). Additional outcomes listed by participants will be reviewed by the outcome committee and, if novel, listed in round 2. The round will close following a 4-week window.

The number of participants in each stakeholder group who respond to round 1 will be assessed at the end of the round. Results will be presented as n (%) values for the following parameters: (1) registrations, (2) respondents who have completed the survey, (3) respondents who completed the round, (4) respondents in each stakeholder group, (5) respondents compared to potential respondents, as identified from the information provided by clinical leads, and (6) new respondents who were not included in original invitation to complete the survey.

Round 2

Participants will be informed regarding the outcome scores from the previous round. After revealing their own score, participants will be invited to rescore each outcome. Any changes in the score from round to round will be noted. The round will close following a 4-week window.

The modified Delphi method encourages repeated reflection and rescoring, promoting whole and stakeholder group convergence upon consensus "core" outcomes [49]. These rounds' results will enable individual outcomes to be classified as shown in Table 1 [42]. These definitions and criteria have been proposed by previous COS developers [17].

The feedback report of the second round will be presented to all participants invited. A priori consensus will be set at 67% of the panel agreeing that a domain will be core, with domains reaching this threshold to be included in this COS. If there are clear discrepancies between stakeholder groups or if controversial arguments emerge, the results will be presented to the Steering Committee for final decisions. Examples exist where patients identified an outcome important to them as a group that might not have been considered by clinicians on their own [17]. Controversial arguments will be reported in the COS and COMS publication on cosmetic gynecological interventions. Round 2's results will also be reviewed by the steering group to consider whether a further Delphi survey round (round 3) is required.

Table 1. Consensus status based on core outcome criteria.

Consensus status	Description	Criteria
Consensus in	Classify as a core outcome	Over 70% of participants in each stakeholder group score this outcome domain "critical" and less than 15% of participants in each stakeholder group score the outcome domain "not important."
Consensus out	Do not classify as a core outcome	Over 70% of participants in each stakeholder group score the outcome domain "not important" and less than 15% of participants in each stakeholder group score the outcome domain "critical."
No consensus	Do not classify as a core outcome	Anything else

Presentation of the COS/COMS

The analyses will be primarily descriptive, with frequency counts provided for the variables. A limited number of analyses for trends within categorical variables (chi-square or Fisher's exact test) will be performed. These analyses examine the relationship between measures of consensus, the different stakeholders, and diagnostic criteria.

Stakeholder Consultation

During this final phase, a consultation chaired by an independent coordinator will be undertaken, with the purpose of selecting outcomes to be validated and included in the COS. In addition, outcomes that do not meet core outcome criteria will be discussed and considered. This consultation will purposefully include various points of view from participants who have completed all rounds of the Delphi survey. During the consensus process, the results from each round of the Delphi survey will be presented. To avoid biased consensus formation among a group of varied participants, the steering committee will consider all opinions [32] in an interactive consultation. To facilitate dissemination and implementation, editors from key journals and funders of cosmetic gynecological research will be invited to participate.

Results

CHORUS aims to develop and sustain a robust research culture and clinical excellence by promoting, conducting, and implementing research that not only contributes to improvements in the knowledge base and patient care, but also informs the development of clinical standards and aims to improve clinical services for patients and users. With the implementations of COS and COMS, comparability of primary research and findings of meta-analyses and systematic reviews will become more scientifically sound and clinically relevant. Commitment to delivering a research agenda that is focused on enhancing clinical and cost-effectiveness and on systematic measures to monitor and improve quality will add value to research and its purpose to inform clinical practice. Funding bodies will not have any involvement in the design, conduction, analysis, and interpretation of data, or in writing the manuscript and the publication process.

Discussion

The efficacy and safety of cosmetic genital procedures, scientific justification, and validation should be confirmed through rigorous evaluation. Meta-analyses based on high-quality trials are highly warranted. The development of core outcome sets (COS) and outcome measures sets (COMS) will form the basis for better quality research to inform clinical practice and support patient-centered care.

As dissemination is the pivotal step in the effective application of trial outcomes, this will be planned in detail, drawing on the necessary expertise, at the outset of any research undertaking. The full report and academic publication will report with reference to the COS–Standards for Reporting statement and checklist [33].

The National Institute for Health and Care Excellence recommends the use of COS when selecting outcomes during evidence scoping and synthesis [39]. As the output of this activity may form the basis of developing guideline recommendations, the COS and COMS could have a direct impact in improving health care for women undergoing cosmetic gynecological interventions. Consensus on both domains and instruments achieved by interdisciplinary groups of different relevant stakeholders, including patients, will improve future health care for women and should be implemented in medical education.

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Authors' Contributions

SDD, GF, JM, and CB conceptualized the study and drafted the manuscript. VN reviewed the literature and drafted the manuscript. MPR reviewed the literature and critically revised the manuscript. GI and JMH critically revised the manuscript. All authors are members of CHORUS, an International Collaboration for Harmonising Outcomes, Research and Standards in Urogynecology and Women's Health (i-chorus.org).

Conflicts of Interest

None declared.

References

1. Liao LM, Creighton SM. Requests for cosmetic genitoplasty: how should healthcare providers respond? BMJ 2007 May 26;334(7603):1090-1092 [FREE Full text] [doi: 10.1136/bmj.39206.422269.BE] [Medline: 17525451]
2. Garcia B, Scheib S, Hallner B, Thompson N, Schiavo J, Peacock L. Cosmetic gynecology-a systematic review and call for standardized outcome measures. Int Urogynecol J 2020 Oct;31(10):1979-1995. [doi: 10.1007/s00192-020-04294-5] [Medline: 32385653]
3. Procedural Statistics. The Aesthetic Society. URL: https://www.surgery.org/media/statistics [accessed 2020-07-25]

4. Özer M, Mortimore I, Jansma EP, Mullender MG. Labiaplasty: motivation, techniques, and ethics. Nat Rev Urol 2018 Mar;15(3):175-189. [doi: 10.1038/nrurol.2018.1] [Medline: 29405204]
5. Zwier S. "What Motivates Her": Motivations for Considering Labial Reduction Surgery as Recounted on Women's Online Communities and Surgeons' Websites. Sex Med 2014 Apr;2(1):16-23 [FREE Full text] [doi: 10.1002/sm2.20] [Medline: 25356297]
6. Joseph AW, Ishii L, Joseph SS, Smith JI, Su P, Bater K, et al. Prevalence of Body Dysmorphic Disorder and Surgeon Diagnostic Accuracy in Facial Plastic and Oculoplastic Surgery Clinics. JAMA Facial Plast Surg 2017 Jul 01;19(4):269-274 [FREE Full text] [doi: 10.1001/jamafacial.2016.1535] [Medline: 27930752]
7. Huayllani M, Eells A, Forte A. Body Dysmorphic Disorder in Plastic Surgery: What to Know When Facing a Patient Requesting a Labiaplasty. Plast Reconstr Surg 2020 Feb;145(2):468e-469e. [doi: 10.1097/PRS.0000000000006490] [Medline: 31985695]
8. Goodman MP, Placik OJ, Matlock DL, Simopoulos AF, Dalton TA, Veale D, et al. Evaluation of Body Image and Sexual Satisfaction in Women Undergoing Female Genital Plastic/Cosmetic Surgery. Aesthet Surg J 2016 Oct;36(9):1048-1057. [doi: 10.1093/asj/sjw061] [Medline: 27084062]
9. Learner HI, Rundell C, Liao L, Creighton SM. 'Botched labiaplasty': a content analysis of online advertising for revision labiaplasty. J Obstet Gynaecol 2020 Oct;40(7):1000-1005. [doi: 10.1080/01443615.2019.1679732] [Medline: 31826680]
10. Boriani F, Giorgini F, Morselli P. Labia Appearance and Patient's Perception: The Importance of Investigating Self-Image, Psychosomatic Suffering, and Expectation for Surgery. Plast Reconstr Surg 2020 Dec;146(6):822e-823e. [doi: 10.1097/PRS.0000000000007402] [Medline: 33234992]
11. Propst K, Ferrando CA. Outcomes of labiaplasty in women with labial hypertrophy. Int Urogynecol J 2021 May;32(5):1247-1251. [doi: 10.1007/s00192-020-04621-w] [Medline: 33245385]
12. Sharp G, Tiggemann M, Mattiske J. A Retrospective Study of the Psychological Outcomes of Labiaplasty. Aesthet Surg J 2017 Mar 01;37(3):324-331. [doi: 10.1093/asj/sjw190] [Medline: 28207030]
13. Sharp G, Maynard P, Hamori C, Oates J, Sarwer D, Kulkarni J. Measuring Quality of Life in Female Genital Cosmetic Procedure Patients: A Systematic Review of Patient-Reported Outcome Measures. Aesthet Surg J 2020 Feb 17;40(3):311-318. [doi: 10.1093/asj/sjz325] [Medline: 31720690]
14. Crouch N, Deans R, Michala L, Liao L, Creighton S. Clinical characteristics of well women seeking labial reduction surgery: a prospective study. BJOG 2011 Nov;118(12):1507-1510. [doi: 10.1111/j.1471-0528.2011.03088.x] [Medline: 21883873]
15. Morselli PG, Lippi A, Giorgini FA, Fabbri E, Pinto V. Informed consent in plastic surgery, evaluation of its effectiveness for mutual satisfaction of patient and doctor: Comparison of methods. J Plast Reconstr Aesthet Surg 2019 Nov;72(11):1847-1855. [doi: 10.1016/j.bjps.2019.05.037] [Medline: 31326321]
16. Bränström R, Pachankis JE. Reduction in Mental Health Treatment Utilization Among Transgender Individuals After Gender-Affirming Surgeries: A Total Population Study. Am J Psychiatry 2020 Aug 01;177(8):727-734. [doi: 10.1176/appi.ajp.2019.19010080] [Medline: 31581798]
17. Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, et al. Developing core outcome sets for clinical trials: issues to consider. Trials 2012 Aug 06;13:132. [doi: 10.1186/1745-6215-13-132] [Medline: 22867278]
18. Durnea CM, Pergialiotis V, Duffy JMN, Bergstrom L, Elfituri A, Doumouchtsis SK, CHORUS, an International Collaboration for Harmonising Outcomes, Research and Standards in Urogynaecology and Women's Health. A systematic review of outcome and outcome-measure reporting in randomised trials evaluating surgical interventions for anterior-compartment vaginal prolapse: a call to action to develop a core outcome set. Int Urogynecol J 2018 Dec;29(12):1727-1745 [FREE Full text] [doi: 10.1007/s00192-018-3781-5] [Medline: 30350116]
19. de Mattos Lourenco TR, Pergialiotis V, Duffy JMN, Durnea C, Elfituri A, Haddad JM, et al. A systematic review on reporting outcomes and outcome measures in trials on synthetic mesh procedures for pelvic organ prolapse: Urgent action is needed to improve quality of research. Neurourol Urodyn 2019 Feb;38(2):509-524. [doi: 10.1002/nau.23871] [Medline: 30431183]
20. Pergialiotis V, Durnea C, Elfituri A, Duffy J, Doumouchtsis S, International Collaboration for Harmonising Outcomes, Research, and Standards in Urogynaecology and Women's Health (CHORUS). Do we need a core outcome set for childbirth perineal trauma research? A systematic review of outcome reporting in randomised trials evaluating the management of childbirth trauma. BJOG 2018 Nov;125(12):1522-1531. [doi: 10.1111/1471-0528.15408] [Medline: 30009461]
21. de Mattos Lourenço TR, Pergialiotis V, Durnea C, Elfituri A, Haddad JM, Betschart C, CHORUS: An International Collaboration for Harmonising Outcomes, Research, and Standards in Urogynaecology and Women's Health. A systematic review of reported outcomes and outcome measures in randomized controlled trials on apical prolapse surgery. Int J Gynaecol Obstet 2019 Apr;145(1):4-11. [doi: 10.1002/ijgo.12766] [Medline: 30671950]
22. Doumouchtsis S, Pookarnjanamorakot P, Durnea C, Zini M, Elfituri A, Haddad J, CHORUS, An International Collaboration for Harmonising Outcomes, Research, and Standards in Urogynaecology and Women's Health (i-chorus.org). A systematic review on outcome reporting in randomised controlled trials on surgical interventions for female stress urinary incontinence: a call to develop a core outcome set. BJOG 2019 Nov;126(12):1417-1422. [doi: 10.1111/1471-0528.15891] [Medline: 31357257]

23. Lourenço TRM, Pergialiotis V, Durnea CM, Elfituri A, Haddad JM, Betschart C, CHORUS: An International Collaboration for Harmonising Outcomes, Research and Standards in Urogynaecology and Women's Health. A systematic review of reported outcomes and outcome measures in randomized trials evaluating surgical interventions for posterior vaginal prolapse to aid development of a core outcome set. Int J Gynaecol Obstet 2020 Mar;148(3):271-281. [doi: 10.1002/ijgo.13079] [Medline: 31814121]
24. Ghai V, Subramanian V, Jan H, Pergialiotis V, Thakar R, Doumouchtsis S, CHORUS: An International Collaboration for Harmonising Outcomes, Research, and Standards in Urogynaecology and Women's Health. A systematic review on reported outcomes and outcome measures in female idiopathic chronic pelvic pain for the development of a core outcome set. BJOG 2021 Mar;128(4):628-634. [doi: 10.1111/1471-0528.16412] [Medline: 32654406]
25. Tsiapakidou S, Nygaard CC, Falconi G, Pape J, Betschart C, Doumouchtsis SK, CHORUS: An International Collaboration for Harmonising Outcomes, Research and Standards in Urogynaecology and Women's Health (i-chorus.org). Systematic review and appraisal of clinical practice guidelines on pelvic organ prolapse using the AGREE II tool. Neurourol Urodyn 2021 Aug;40(6):1402-1413. [doi: 10.1002/nau.24709] [Medline: 34350610]
26. Chiarotto A, Terwee CB, Deyo RA, Boers M, Lin CC, Buchbinder R, et al. A core outcome set for clinical trials on non-specific low back pain: study protocol for the development of a core domain set. Trials 2014 Dec 26;15:511 [FREE Full text] [doi: 10.1186/1745-6215-15-511] [Medline: 25540987]
27. Merkel PA, Aydin SZ, Boers M, Direskeneli H, Herlyn K, Seo P, et al. The OMERACT core set of outcome measures for use in clinical trials of ANCA-associated vasculitis. J Rheumatol 2011 Jul;38(7):1480-1486 [FREE Full text] [doi: 10.3899/jrheum.110276] [Medline: 21724720]
28. Tugwell P, Boers M, Brooks P, Simon L, Strand V, Idzerda L. OMERACT: an international initiative to improve outcome measurement in rheumatology. Trials 2007 Nov 26;8:38 [FREE Full text] [doi: 10.1186/1745-6215-8-38] [Medline: 18039364]
29. Tugwell P, Boers M. Developing consensus on preliminary core efficacy endpoints for rheumatoid arthritis clinical trials. OMERACT Committee. J Rheumatol 1993 Mar;20(3):555-556. [Medline: 8478872]
30. Tugwell P, Boers M. OMERACT conference on outcome measures in rheumatoid arthritis clinical trials: introduction. J Rheumatol 1993 Mar;20(3):528-530. [Medline: 8478864]
31. Doumouchtsis S. Developing core outcome sets (COS) and core outcome measures sets (COMS) in cosmetic gynaecological interventions. Comet Initiative 2020. 2020 Jul 31. URL: https://comet-initiative.org/Studies/Details/1592 [accessed 2021-10-25]
32. Khan K, Chief Editors of Journals participating in The CROWN Initiative. The CROWN Initiative: Journal editors invite researchers to develop core outcomes in women's health. Best Pract Res Clin Obstet Gynaecol 2019 May;57:e1-e4 [FREE Full text] [doi: 10.1016/j.bpobgyn.2014.06.002] [Medline: 25134450]
33. Kirkham JJ, Davis K, Altman DG, Blazeby JM, Clarke M, Tunis S, et al. Core Outcome Set-STAndards for Development: The COS-STAD recommendations. PLoS Med 2017 Nov;14(11):e1002447 [FREE Full text] [doi: 10.1371/journal.pmed.1002447] [Medline: 29145404]
34. Rada M, Pergialiotis V, Betschart C, Falconi G, Haddad J, Doumouchtsis S. A protocol for developing, disseminating, and implementing a core outcome set for stress urinary incontinence. Medicine (Baltimore) 2019 Sep;98(37):e16876 [FREE Full text] [doi: 10.1097/MD.0000000000016876] [Medline: 31517813]
35. Doumouchtsis SK, Rada MP, Pergialiotis V, Falconi G, Haddad JM, Betschart C. A protocol for developing, disseminating, and implementing a core outcome set (COS) for childbirth pelvic floor trauma research. BMC Pregnancy Childbirth 2020 Jun 26;20(1):376 [FREE Full text] [doi: 10.1186/s12884-020-03070-z] [Medline: 32591018]
36. Duffy JM, van 't Hooft J, Gale C, Brown M, Grobman W, Fitzpatrick R, International Collaboration to Harmonise Outcomes for Pre-eclampsia (iHOPE). A protocol for developing, disseminating, and implementing a core outcome set for pre-eclampsia. Pregnancy Hypertens 2016 Oct;6(4):274-278. [doi: 10.1016/j.preghy.2016.04.008] [Medline: 27939467]
37. Hirsch M, Duffy JMN, Barker C, Hummelshoj L, Johnson NP, Mol B, International Collaboration to Harmonize Outcomes and Measures for Endometriosis (iHOME). Protocol for developing, disseminating and implementing a core outcome set for endometriosis. BMJ Open 2016 Dec 21;6(12):e013998 [FREE Full text] [doi: 10.1136/bmjopen-2016-013998] [Medline: 28003300]
38. Chan A, Tetzlaff J, Gøtzsche PC, Altman D, Mann H, Berlin J, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 2013 Jan 08;346:e7586 [FREE Full text] [doi: 10.1136/bmj.e7586] [Medline: 23303884]
39. Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, et al. The COMET Handbook: version 1.0. Trials 2017 Jun 20;18(Suppl 3):280 [FREE Full text] [doi: 10.1186/s13063-017-1978-4] [Medline: 28681707]
40. Rada MP, Jones S, Falconi G, Milhem Haddad J, Betschart C, Pergialiotis V, CHORUS: An International Collaboration for Harmonising Outcomes, Research and Standards in Urogynaecology and Women's Health. A systematic review and meta-synthesis of qualitative studies on pelvic organ prolapse for the development of core outcome sets. Neurourol Urodyn 2020 Mar;39(3):880-889. [doi: 10.1002/nau.24297] [Medline: 32040864]
41. Brooks P, Boers M, Simon LS, Strand V, Tugwell P. Outcome measures in rheumatoid arthritis: the OMERACT process. Expert Rev Clin Immunol 2007 May;3(3):271-275. [doi: 10.1586/1744666X.3.3.271] [Medline: 20477671]

42. Sinha IP, Smyth RL, Williamson PR. Using the Delphi technique to determine which outcomes to measure in clinical trials: recommendations for the future based on a systematic review of existing studies. PLoS Med 2011 Jan 25;8(1):e1000393 [FREE Full text] [doi: 10.1371/journal.pmed.1000393] [Medline: 21283604]
43. Chiarotto A, Ostelo RW, Turk DC, Buchbinder R, Boers M. Core outcome sets for research and clinical practice. Braz J Phys Ther 2017;21(2):77-84 [FREE Full text] [doi: 10.1016/j.bjpt.2017.03.001] [Medline: 28460714]
44. Ma C, Panaccione R, Fedorak RN, Parker CE, Khanna R, Levesque BG, et al. Development of a core outcome set for clinical trials in inflammatory bowel disease: study protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey. BMJ Open 2017 Jun 09;7(6):e016146 [FREE Full text] [doi: 10.1136/bmjopen-2017-016146] [Medline: 28601837]
45. Galanis P. The Delphi method. Arch Hell Med 2018;35(4):564-570.
46. Nelson RL. Systematic reviews and research waste. Lancet 2016 Jan 09;387(10014):124. [doi: 10.1016/S0140-6736(15)01355-0] [Medline: 26841994]
47. Glasziou P, Altman DG, Bossuyt P, Boutron I, Clarke M, Julious S, et al. Reducing waste from incomplete or unusable reports of biomedical research. Lancet 2014 Jan 18;383(9913):267-276. [doi: 10.1016/S0140-6736(13)62228-X] [Medline: 24411647]
48. Gopalakrishna G, Mustafa RA, Davenport C, Scholten RJ, Hyde C, Brozek J, et al. Applying Grading of Recommendations Assessment, Development and Evaluation (GRADE) to diagnostic tests was challenging but doable. J Clin Epidemiol 2014 Jul;67(7):760-768 [FREE Full text] [doi: 10.1016/j.jclinepi.2014.01.006] [Medline: 24725643]
49. Boog B. Qualitative Research Practice. JSI 2005 Jun 29;14(2):47. [doi: 10.18352/jsi.39]

Abbreviations

AE: adverse event
CHORUS: An International Collaboration for Harmonising Outcomes, Research and Standards in Urogynecology and Women's Health
COMET: Core Outcome Measures in Effectiveness Trials
COMS: Core Outcome Measure Set
COS: Core Outcome Set
COS-STAD: Core Outcome Set-Standards for Development
CROWN: Core Outcomes in Women's Health
EG: expert guidelines
GRADE: Grading of Recommendations Assessment, Development and Evaluation
ISAPS: International Society of Aesthetic Plastic Surgery
IUGA: International Urogynecological Association
SO: stakeholder opinions
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SR: systematic review

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Corrigenda and Addenda

Correction: The Good Food for Learning Universal Curriculum-Integrated Healthy School Lunch Intervention: Protocol for a Two-Year Matched Control Pre-Post and Case Study

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Related Article:

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In "The Good Food for Learning Universal Curriculum-Integrated Healthy School Lunch Intervention: Protocol for a Two-Year Matched Control Pre-Post and Case Study" (JMIR Res Protoc 2021;10(9):e30899), one error was noted.

In the originally published paper, one author, Sylvana Tu, was not included in the list of authors. Sylvana Tu has now been included in the authorship list between authors Sinikka Elliott and Brent Hills. Sylvana Tu's author affiliation has also been added as follows:

Saskatchewan Population Health Evaluation and Research Unit, University of Saskatchewan, Saskatoon, SK, Canada

This affiliation has been added as affiliation 9 in the corrected paper, and the remaining affiliations have been renumbered accordingly.

The full list of authorship and affiliations was as follows in the originally published paper:

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This has been corrected to:

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The correction will appear in the online version of the paper on the JMIR Publications website on November 3, 2021, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Text Messaging Versus Email Messaging to Support Patients With Major Depressive Disorder: Protocol for a Randomized Hybrid Type II Effectiveness-Implementation Trial

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Related Article:

Correction of: https://www.researchprotocols.org/2021/10/e29495

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In "Text Messaging Versus Email Messaging to Support Patients With Major Depressive Disorder: Protocol for a Randomized Hybrid Type II Effectiveness-Implementation Trial" (JMIR Res Protoc 2021;10(10):e29495) the authors noted two errors.

1. In the originally published paper, author affiliations 1 and 2 were numbered incorrectly. The numbering of these affiliations has been switched in the corrected paper.

2. The equal contribution symbol '*' for author Felix Osiogo has been removed.

The complete list of authorship and affiliations was originally published as follows:

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This has been corrected to the following:

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The correction will appear in the online version of the paper on the JMIR Publications website on November 5, 2021, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: National Disability Insurance Scheme and Lived Experience of People Presenting to the Emergency Department: Protocol for a Mixed Methods Study

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Related Article:

Correction of: https://www.researchprotocols.org/2021/11/e33268

(JMIR Res Protoc 2021;10(11):e34866) doi:10.2196/34866

KEYWORDS

Lived experience; National Disability Insurance Scheme; emergency department; psychosocial disability; communication pathways

In "National Disability Insurance Scheme and Lived Experience of People Presenting to the Emergency Department: Protocol for a Mixed Methods Study" (JMIR Res Protoc 2021;10(11):e33268) the authors noted some errors. The following changes have been made to correct these errors:

Title

In the originally published article, the title read as follows:

> *National Disability Insurance Scheme and the Lived Experience of Psychosocial Disability for People Presenting to the Emergency Department: Protocol for a Mixed Methods Study*

In the corrected version, the title has been revised to:

> *National Disability Insurance Scheme and Lived Experience of People Presenting to the Emergency Department: Protocol for a Mixed Methods Study*

Author metadata

In the originally published article, degrees for author Nicholas Gerard Procter appeared as follows:

> *BASoc, PsycNurs, MBA, PhD*

In the corrected version, these degrees are revised as follows:

> *BA, MBA, PhD*

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Abstract

- Under *Background*, the sentence "There are missed opportunities for early intervention and care continuity that could potentially inform ED practitioners to revise current

practices" was changed to "There are missed opportunities for early support and care continuity that could potentially inform ED practitioners to revise current practices."
- Under *Objective*, the sentence "…to gain knowledge from ED clinicians around processes for continuity of care with this population group" was changed to "…to gain knowledge from ED clinicians around processes for improving continuity of care and consumer experience."
- Under *Methods*, the sentence "Interviews will focus on the lived experience voice exploring potential indicators that have led to an ED presentation, alongside an analysis of associated clinical and administrative documentation and communications" was changed to "Interviews will focus on the lived experience voice exploring concerns that have led to an ED presentation, alongside an analysis of associated clinical and administrative documentation and communications."
- Under *Conclusions*, the sentence "…pathways of care for this vulnerable group of people, while also informing health policy" was changed to "…pathways of care for consumers and carers, while also informing health policy."

Introduction

- In the first paragraph, the sentence "In South Australia, there were 519,607 total presentations at EDs, with 23,739 (4.5%) presentations classified as "Mental and Behavioural Disorders," which represents a 1% increase compared with the national average" was changed to "In South Australia, there were 519,607 total presentations at EDs, with 23,739 (4.5%) of peoples' presentations classified due to mental health–related distress which represents a 1% increase compared with the national average."
- In the first paragraph, the sentence "…disconnection with support networks, or the inability to navigate access across multiple services. Those with a PSD…" was changed to "…disconnection with support networks, or difficulties navigating access across multiple services. Those living with a PSD…."
- In the second paragraph, the sentence "Those in a mental health crisis periodically have the longest wait times in the ED and, at times, leave before treatment is completed. Alternatively, they could present to the ED…" was changed to "People experiencing mental health crisis periodically have the longest wait times in the ED and, at times, leave before care is completed. Alternatively, consumers can present to the ED…."
- In the second paragraph, the sentence "Postdischarge from clinical care represents a time of greater risk of dying by suicide, possibly due to inadequate or a rationing of care. Conversely, positive experiences of continuity of care practices contribute to favorable patient outcomes" was changed to "Postdischarge from clinical care represents a time of greater risk of dying by suicide, reflecting critical concerns about the quality of support and care being offered. Generally, continuity of care recognizes that consumers have relational continuity with providers who are trusted, provide personalized responses, and have shared understanding of the person's goals."
- In the third paragraph, the sentence "Lack of psychiatric beds in hospitals can also be a cause for delayed treatment" was changed to "Lack of psychiatric beds in hospitals can also be a cause for delayed care."
- In the third paragraph, the sentence "As the numbers of psychiatric beds are reducing and patients are being increasingly discharged from the ED to home (to be cared for by community services), the aim of this study is to discover how strategies used for implementing communication pathways contribute to continuity of care for this population group" was changed to "As the numbers of psychiatric beds are reducing and consumers are being increasingly discharged from the ED to home (to be supported by community services), the aim of this study is to discover how strategies used for implementing communication pathways contribute to continuity of care and improved experience."
- In the fourth paragraph, the sentence "…services and outcomes for patients" was changed to "…services and person-centered, or -led outcomes."

Methods

- Under *Aims*, the sentence "PSD was soon added to the NDIS, with streamlined access for those with a PSD implemented in April 2019. A primary focus of this study will be to understand and clarify the preferred communication pathways between the NDIS, ED, and those with a PSD NDIS plan. To inform health policy, this study will discover and interpret human behavior, perceptions, and the meaning individuals make of their experiences…" was changed to "PSD was soon added to the NDIS, with streamlined access for people with a PSD implemented in April 2019. A primary focus of this study will be to understand and clarify the preferred communication pathways between the NDIS, ED, and consumers with a PSD NDIS plan. To inform health policy, this study will discover and interpret the meaning individuals make of their experiences…."
- Under *Aims*, the sentence "…mental health community support services at transfer of care for those with mental health concerns or who are in suicidal crisis?" was changed to "…mental health community support services for people with mental health concerns or who are in suicidal crisis?"
- Under *Research Questions*, in the first paragraph, the phrase "with those with lived experience" was changed to "with people with lived experience."
- Under *Research Questions*, the first question "How do those with lived experience, carers, and families experience service integration and coordination across emergency care and their NDIS providers? Are there signs and/or behaviors that 1. NDIS providers should be alert to prior to clients presenting to the ED? Can awareness of these signs and/or behaviors be a catalyst to prevent an ED presentation?" was revised as "How do those with lived experience, carers, and families experience service integration and coordination across emergency care and their NDIS providers? Are there concerns and preferences that 1. NDIS providers should be alert to prior to clients presenting to the ED? Can awareness

of these concerns and preferences be a catalyst to prevent an ED presentation?"
- Under *Study Design*, the sentence "The phenomena to be discovered and interpreted for this study are:…" was changed to "The study is focused on exploring and interpreting…."
- Under *Study Design*, the sentence "Data collection will first aim to discover the lived experience voice…" was changed to "Data collection will first aim to elicit the lived experience voice…."
- Under *Study Design*, the sentence "Primarily, the lived experience interviews and of NDIS support workers/coordinators (participant group 2) with interviews and of NDIS…" was changed to "Primarily, lived experience perspectives, including both consumer and carer perspectives will be generated via interviews and NDIS…."

Table 1

- In Table 1, under column *Exclusion criteria* and row *1*, the phrase "Anyone that is unwell and unable to give informed consent;" was changed to "Anyone that is unable to give informed consent;"

Results

- The first sentence "The results of this study will provide insight for strengthening discharge communication pathways to enhance continuity of care to improve connection with community mental health services and outcomes for patients" was changed to "The results of this study will provide insight for strengthening discharge communication pathways between EDs and community mental health services so that these reflect person-centered and person-led care outcomes."

Discussion

- Under *Conclusion*, the sentence "…lived experience to stay well and to inform health policy" was changed to "…lived experience to have improved voice and influence health policy."

The corrections will appear in the online version of the paper on the JMIR Publications website on November 25, 2021, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Protocol

Quality of Primary Care for the Adult Population With Autism Spectrum Disorder: Protocol for a Scoping Review

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Abstract

Background: A strong primary care system is vital to overall health. Research on the primary care of people with autism spectrum disorder (ASD) has mostly focused on children. A synthesis of the existing literature related to the quality of primary care for the adult population with ASD would elucidate what is known about the topic as well as inform future research and clinical practice.

Objective: The purpose of our scoping review is to describe what is known about the quality of primary care for adults with ASD and identify knowledge gaps.

Methods: Prior to beginning the literature search, we reviewed literature related to defining both primary care and primary care quality to establish the context and concept of the research question. The search strategy was designed and executed by a research librarian. The MEDLINE, CINAHL, EMBASE, PsycINFO, and ProQuest Dissertations and Theses databases were searched for relevant literature. Grey literature will include relevant reports from government websites and associations with a focus on ASD. Two members of the research team will independently screen the academic and grey literature. Quantitative, qualitative, or mixed methods study designs involving the quality of primary care services or patient-centered care for adults with ASD are eligible for inclusion in our scoping review. Studies that make it past the full-text review will undergo data extraction and quality appraisal by 2 independent reviewers. The data extraction results will be presented in a tabular format to clearly present what is known about the quality of primary care for adults with ASD; this table will be accompanied by a narrative synthesis. Literature selected for extraction will be coded for themes, which will form the basis of a thematic synthesis. The scoping review will follow the guidance proposed by the Joanna Briggs Institute.

Results: The search of electronic databases was conducted in October 2020, and it returned 2820 results. This research is still in progress. The results from our scoping review are expected to be available by fall 2021.

Conclusions: The results from our scoping review will be useful for guiding future research on the quality of primary care for adults with ASD.

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KEYWORDS

autism spectrum disorder; primary care; family physician; quality; scoping review; protocol

Introduction

Background

Autism spectrum disorder (ASD) was first described in 1943 by Kanner [1]. In terms of presentation, ASD symptoms fall along a spectrum but often involve deficits in reciprocal social interaction and communication as well as the presence of restrictive and repetitive behaviors [2,3]. The global prevalence of ASD is estimated to be 1 in 160 persons [4]. It has been noted that people with ASD have poorer health outcomes and use the health care system differently from the general population [5,6]. Primary care providers are often an individual's first point of contact with the health care system, and they facilitate access to additional health care services [7]. The majority of ASD research has focused on children, and as such, most primary care research related to ASD occurs in a pediatric care setting. There is little known about how ASD in adulthood is managed within the adult primary care system. This represents a significant gap in the literature, as people with ASD have a high number of physical and psychiatric comorbidities, which may worsen as they continue to age [5]. The existing literature on the primary care of adults with ASD must be examined to guide future research in this field.

There has been much research on defining the attributes of primary care and the quality of care [7-9]. One framework suggests that there are 2 main measures of quality—accessibility and effectiveness [7]. Under this framework, effectiveness is broken down into the effectiveness of clinical care and patient-centeredness [7]. Similarly, one systematic review indicated that patient-centeredness and the quality of the following primary care services are indicative of primary care quality: the prescribing behaviors of primary care providers, diagnosis and treatment in primary care, the management of chronic diseases, mental health care, maternal and child health care, preventive care, and health promotion [8]. Patient-centered care is "an approach to practice established through the formation and fostering of healthful relationships between all care providers, service users and others significant to them in their lives…underpinned by values of respect for persons, individual right to self-determination, mutual respect and understanding" [10]. The focus of these frameworks on clinical care and patient-centered care makes them appropriate for the study of ASD due to the medical complexities and interpersonal deficits associated with ASD.

The objective of our scoping review is to investigate the evidence related to the quality of primary care for adults with ASD. The study will review literature involving an assessment of primary care quality for adults with ASD, including assessments of the quality of the clinical care provided as well as the quality of interpersonal interactions among care providers, patients, and patients' families [7,11]. This conceptualization will guide the screening and extraction of the literature. As indicated by the Joanna Briggs Institute, scoping reviews are an appropriate approach for synthesizing existing evidence and identifying gaps in available knowledge [12]. Furthermore, a preliminary literature search returned few literature results. This undermined the feasibility of a systematic review.

As ASD is a lifelong condition, individuals diagnosed with ASD will inevitably encounter the adult primary care system. The core features of ASD include difficulties with social interaction and communication, which can complicate the receipt of medical care. Physicians' lack of understanding of ASD, as well as poor communication with health care providers, presents barriers to health care for adults with ASD [13]. This review may shed light on whether the current adult primary care system is meeting the needs of adults with ASD, which in turn may inspire the design and evaluation of appropriate care models.

Review Questions

Our main research question is as follows: what is known about the quality of primary care for the adult population (aged ≥18 years) with a diagnosis of ASD receiving care in the adult primary care system? The following are our secondary research questions: (1) what types of patient-centered health or health service measures have been reported in the literature related to the primary care of adults with ASD and (2) what are the evidence gaps related to the quality of primary care for adults with ASD?

Methods

This paper describes a scoping review protocol that follows the guidance proposed by the Joanna Briggs Institute [12].

Inclusion Criteria

The population, concept, and context approach was used to guide the construction of the protocol inclusion criteria [12].

Participants

Our scoping review will include studies involving individuals with ASD who are over the age of 18 years. In terms of presentation, autism symptoms fall along a spectrum but often involve deficits in reciprocal social interaction and communication as well as the presence of restrictive and repetitive behaviors; symptoms must be present "in the early developmental period" [2,3]. To optimize the sensitivity of the search strategy and ensure that all articles related to ASD are included in our study, the search strategy was not restricted to articles involving individuals with a formal diagnosis of ASD. The ASD definitions that were identified in each individual study were used to guide the literature screening and extraction process.

Concept

All studies that include an assessment of primary care quality will be included in the scoping review. To assess primary care quality, we will include any literature assessing patient-centered care as well as the quality of primary care services (ie, prescribing behavior, diagnosis and treatment, the management

of chronic diseases, mental health care, maternal and child health care, health promotion, and preventive care) [8].

Patient-centered care is a complex concept. This scoping review will use a broad definition of patient-centered care and include all studies examining concepts related to patients' relationships with care providers, patient and family involvement, and contexts in which care is delivered [10,11,14]. Literature with structured or unstructured measures of patient-centered care will be included.

Context

The Institute of Medicine defines primary care as "the provision of integrated, accessible health care services by clinicians who are accountable for addressing a large majority of personal health care needs, developing a sustained partnership with patients, and practicing in the context of family and community" [15]. In this definition, a clinician "has direct contact with patients and may be a physician, nurse practitioner, or physician assistant" [15]. For the purposes of this review, included studies must indicate that the main provider of primary care is a family physician, general practitioner, internist, or advanced practice nurse (eg, a nurse practitioner) [16]. This scoping review will also include solo and group practice models, provided that the primary responsible provider is one of the provider types listed above. According to the Institute of Medicine, primary care can occur in a variety of health care settings (eg, clinicians' offices, nursing homes, schools, etc) [15]. The scoping review will include studies in which primary care was delivered in a clinic setting (eg, a walk-in clinic) or during a home visit. Although the population and context of interest for this scoping review include young adults with ASD who are transitioning to adult primary care, studies specific to the process of transitioning from pediatric care to adult care will be excluded.

Types of Studies

Our scoping review will consider quantitative, qualitative, and mixed methods study designs for inclusion. Original journal articles, including doctorate theses, as well as grey literature will be considered in this scoping review. Editorials, opinion papers, conference abstracts, and policy analyses will be excluded. There will be no restrictions on the language or year of publication during the literature search. All abstracts will be considered for a full-text review. If an article that is considered for the full-text review is not available in English, then a translation will be requested.

Search Methods

Search Strategy

The search strategy for the retrieval of studies from electronic bibliographic databases and grey literature sources was designed by one of the authors (AF)—a research librarian. The initial search will involve a keyword search of MEDLINE (via Ovid). The titles and abstracts of retrieved articles will be reviewed to identify appropriate keywords and index terms. The final search will be designed in MEDLINE (via Ovid), translated, and conducted in select databases. Table 1 presents the full MEDLINE search strategy. Backward and forward citation searching will be performed on articles that are selected for data extraction. If required, the authors of selected studies will be contacted to obtain full articles or further information.

Table 1. Ovid MEDLINE search strategy.[a]

Search number	Search strings	Number of studies found
1	*Primary Health Care*	78,551
2	*Physicians/ or Physician Assistants*	95,184
3	*exp General Practice/ or exp General Practitioners*	81,530
4	*exp Primary Care Nursing*	496
5	*office visits/ or community mental health services/ or ambulatory care/ or community health services/ or community health nursing/ or community medicine*	118,668
6	*((primary or basic) adj2 (healthcare or care)).tw,kf*	150,228
7	*((general or family) adj (physician or physicians or doctor or doctors or practitioner or practitioners or practice)).tw,kf.*	105,743
8	*family medicine.tw,kf.*	11,093
9	*((physician or doctor or physicians or doctors) adj (assistant or assistants or extender or extenders)).tw,kf.*	4590
10	*(internist or internists).tw,kf.*	7311
11	*nurse practitioners/ or family nurse practitioners/*	17,764
12	*nurse specialists/ or nurse clinicians/*	8429
13	*(nurse adj (specialist* or practitioner* or clinician*)).tw,kf.*	16,172
14	*walk in clinic.tw,kf*	265
15	*advanced practice registered nurse.tw,kf*	193
16	*first contact.tw,kf.*	2522
17	*exp child development disorders, pervasive/*	36,166
18	*(autis* or asperger* or ASD or pervasive development disorder*).tw,kf.*	57,925
19	17 *or* 18	61,672
20	1 *or* 2 *or* 3 *or* 4 *or* 5 *or* 6 *or* 7 *or* 8 *or* 9 *or* 10 *or* 11 *or* 12 *or* 13 *or* 14 *or* 15 *or* 16	507,395
21	19 *and* 20	820

[a]The date of search was October 22, 2020.

Information Sources

The databases that will be searched will include MEDLINE (via Ovid), CINAHL (via EBSCO), EMBASE (via Embase.com), PsycINFO (via EBSCO), and ProQuest Dissertations and Theses. The search for grey literature will include searching for reports on the websites of departments and ministries of health and associations with a focus on ASD. This will help us to identify reports related to primary care for adults with ASD.

Study Selection

After the completion of the literature search, the research librarian will remove any duplicate citations and upload the remaining citations into Covidence—a web-based software program for managing literature reviews [17]. By using Covidence, 2 team members (SMA and AW) will independently assess the results of the published and grey literature searches. The same screening criteria will be used for all types of included evidence. In the first phase, the titles and abstracts of all records will be assessed against the following screening questions: (1) was a quantitative, qualitative, or mixed methods study design used; (2) do the study's participants involve or reference adults with ASD; (3) does the study involve the receipt of health care from a primary care clinician (family physician, general practitioner, internist, or advanced practice nurse) in a primary care setting (clinic or home visit); and (4) is there an assessment of the quality of clinical services or patient-centered care? To maximize the inclusion of relevant studies, a title or abstract that appears to meet all screening criteria but lacks sufficient detail for fully assessing a study's eligibility will move forward to the full-text review. All discrepancies about whether a study meets the inclusion criteria will be resolved by consensus; in cases where a consensus cannot be reached, a third team member will be consulted.

Prior to the initial screening phase, the screening questions will be pilot-tested by the two reviewers using a sample of 50 articles retrieved from the MEDLINE (Ovid) database. The team members will meet weekly to discuss discrepancies and make modifications to the eligibility criteria and definitions guiding the review. Once ≥75% agreement is achieved, the initial phase of screening will commence [12].

The next phase of screening will involve reviewing the full texts of all retained citations by using the same screening questions. Disagreements about study inclusion will be resolved by a third team member (SA). The reasons for exclusion will be documented. The results of the search and screening will be reported in the final scoping review and presented in a PRISMA

(Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [18].

Although scoping reviews do not generally include an appraisal of the quality of included literature [12,18], studies that are included in our scoping review will undergo critical appraisal. A quality appraisal will add another layer to the findings related to research gaps in the primary care of adults with ASD and thus better direct future research endeavors. Included studies will be appraised by using the 2018 version of the Mixed Methods Appraisal Tool [19]—a reliable tool that can be applied to the appraisal of quantitative, qualitative, and mixed methods study designs [19-21].

Data Extraction

Two reviewers will use a tool designed by the study team to independently extract information from sources based on predefined criteria. The tool is displayed in Multimedia Appendix 1. The effectiveness of clinical care and the effectiveness of patient-centered care are the aspects of quality that will be extracted. Following the extraction of data from the first 2 included sources, the two reviewers will meet to determine whether the tool extracts all relevant information and modify the tool as necessary before resuming the review and extraction of the remainder of the sources [12].

Data Analysis and Presentation

We will evaluate the number of studies related to the quality of primary care for adults with ASD. We will describe the trends in the studied sample, the study designs, the aspects of quality that were measured, and the methods of quality assessment. The results of the scoping review will be presented in a table, which will be accompanied by a narrative synthesis that will connect the results to the research objectives of the scoping review [12]. The narrative synthesis will involve a summary and description of the findings of the extracted studies. Our scoping review will use a data-based convergent synthesis design whereby all included studies will be analyzed by using a qualitative approach (ie, thematic synthesis) [22]. If required, data transformation will be performed. The analysis will be carried out by one author (SMA) and validated by another author (AW). Qualitative data analysis software will be used to code the included literature for themes. These themes will form the basis of the qualitative thematic synthesis. The results will be reported by using the PRISMA scoping review reporting guidelines [18].

Results

The search of electronic databases was conducted in October 2020. A total of 2820 results were retrieved, of which 34 were identified as duplicates. Our scoping review was in the full-text screening phase in February 2021. Data extraction and thematic synthesis will occur during the summer of 2021. The completed scoping review is expected to be submitted for publication in December 2021.

Discussion

Our scoping review will examine the available evidence related to the quality of primary care for adults with ASD and seek to identify gaps in existing knowledge. The scoping review protocol presented in this paper is novel; to our knowledge, no review has been conducted on the quality of primary care services for the adult population with ASD [23-25]. Reviews that focus on health care for adults with ASD have been specific to access to health care and not to the quality of the services received [13,26,27]. This scoping review will identify gaps in the literature and provide insight into future research needs related to the provision of quality primary care for adults with ASD.

Acknowledgments

This protocol and the subsequent review will contribute toward the primary author's (SMA) doctoral degree. The review is being supported through grants from the Janeway Research Foundation, Mitacs, International Grenfell Association and Research & Graduate Studies Office, Faculty of Medicine.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Data extraction form.
[DOCX File , 15 KB - resprot_v10i11e28196_app1.docx]

References

1. Kanner L. Autistic disturbances of affective contact. Nervous Child 1943;2:217-250.
2. American Psychiatric Association. Neurodevelopmental Disorders. In: Diagnostic and statistical manual of mental disorders, 5th edition. Arlington, Virginia: American Psychiatric Association; 2013.
3. World Health Organization. Mental and behavioural disorders. In: International Statistical Classification of Diseases and Related Health Problems, 10th Revision. Geneva, Switzerland: World Health Organization; 2010.
4. Elsabbagh M, Divan G, Koh YJ, Kim YS, Kauchali S, Marcín C, et al. Global prevalence of autism and other pervasive developmental disorders. Autism Res 2012 Jun;5(3):160-179 [FREE Full text] [doi: 10.1002/aur.239] [Medline: 22495912]

5. Croen LA, Zerbo O, Qian Y, Massolo ML, Rich S, Sidney S, et al. The health status of adults on the autism spectrum. Autism 2015 Oct;19(7):814-823. [doi: 10.1177/1362361315577517] [Medline: 25911091]
6. Schendel DE, Overgaard M, Christensen J, Hjort L, Jørgensen M, Vestergaard M, et al. Association of psychiatric and neurologic comorbidity with mortality among persons with autism spectrum disorder in a Danish population. JAMA Pediatr 2016 Mar;170(3):243-250. [doi: 10.1001/jamapediatrics.2015.3935] [Medline: 26752506]
7. Campbell SM, Roland MO, Buetow SA. Defining quality of care. Soc Sci Med 2000 Dec;51(11):1611-1625. [doi: 10.1016/s0277-9536(00)00057-5] [Medline: 11072882]
8. Kringos DS, Boerma WGW, Hutchinson A, van der Zee J, Groenewegen PP. The breadth of primary care: a systematic literature review of its core dimensions. BMC Health Serv Res 2010 Mar 13;10:65 [FREE Full text] [doi: 10.1186/1472-6963-10-65] [Medline: 20226084]
9. Lévesque JF, Haggerty JL, Burge F, Beaulieu MD, Gass D, Pineault R, et al. Canadian experts' views on the importance of attributes within professional and community-oriented primary healthcare models. Healthc Policy 2011 Dec;7(Spec Issue):21-30 [FREE Full text] [Medline: 23205033]
10. McCormack B, McCance T, Klopper H. Person-Centred Practice in Nursing and Health Care: Theory and Practice (Second Edition). West Sussex, England: Wiley Blackwell; 2017:17-60.
11. Kitson A, Marshall A, Bassett K, Zeitz K. What are the core elements of patient-centred care? A narrative review and synthesis of the literature from health policy, medicine and nursing. J Adv Nurs 2013 Jan;69(1):4-15. [doi: 10.1111/j.1365-2648.2012.06064.x] [Medline: 22709336]
12. Peters M, Godfrey C, McInerney P, Munn Z, Tricco A, Khalil H. Chapter 11: Scoping reviews. In: Aromataris E, Munn Z, editors. JBI Manual for Evidence Synthesis. Adelaide, Australia: Joanna Briggs Institute; 2020.
13. Mason D, Ingham B, Urbanowicz A, Michael C, Birtles H, Woodbury-Smith M, et al. A systematic review of what barriers and facilitators prevent and enable physical healthcare services access for autistic adults. J Autism Dev Disord 2019 Aug;49(8):3387-3400 [FREE Full text] [doi: 10.1007/s10803-019-04049-2] [Medline: 31124030]
14. de Silva D. Helping Measure Person-Centred Care: A Review of Evidence About Commonly Used Approaches and Tools Used to Help Measure Person-Centred Care. London, England: The Health Foundation; 2014:11-39.
15. Institute of Medicine, Committee on the Future of Primary Care. In: Donaldson MS, Yordy KD, Lohr KN, Vanselow NA, editors. Primary Care: America's Health in a New Era. Washington, D.C: The National Academies Press; 2000:33-36.
16. Primary care. American Academy of Family Physicians. URL: https://www.aafp.org/about/policies/all/primary-care.html [accessed 2020-09-15]
17. Covidence - Better systematic review management. Covidence. URL: https://www.covidence.org/ [accessed 2021-10-20]
18. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and explanation. Ann Intern Med 2018 Oct 02;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
19. Hong QN, Fàbregues S, Bartlett G, Boardman F, Cargo M, Dagenais P, et al. The Mixed Methods Appraisal Tool (MMAT) version 2018 for information professionals and researchers. Education for Information 2018 Dec 18;34(4):285-291. [doi: 10.3233/EFI-180221]
20. Pace R, Pluye P, Bartlett G, Macaulay AC, Salsberg J, Jagosh J, et al. Testing the reliability and efficiency of the pilot Mixed Methods Appraisal Tool (MMAT) for systematic mixed studies review. Int J Nurs Stud 2012 Jan;49(1):47-53. [doi: 10.1016/j.ijnurstu.2011.07.002] [Medline: 21835406]
21. Pluye P, Gagnon MP, Griffiths F, Johnson-Lafleur J. A scoring system for appraising mixed methods research, and concomitantly appraising qualitative, quantitative and mixed methods primary studies in Mixed Studies Reviews. Int J Nurs Stud 2009 Apr;46(4):529-546. [doi: 10.1016/j.ijnurstu.2009.01.009] [Medline: 19233357]
22. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. BMC Med Res Methodol 2008 Jul 10;8:45 [FREE Full text] [doi: 10.1186/1471-2288-8-45] [Medline: 18616818]
23. Rogers K, Zeni MB. Systematic review of medical home models to promote transitions to primary adult health care for adolescents living with autism spectrum disorder. Worldviews Evid Based Nurs 2015 Apr;12(2):98-107. [doi: 10.1111/wvn.12085] [Medline: 25774018]
24. Mazurek MO, Parker RA, Chan J, Kuhlthau K, Sohl K, ECHO Autism Collaborative. Effectiveness of the Extension for Community Health Outcomes model as applied to primary care for autism: A partial stepped-wedge randomized clinical trial. JAMA Pediatr 2020 May 01;174(5):e196306 [FREE Full text] [doi: 10.1001/jamapediatrics.2019.6306] [Medline: 32150229]
25. Ames JL, Massolo ML, Davignon MN, Qian Y, Cerros HJ, Croen LA. Transitioning youth with autism spectrum disorders and other special health care needs into adult primary care: A provider survey. Autism 2021 Apr;25(3):731-743. [doi: 10.1177/1362361320926318] [Medline: 32551940]
26. Calleja S, Islam FMA, Kingsley J, McDonald R. Healthcare access for autistic adults: A systematic review. Medicine (Baltimore) 2020 Jul 17;99(29):e20899 [FREE Full text] [doi: 10.1097/MD.0000000000020899] [Medline: 32702830]
27. Doherty AJ, Atherton H, Boland P, Hastings R, Hives L, Hood K, et al. Barriers and facilitators to primary health care for people with intellectual disabilities and/or autism: an integrative review. BJGP Open 2020 Aug 25;4(3):bjgpopen20X101030 [FREE Full text] [doi: 10.3399/bjgpopen20X101030] [Medline: 32605913]

Abbreviations

ASD: autism spectrum disorder
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Approaches and Criteria for Provenance in Biomedical Data Sets and Workflows: Protocol for a Scoping Review

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Abstract

Background: Provenance supports the understanding of data genesis, and it is a key factor to ensure the trustworthiness of digital objects containing (sensitive) scientific data. Provenance information contributes to a better understanding of scientific results and fosters collaboration on existing data as well as data sharing. This encompasses defining comprehensive concepts and standards for transparency and traceability, reproducibility, validity, and quality assurance during clinical and scientific data workflows and research.

Objective: The aim of this scoping review is to investigate existing evidence regarding approaches and criteria for provenance tracking as well as disclosing current knowledge gaps in the biomedical domain. This review covers modeling aspects as well as metadata frameworks for meaningful and usable provenance information during creation, collection, and processing of (sensitive) scientific biomedical data. This review also covers the examination of quality aspects of provenance criteria.

Methods: This scoping review will follow the methodological framework by Arksey and O'Malley. Relevant publications will be obtained by querying PubMed and Web of Science. All papers in English language will be included, published between January 1, 2006 and March 23, 2021. Data retrieval will be accompanied by manual search for grey literature. Potential publications will then be exported into a reference management software, and duplicates will be removed. Afterwards, the obtained set of papers will be transferred into a systematic review management tool. All publications will be screened, extracted, and analyzed: title and abstract screening will be carried out by 4 independent reviewers. Majority vote is required for consent to eligibility of papers based on the defined inclusion and exclusion criteria. Full-text reading will be performed independently by 2 reviewers and in the last step, key information will be extracted on a pretested template. If agreement cannot be reached, the conflict will be resolved by a domain expert. Charted data will be analyzed by categorizing and summarizing the individual data items based on the research questions. Tabular or graphical overviews will be given, if applicable.

Results: The reporting follows the extension of the Preferred Reporting Items for Systematic reviews and Meta-Analyses statements for Scoping Reviews. Electronic database searches in PubMed and Web of Science resulted in 469 matches after deduplication. As of September 2021, the scoping review is in the full-text screening stage. The data extraction using the pretested charting template will follow the full-text screening stage. We expect the scoping review report to be completed by February 2022.

Conclusions: Information about the origin of healthcare data has a major impact on the quality and the reusability of scientific results as well as follow-up activities. This protocol outlines plans for a scoping review that will provide information about current approaches, challenges, or knowledge gaps with provenance tracking in biomedical sciences.

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KEYWORDS

provenance; biomedical; workflow; data sharing; lineage; scoping review; data genesis; scientific data; digital objects; healthcare data

Introduction

The (re-)use of electronic medical and patient-related data offers enormous potential for further investigations in clinical research [1,2]. Different national initiatives such as the French Health Data Hub initiative or the German Medical Informatics Initiatives are committed to better knowledge discovery and data sharing in the health care domain [3]. Resulting outcomes enable patients and physicians a safe and rapid access to therapies or treatment options. Subsequently, treatment costs can be reduced. In this context, the access to quality-assured, traceable, and hence, credible shared data is essential. Providing information about the origin of data demands concepts for traceability to gain understanding for the relationships between results and source data. There is an increasing interest and need to ensure traceability throughout scientific practice. Consequently, a systematic knowledge compilation regarding provenance and potential gaps is needed.

Provenance describes the origin of data. A basic understanding of the term "provenance" is given with the description "what happened" to the data [4]. Several different models exist to formally express provenance information, for instance, the World Wide Web Consortium PROV standard or CWLProv [5,6]. Advantages and opportunities of providing data provenance have been demonstrated, for instance, from the experiences in the EU-Horizon 2020 TRANSFoRm project [4]. Moreover, the importance of provenance and the relation to provenance within electronic health records is pointed out in the study of Johnson et al [7]. A previously published systematic review of provenance systems already investigated tools and systems [8]. However, our own work aims to understand current approaches and criteria as well as knowledge gaps for provenance in biomedical as well as domain-independent research.

The fields of research data management and FAIR (findable-accessible-interoperable-reusable) data principles consider provenance as one of the research pillars [9]. As such, a provenance-oriented approach requires thorough planning, execution, and evaluation of data management processes in the respective application domain [1]. While capturing provenance information in the research, adherence to criteria such as consistency, interoperability, and confidentiality are required across all software tools [2]. Furthermore, data privacy issues have to be respected during modeling to keep compliance with national and international requirements such as the European General Data Protection Regulation [10,11].

Process quality with the associated workflow quality can be achieved by monitoring and troubleshooting in applications or in data integration scenarios such as Extract-Transform-Load jobs. This implies workflow requirements to be established on a fine- or coarse-grained provenance level for troubleshooting [12]. Addressing data quality issues should support in reaching completeness, accuracy, and timeliness of the data and creates trust in it. However, heterogeneous data sources, dynamic infrastructures, data exchange across boundaries, and lack of standards for quality measures characterize the current state of electronic health record data sets [13]. Contrarily, provenance information strengthens the credibility of the data and proves that data have not been intentionally or unintentionally changed in its life cycle [14]. The concept and implementation of provenance is essential in most scientific domains such as environmental fields (geoprocessing workflows or climate assessments), in fusion engineering, or material sciences [15,16]. Since the use of machine learning techniques within the scope of decision support is becoming increasingly popular for medical researchers, they are under the obligation to prove their reproducibility [17]. Therefore, systematic knowledge about the "what happened" and about reproducibility metrics such as data sets and code accessibility is indispensable and is in need of further investigation to provide provenance [18].

The aim of this scoping review is to investigate existing evidence regarding approaches and criteria for provenance tracking as well as disclosing current knowledge gaps in the biomedical domain. This comprises modeling aspects as well as metadata frameworks for meaningful and usable provenance information during creation, collection, and processing of (sensitive) scientific biomedical data. The review also covers the examination of quality aspects of provenance criteria.

Methods

Design

The individual elements from the framework of Arksey and O'Malley [19] will be used as a roadmap for this scoping review. Essential methodological steps will cover the stages (1) identification of the research questions, (2) identification of relevant studies, (3) study selection, (4) data extraction and charting, and (5) collating, summarizing, and reporting the results. Any subsequent deviations of the final report from the scoping review protocol will be clearly highlighted and explained in the scoping review report.

Ethics

Ethical approval was not required because only literature will be evaluated without processing sensitive patient data.

Stage 1: Identification of the Research Questions

At first, an informal prescreening of relevant literature in PubMed and Web of Science as well as grey literature from conferences or organizations was carried out to determine the

keywords in scope. Relevant literature was identified with the support of a librarian. PubMed was searched using the keywords "provenance" and "tracking." The reviewer team explored, studied, and scrutinized additional literature based on search combinations of terms linked to the topic "provenance." Ten publications were selected and reviewed by the team in an iterative process to guide the implementation of the research questions. During this step, keywords from titles and abstracts were gathered and analyzed by implementing the search strategy based on them. The following research questions were generated to meet the objective of this scoping review before study conduction: to investigate existing evidence regarding approaches and criteria for provenance tracking as well as disclosing current knowledge gaps in the biomedical domain. This review covers modeling aspects as well as metadata frameworks for meaningful and usable provenance information during creation, collection, and processing of (sensitive) scientific biomedical data. This review also covers the examination of quality aspects of provenance criteria.

Research question 1: Which potential (methodological) approaches exist for the classification and tracking of provenance criteria and methods in a biomedical or domain-independent context?

Research question 2: How can the potential value of provenance information be harnessed and by whom? How can usability be provided?

Research question 3: What are the challenges and potential problems or bottlenecks for the accomplishment of provenance?

Research question 4: Which guidelines or demands for the consideration of provenance criteria in a biomedical or domain-independent context have to be followed?

Research question 5: How completely can provenance be mapped in the data lifecycle or during data management?

Stage 2: Identification of Relevant Studies

Relevant publications will be retrieved using concepts together with their associated keywords as selected from "Stage 1: Identification of the research questions." Concepts are categorized into 4 groups: target domain, provenance, provenance properties, and objective. Target domain refers to the context of the research topic and includes studies with a biomedical, health care, clinical, or scientific background. Scientific background is limited to domain-independent studies and excludes all other domain-specific studies. The concept "provenance" concerns the information about the genesis of a given object while the concept "provenance properties" covers specific requirements tied to the term "provenance" or describes selected characteristics in this context. The concept "objective" embraces the range of purpose or the intention of provenance. Table 1 provides an overview of the eligibility criteria derived from the categorization of the concepts together with the defined terms and their matching keywords.

Table 1. Concepts and matching keywords (eligibility criteria).

Concepts	Matching keywords (inclusion criteria)
Target domain	biomed*[a], EHR, electronic health record, healthcare, clinical, scientific[b]
Provenance	provenance, prov, lineage
Provenance properties	interop*, (data NEAR/2 [flow, quality, transformation]), metadata, workflow, semantic, framework, annotat*, ontolog*, management, document*, (model NEAR/2 provenance)
Objective	audit*, decision support, ETL, Extract-Transform-Load, FHIR, record linking, machine learning, reproducib*, transparen*, track*, implement*

[a]The * symbol (wildcard character) replaces or represents one or more characters.

[b]Will be used in a domain-independent context only.

A comprehensive search strategy for identifying the relevant literature, based on the given table, was implemented in PubMed and Web of Science. Medical subject headings were applied in PubMed. Additionally, the Boolean operators AND OR were used within the search strategy for combining the individual concepts and their associated keywords.

The inclusion criteria comprised all papers in the English language and published between January 1, 2006 and March 23, 2021. The concepts and their related keywords, as shown in Table 1, are considered during the selection of the papers within the biomedical or domain-independent area. The start date for inclusion of literature was chosen owing to the initiation of the Open Provenance Model in 2006 as a result of the Provenance Challenge series [20]. Grey literature from relevant project reports and proceedings were searched and reviewed for eligibility. All search results were exported to a reference management tool to eliminate duplications. Unique results were exported to the web-based screening tool Rayyan (Qatar Computing Research Institute) [21]. The PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-analyses extension for Scoping Reviews) will be used for reporting of this scoping review [22].

Stage 3: Study Selection

During the scoping review process, decisions to select or eliminate studies are tracked using Rayyan. That way, independent screening by the reviewers is enabled. Rayyan allows citation sharing and blinded comparison of decisions for inclusion and exclusion of selected studies. All imported publications will be screened by reading the title and abstract by all 4 reviewers. Title-abstract screening is the process of reviewing the references for inclusion based solely upon their title and abstract. Reviewers will screen out irrelevant references whereby the inclusion and exclusion criteria serve as the basis for their eligibility decision. Conflicts will be resolved since at least 3 unified classifications are necessary for inclusion or

exclusion of a publication in an unblinded modus. The included (=eligible) publications will be examined in a full-text screening phase to determine the extent to which they can answer the research questions. Each publication must be read by 2 researchers to determine the relevance to the research questions. If there is no joint agreement, an independent researcher will be consulted. A description and a PRISMA flow chart of the selection process with frequencies for references considered in the different databases will be provided as well as counting in the subsequent title-abstract screening process based on the eligibility criteria.

Stage 4: Data Extraction and Charting

The data collection process will be documented by the reviewers while using the collectively developed template as provided in Table 2. The approach to data extraction needs to be consistent with the research question and purpose. This charting form will be pretested and will be used after closed alignment between the reviewers. “Pretested” means that 2 reviewers will independently complete the template for 5 studies ahead of the main study. They will compare the result with regard to a consistent approach and agree on necessary updates in the template, if necessary. Reviewers will diligently extract and update the study data from the identified papers in scope during their full-text review in an iterative process.

Table 2. Data charting template for key information from eligible papers.

Metadata publication	Characteristic extraction and specification
Title[a]	Title
Citation details[a]	Author (1st), journal, DOI
Year of publication[a]	For example, YYYY
Publication type[a]	Journal or website or conference, etc
Study type[a]	Use case or development or evaluation
Continent of study	For example, Australia
Institute[a]	Contributing institute (corresponding author or—if not provided—1st author)
Corresponding author’s discipline	For example, data architect
Funding source	Public or industry or none or missing
Objective[a]	Aim of the publication
Methods	Strategies, processes, or techniques utilized in the collection or analyzing of data, how is the validity of the study judged
Summary results[a]	Short description of results
Conclusion	Short description of conclusion
Target domain[a]	Name specific domain or domain independent
Keywords	List keywords from abstract
Metadata to key findings related to research questions	Characteristic extraction and specification
Research question 1: Approaches for classification and tracking of provenance criteria and methods in biomedical or domain-independent context	Provide description in the domain for data suitability or data availability and other requirements or factors on data or systems regarding the trace of the data history (eg, role of provenance in terms of domain standards, ie, interoperability standards, FAIR [findable-accessible-interoperable-reusable] data, relation to metadata and model use, representation formalisms, etc), check definition of provenance
Research question 2: Potential value of provenance information	Provide possible use case description and types of data sources included, usability including effect on target domain and by whom it can be used and who will be the stakeholders; problems, if provenance is not available
Research question 3: Potential problems or bottlenecks for the accomplishment of provenance	Describe any challenges (eg, legal, organizational, or technical conditions) or problems that occurred during implementation phase of provenance
Research question 4: Guidelines or demands for the consideration of provenance to be adhered to	Describe any valid domain standard requirement, for example, legal, guidelines, rules
Research question 5: Completeness of provenance information during data management process or data life cycle	Describe any measurement or outcome available for completeness of provenance information

[a]Obligatory input.

Stage 5: Collating, Summarizing, and Reporting the Results

The charting results from stage 4 will be presented in the following steps [19]. Analysis will be given by a qualitative evaluation and by summary statistics, charts, or equivalent appraisal. The reporting of the results and outcome will be aligned to the research questions. The meaning of the findings and their relation to the overall objectives will be discussed. Implications for future research, practice, and policy will be outlined. The reporting of the results will be aligned with the PRISMA-ScR reporting guidelines [22].

Results

Schedule

The scoping review started with a tentative search of the databases in PubMed and Web of Science in early 2021 (see stages 1-3) and resulted in 469 matches. These papers will be subjected to title-abstract screening in an interactive selection process for eligibility, followed by a full-text screening stage. These papers will be examined within an iterative selection process for inclusion into data charting (see stage 4). Data extraction will be finalized during the 4th quarter of 2021. The scoping review will be completed by summarizing and synthesizing the results by February 2022 (see stage 5).

Anticipated Outcomes

The scoping review will identify potentially relevant initiatives on provenance, and it will provide an overview of the evidence, gaps, and limitations for provenance criteria. All the evidence will be elaborated on the basis of the research questions. As such, the review can serve as preparatory work for achieving a comprehensive usable result on approaches and criteria for provenance. Based on the review results, the quality of the provenance criteria will be examined for a potential demarcation regarding minimum requirements for structuredness and completeness of provenance. We believe that this investigation supports provenance research with respect to the implementation of provenance in secondary use projects such as the German Medical Informatics Initiative. Within the Medical Informatics in Research and Care in University Medicine consortium, as part of the Medical Informatics Initiative, provenance has an important meaning to bioinformaticians and researchers [23].

Discussion

Implications for future work will be derived from the current status of research activities and their underlying concepts. We anticipate that implications will encompass conceptual and modeling approaches up to the generation of provenance-aware data as well as gaps in the current practices within the health care domain. We believe that our results will support the further development of guidelines, thereby overcoming the identified challenges and disclosing new opportunities for the classification and tracking of provenance criteria. Evidence will assist in recognizing and defining the preconditions for data sharing. It will further characterize data suitability and categories (eg, data governance, relevance, quality) at a fitness for purpose level in the health domain, considering the interests of different stakeholders. Finally, the scoping review will provide insights into whether a further assessment of the results is useful within a full systematic review.

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Conflicts of Interest

None declared.

References

1. Jayapandian CP, Zhao M, Ewing RM, Zhang G, Sahoo SS. A semantic proteomics dashboard (SemPoD) for data management in translational research. BMC Syst Biol 2012;6 Suppl 3:S20 [FREE Full text] [doi: 10.1186/1752-0509-6-S3-S20] [Medline: 23282161]
2. Curcin V, Miles S, Danger R, Chen Y, Bache R, Taweel A. Implementing interoperable provenance in biomedical research. Future Generation Computer Systems 2014 May;34:1-16. [doi: 10.1016/j.future.2013.12.001]
3. Cuggia M, Combes S. The French Health Data Hub and the German Medical Informatics Initiatives: Two national projects to promote data sharing in healthcare. Yearb Med Inform 2019 Aug;28(1):195-202 [FREE Full text] [doi: 10.1055/s-0039-1677917] [Medline: 31419832]
4. Curcin V. Embedding data provenance into the Learning Health System to facilitate reproducible research. Learn Health Syst 2017 Apr;1(2):e10019 [FREE Full text] [doi: 10.1002/lrh2.10019] [Medline: 31245557]
5. Groth P, Moreau L. PROV-overview. W3C. URL: https://www.w3.org/TR/prov-overview/ [accessed 2021-06-10]
6. Khan FZ, Soiland-Reyes S, Sinnott RO, Lonie A, Goble C, Crusoe MR. Sharing interoperable workflow provenance: A review of best practices and their practical application in CWLProv. Gigascience 2019 Nov 01;8(11):1-27 [FREE Full text] [doi: 10.1093/gigascience/giz095] [Medline: 31675414]

7. Johnson KE, Kamineni A, Fuller S, Olmstead D, Wernli KJ. How the provenance of electronic health record data matters for research: a case example using system mapping. EGEMS (Wash DC) 2014;2(1):1058 [FREE Full text] [doi: 10.13063/2327-9214.1058] [Medline: 25821838]
8. Pérez B, Rubio J, Sáenz-Adán C. A systematic review of provenance systems. Knowl Inf Syst 2018 Feb 17;57(3):495-543. [doi: 10.1007/s10115-018-1164-3]
9. Jauer M, Deserno T. Data provenance standards and recommendations for FAIR data. Stud Health Technol Inform 2020 Jun 16;270:1237-1238. [doi: 10.3233/SHTI200380] [Medline: 32570597]
10. Hume S, Sarnikar S, Noteboom C. Enhancing traceability in clinical research data through a metadata framework. Methods Inf Med 2020 May;59(2-03):75-85. [doi: 10.1055/s-0040-1714393] [Medline: 32894879]
11. Sahoo SS, Nguyen V, Bodenreider O, Parikh P, Minning T, Sheth AP. A unified framework for managing provenance information in translational research. BMC Bioinformatics 2011 Nov 29;12:461 [FREE Full text] [doi: 10.1186/1471-2105-12-461] [Medline: 22126369]
12. Zheng N, Alawini A, Ives Z. 2019 Apr Presented at: 35th International Conference on Data Engineering (ICDE); 2019; Macao, China p. 184-195 URL: http://europepmc.org/abstract/MED/31595143 [doi: 10.1109/ICDE.2019.00025]
13. Margheri A, Masi M, Miladi A, Sassone V, Rosenzweig J. Decentralised provenance for healthcare data. Int J Med Inform 2020 Sep;141:104197. [doi: 10.1016/j.ijmedinf.2020.104197] [Medline: 32540775]
14. Wing JM. The data life cycle. Harvard Data Science Review 2019 Jun 23:1-6. [doi: 10.1162/99608f92.e26845b4]
15. Schissel D, Abla G, Flanagan S, Greenwald M, Lee X, Romosan A, et al. Automated metadata, provenance cataloging and navigable interfaces: Ensuring the usefulness of extreme-scale data. Fusion Engineering and Design 2014 May;89(5):745-749. [doi: 10.1016/j.fusengdes.2014.01.053]
16. Yakutovich A, Eimre K, Schütt O, Talirz L, Adorf C, Andersen C, et al. AiiDAlab – an ecosystem for developing, executing, and sharing scientific workflows. Computational Materials Science 2021 Feb;188:110165 [FREE Full text] [doi: 10.1016/j.commatsci.2020.110165]
17. Samuel S, Löffler F, König-Ries B. Machine learning pipelines: provenance, reproducibility and FAIR data principles. arXiv.org. URL: http://arxiv.org/abs/2006.12117 [accessed 2021-05-16]
18. McDermott MBA, Wang S, Marinsek N, Ranganath R, Foschini L, Ghassemi M. Reproducibility in machine learning for health research: Still a ways to go. Sci Transl Med 2021 Mar 24;13(586):eabb1655. [doi: 10.1126/scitranslmed.abb1655] [Medline: 33762434]
19. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. International Journal of Social Research Methodology 2005 Feb;8(1):19-32. [doi: 10.1080/1364557032000119616]
20. Moreau L, Ludäscher B, Altintas I, Barga R, Bowers S, Callahan S, et al. Special issue: the first Provenance Challenge. Concurrency Computat.: Pract. Exper 2008 Apr 10;20(5):409-418. [doi: 10.1002/cpe.1233]
21. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016 Dec 05;5(1):210 [FREE Full text] [doi: 10.1186/s13643-016-0384-4] [Medline: 27919275]
22. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for Scoping Reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018 Oct 02;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
23. Pugliese P, Knell C, Christoph J. Exchange of clinical and omics data according to FAIR principles: a review of open source solutions. Methods Inf Med 2020 Jun;59(S 01):e13-e20 [FREE Full text] [doi: 10.1055/s-0040-1712968] [Medline: 32620018]

Abbreviations

PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Enamel Renal Syndrome: Protocol for a Scoping Review

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Abstract

Background: Enamel renal syndrome (ERS) (OMIM 204690) is a rare autosomal recessive disorder characterized by hypoplastic amelogenesis imperfecta, failed tooth eruption, intrapulpal calcifications, gingival enlargement, and nephrocalcinosis. The rarity of the condition and the variability of the phenotype has led to ERS not being fully characterized.

Objective: This scoping review aims to account for the range and current state of knowledge on ERS and synthesize these findings into a comprehensive summary, focusing on the pathophysiology, genotype-phenotype correlations, and patient management from a dental perspective.

Methods: The authors will conduct a systematic search of PubMed (MEDLINE), BioMed Central, EbscoHost Web, Web of Science, and WorldCat. We will include all studies with human participants with a confirmed diagnosis of ERS. Articles will be screened in two stages (ie, initially by title and abstract screening and then full-text screening by two independent reviewers). Data extraction will be conducted using a customized electronic data extraction form. We will provide a narrative synthesis of the findings from the included studies. We will structure the results according to themes.

Results: This protocol is registered with the Open Science Framework. The electronic search was conducted in July 2020 and updated in April 2021. The research findings will be published in an open access journal.

Conclusions: Dentists should be able to identify patients with clinical features of ERS so that they receive appropriate referrals for renal evaluation, genetic counseling, and oral rehabilitation to increase the patient's quality of life. A scoping review is the most appropriate method to conduct this comprehensive exploration of the current evidence, which may be sparse due to the rarity of the condition. It will also enable us to identify gaps in the research.

Trial Registration: Open Science Framework; https://osf.io/cghsa

International Registered Report Identifier (IRRID): DERR1-10.2196/29702

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KEYWORDS

enamel renal syndrome; amelogenesis imperfecta; gingival fibromatosis; FAM20A gene; nephrocalcinosis; dentistry; failed tooth eruption; scoping review; dentist; renal evaluation; oral rehabilitation; quality of life; rare conditions; pathophysiology; dental perspective

Introduction

Enamel renal syndrome (ERS) (OMIM 204690) is a rare autosomal recessive disorder characterized by hypoplastic amelogenesis imperfecta (AI), failed tooth eruption, intrapulpal calcifications, gingival enlargement, and nephrocalcinosis [1]. In 1972, MacGibbon [2] described a condition presenting with renal dysfunction and enamel hypoplasia in several members of the same family. Although there has been an increasing number of publications about ERS in recent years, the rarity of the condition and the variability of the phenotype has led to ERS not being fully characterized.

Several phenotypes have been identified under various terms, including AI syndrome, AI with interradicular dentine dysplasia, AI with odontogenic fibroma-like hamartomas around nonerupted teeth, AI with gingival fibromatosis [3], MacGibbon syndrome, and Lubinsky-MacGibbon syndrome [4]. The lack of strict diagnostic criteria has led to patient's renal status being overlooked within those phenotypes, along with underestimation of the actual disease prevalence [3]. This rare genetic entity accounts for less than 1 in 100,000 individuals of the global population, with only 70 cases in 50 different families being documented at present [5].

Recently, high throughput genetic technologies such as whole exome sequencing, next generation sequencing, and bioinformatics analysis implicated mutations in FAM20A (FAMily with sequence similarity 20A) as the defective gene in ''Amelogenesis Imperfecta and Gingival Fibromatosis Syndrome'' (AIGFS; OMIM 614253). A comprehensive review of AIGFS's clinical aspect delineated a similar distinctive oral phenotype to ERS [6]. It is believed that both syndromes reflect different phenotypes of the same disease with frequent renal dysfunction association in ERS [3]. More than 40 homozygous or combined heterozygous FAM20A mutations have been identified in families (Human Gene Mutation Database). The protein encoded by the FAM20A gene is secreted by ameloblasts, odontoblasts, gingival, and dental pulp cells, reflecting an important role during enamel development and gingival homeostasis [1,7].

Generally, patients with ERS seek dental management, as the initial chief complaint relates to the lack of enamel and failure of permanent tooth eruption at a young age [6]. A review by de la Dure-Molla and colleagues [3] suggested a distinctive pathognomonic oral profile for patients with ERS (Textbox 1).

In addition to the "common profile" of ERS, several atypical features have been reported in the literature. Pêgo et al [8] reported an association of hypertrichosis and hearing loss in two patients with ERS. Hearing loss is a common feature of Raine syndrome (OMIM 259775), a syndrome caused by FAM20C mutation. This may explain the presence of such a feature in ERS [8]. A few characteristics that are considered atypical manifestations in individuals with ERS have been documented in a study conducted by Dourado et al [1]. These were malocclusion, periodontal disease, supraincisive diastema, and intellectual disability. One study documented a case in which all the permanent teeth had erupted, which is considered highly atypical of ERS [5].

It is clear from the growing list of atypical features of ERS that there is still much that is not known and poorly understood about ERS. This scoping review aims to account for the range and current state of knowledge on ERS. These findings will be synthesized into a comprehensive summary, focusing on the pathophysiology, genotype-phenotype correlations, and patient management from a dental perspective. The authors also aim to elucidate research gaps to inform future research and provide a useful summary for clinicians treating patients with ERS.

Textbox 1. Common oro-dental features of Enamel Renal Syndrome (ERS) according to de la Dure Molla et al [3].

Common oro-dental features of ERS

- Generalized thin hypoplastic or absent enamel
- Primary and permanent teeth affected
- Flat cusps on posterior teeth
- Relative microdontia and spaced teeth
- Intrapulpal calcifications
- Delayed tooth eruption
- Impacted posterior teeth with hyperplastic follicle (hamartoma-like) and altered eruption pathway
- Root dilacerations of impacted teeth
- Gingival fibromatosis (variable severity)
- Gingival and dental follicle ectopic calcification on biopsies
- Semilunar shape of central incisor edge
- Crown resorption of nonerupted teeth
- Anterior open bite
- Root hypercementosis and interradicular dentine dysplasia
- Supernumerary teeth

Methods

We will undertake this scoping review following the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews) guidelines [9]. This study is registered with the Open Science Framework (OSF) [10].

Research Questions

The primary research question is "what is known from the existing literature about the oro-dental features of ERS?" The research subquestions are as follows:

- Which methods are used to diagnose ERS?
- What are the clinical and radiographic finding in patients with ERS?
- What are the oral histological findings in patients with ERS?
- What phenotype-genotype correlations have been established?
- What guidelines exist for dentists and dental specialists managing patients with ERS?
- What gaps in the literature exist regarding ERS from the dentist's perspective?

Information Sources and Search Strategy

The authors will perform a search of the following online databases: PubMed (MEDLINE), BioMed Central, EbscoHost Web, Web of Science, and WorldCat. Additional studies will be sought using the reference lists of included studies and searching Google Scholar. An example of the search strategy is presented in Table 1. The search will be tailored to each database. The search will be limited to title and abstracts to find studies focused on ERS. No other limiters will be used in the search. References will be managed in Zotero reference manager software (Corporation for Digital Scholarship).

Table 1. Example of search strategy to be used in this study (PubMed, Medline; July 23, 2020; limits: none).

No.	Search	Result, n
1	enamel renal syndrome[Title/Abstract] OR FAM20A[Title/Abstract]	52
2	((ENAMEL-RENAL-GINGIVAL SYNDROME[Title/Abstract]) OR (AMELOGENESIS IMPERFECTA, HYPOPLASTIC, WITH NEPHROCALCINOSIS[Title/Abstract])) OR (AMELOGENESIS IMPERFECTA[Title/Abstract] AND GINGIVAL FIBROMATOSIS SYNDROME[Title/Abstract])	19
3	amelogenesis imperfecta type IG[Title/Abstract]	1
4	#1 OR #2 OR #3	60

Inclusion Criteria

This scoping review will include all research related to our objectives. All primary studies will be included, and review articles will be used for hand-searching of reference lists. No restrictions will be placed on the time frame, language, or gray literature. The population of interest will be limited to human participants (of any age) with a confirmed molecular or clinical diagnosis of ERS. ERS (OMIM 204690) is also known as AI type IG or AI1G, enamel-renal gingival syndrome, AIGFS, and AI with nephrocalcinosis. ERS is caused by homozygous or compound heterozygous mutation in the FAM20A gene (gene number 611062) on chromosome 17q24. The oral clinical features of ERS are considered to be pathognomonic [3]; thus, a clinical diagnosis is considered acceptable for inclusion.

Study Selection

Articles will be screened in two stages (ie, initially by title and abstract screening, and then full-text screening by two independent reviewers, authors SK and IAR). Any failure of consensus will be resolved by a senior third party (author MC). The degree of agreement between reviewers for each of these steps will be quantified with a kappa statistic with a 95% CI.

Data Items and Extraction

Data extraction will be conducted by each reviewer independently (IAR and SK). An electronic data extraction form will be custom-made for this review, piloted, and amended as required. The data collection form will include the fields in Textbox 2.

Textbox 2. Data extraction fields.

Study information

- Author(s), title, year of publication, journal
- Study setting
- Study design

Study population

- Sample size
- Baseline characteristics, demographics
- Any additional abnormalities or medical conditions
- Any therapies that the patients might have received

Enamel renal syndrome (ERS)

- Method of diagnosis
- Family history of the condition
- Genetic variation

Outcome

- Prevalence of ERS
- Molecular findings
- Clinical findings (intraoral, extraoral, hematological and other biomarkers, nephrological, other findings)
- Radiographic findings
- Transcriptomic findings of oral tissues
- Dental ultrastructural findings
- Any additional findings

Synthesis of Results

We will provide a narrative synthesis of the findings from the included studies. We will structure the results according to themes in the following manner to provide a coherent summary of findings: characteristics of included studies (location, study design), baseline characteristics of the participants/population (eg, age and sex), the prevalence of ERS, methods of diagnosis, clinical findings (oral and extraoral), radiographic findings, histological findings, nephrological findings, atypical findings, biomarkers, genotype-phenotype correlation, atypical/novel findings, and additional findings.

Results

There was no patient participation in this study. This protocol was completed in July 2020 and registered in OSF [10] in August 2020. The electronic search for literature was undertaken in July 2020 and updated in April 2021. The first search yielded 122 titles. This study is intended for open access publication for wide dissemination of the findings.

Discussion

This scoping review aims to determine the current state of knowledge on ERS and synthesize these findings into a comprehensive summary, focusing on the pathophysiology, genotype-phenotype correlations, and patient management from a dental perspective. We also aim to identify research gaps to inform future research and provide a useful summary for clinicians treating patients with ERS.

ERS is a rare disorder and not much awareness exists around the condition, even within the dental fraternity [11]. Conversely, AI is a relatively common disorder of enamel formation encountered by dentists and often occurs as an isolated trait or part of a syndrome [1]. Because dentists are often the first point of call for these patients, it is important that the dentist is able to identify patients with ERS and differentiate it from AI so that they receive appropriate referrals for renal evaluations and genetic counselling [5]. It is also important to provide the patient with oral rehabilitation to increase the patient's quality of life, which can be severely impaired by this condition [5]. Primary failure of eruption is difficult to manage, and there is no current literature about assisted eruption with orthodontic traction in patients with ERS [11]. It does appear that the normal eruptive process of teeth is altered leading to impaction and ankylosis [11]. Progressive embedding of the teeth has also been reported [4]. Therefore, orthodontic treatment may be unpredictable. Current management involves surgical interventions and the placement of a fixed or removable dental prosthesis [12,13]. There is a need for guidelines on the dental management of patients with ERS and the development of referral protocols.

Identifying patients with ERS may not be as straightforward as it was previously believed to be. According to de la Dure-Molla et al [3], the oral features of ERS described in Table 1 are considered pathognomonic. However, more recent studies have found significant variability in phenotypes including identifying a patient with a pathogenic variant of the FAM20A gene and a full complement of erupted permanent teeth [5]. Therefore, a review is needed to consolidate this growing body of evidence and present it in a manner that is practical for the dental clinician. We believe that a scoping review is the most appropriate method to conduct a comprehensive exploration of the current evidence, which may be sparse due to the rarity of the condition. It will also enable us to identify gaps in the research.

Authors' Contributions

SK and IAR were jointly responsible for the development and writing of this protocol. MC was responsible for the conception of the study and acted in a supervisory capacity. All authors read, edited, and approved the final manuscript, and are jointly responsible for the work.

Conflicts of Interest

None declared.

References

1. Dourado M, Dos Santos C, Dumitriu S, Iancu D, Albanyan S, Kleta R, et al. Enamel renal syndrome: a novel homozygous FAM20A founder mutation in 5 new Brazilian families. Eur J Med Genet 2019 Nov;62(11):103561. [doi: 10.1016/j.ejmg.2018.10.013] [Medline: 30394349]
2. MacGibbon D. Generalized enamel hypoplasia and renal dysfunction. Aust Dent J 1972 Feb;17(1):61-63 [FREE Full text] [doi: 10.1111/j.1834-7819.1972.tb02747.x] [Medline: 4504766]
3. de la Dure-Molla M, Quentric M, Yamaguti P, Acevedo A, Mighell AJ, Vikkula M, et al. Pathognomonic oral profile of enamel renal syndrome (ERS) caused by recessive FAM20A mutations. Orphanet J Rare Dis 2014 Jun 14;9:84 [FREE Full text] [doi: 10.1186/1750-1172-9-84] [Medline: 24927635]
4. Debnath K, Couthino A, Chatterjee A, Shenoy S. Enamel renal gingival syndrome: a rare case report. J Indian Soc Periodontol 2019;23(1):69-72 [FREE Full text] [doi: 10.4103/jisp.jisp_532_18] [Medline: 30692747]
5. Nitayavardhana I, Theerapanon T, Srichomthong C, Piwluang S, Wichadakul D, Porntaveetus T, et al. Four novel mutations of FAM20A in amelogenesis imperfecta type IG and review of literature for its genotype and phenotype spectra. Mol Genet Genomics 2020 Jul;295(4):923-931. [doi: 10.1007/s00438-020-01668-8] [Medline: 32246227]
6. Wang S, Reid B, Dugan S, Roggenbuck J, Read L, Aref P, et al. FAM20A mutations associated with enamel renal syndrome. J Dent Res 2014 Jan;93(1):42-48 [FREE Full text] [doi: 10.1177/0022034513512653] [Medline: 24196488]
7. O'Sullivan J, Bitu C, Daly S, Urquhart J, Barron M, Bhaskar S, et al. Whole-exome sequencing identifies FAM20A mutations as a cause of amelogenesis imperfecta and gingival hyperplasia syndrome. Am J Hum Genet 2011 May 13;88(5):616-620 [FREE Full text] [doi: 10.1016/j.ajhg.2011.04.005] [Medline: 21549343]
8. Pêgo SPB, Coletta RD, Dumitriu S, Iancu D, Albanyan S, Kleta R, et al. Enamel-renal syndrome in 2 patients with a mutation in FAM20 A and atypical hypertrichosis and hearing loss phenotypes. Oral Surg Oral Med Oral Pathol Oral Radiol 2017 Feb;123(2):229-234.e2. [doi: 10.1016/j.oooo.2016.09.226] [Medline: 28086997]
9. Tricco A, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018 Oct 02;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
10. Roomaney I, Kabbashi S, Chetty M. Enamel renal syndrome: a scoping review. OSF Registries. 2020 Aug 19. URL: https://osf.io/cghsa [accessed 2021-06-11]
11. Reddy P, Aravelli S, Goud S, Malathi L. Amelogenesis imperfecta with nephrocalcinosis: a rare association in siblings. Cureus 2019 Jul 01;11(7):e5060 [FREE Full text] [doi: 10.7759/cureus.5060] [Medline: 31516772]
12. Mauprivez C, Nguyen J, de la Dure-Molla M, Naveau A. Prosthetic rehabilitation of a patient with rare and severe enamel renal syndrome. Int J Prosthodont 2018;31(1):31–34. [doi: 10.11607/ijp.5322] [Medline: 29166418]
13. Costa D, Dourado M, Figueiredo de Carvalho M, Santos R, da Cruz Batista M, Mesquita A. Enamel renal syndrome: a case history report. Int J Prosthodont 2017;30(1):22-24. [doi: 10.11607/ijp.4916] [Medline: 28085972]

Abbreviations

AI: amelogenesis imperfecta
AIGFS: amelogenesis imperfect and gingival fibromatosis syndrome
OSF: Open Science Framework
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews

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