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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.
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, sensor, 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 consolidated 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

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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 imminent 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’s $d=0.50$, applying a 2-tailed $\alpha$ 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.

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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 $\geq 34$ 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. 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.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Content of measure</th>
<th>Timing of measures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
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<tr>
<td>Demographic questionnaire</td>
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</tr>
<tr>
<td>ACESb</td>
<td>Adverse childhood experiences</td>
<td>✓</td>
</tr>
<tr>
<td>DES-IIc</td>
<td>Dissociative symptoms</td>
<td>✓</td>
</tr>
<tr>
<td>BSSd</td>
<td>Suicidal ideation</td>
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<tr>
<td>CSSRS—clinician rated</td>
<td>Suicidal ideation</td>
<td>✓</td>
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<tr>
<td>CSSRS—past week (self-rated)</td>
<td>Suicidal ideation</td>
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<tr>
<td>BDI-IIf</td>
<td>Depressive symptoms</td>
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<tr>
<td>PHQ-9g</td>
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<td>GAD-7h</td>
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<tr>
<td>DERSj</td>
<td>Emotional dysregulation</td>
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</tr>
</tbody>
</table>

aIndicates the timing of the respective measures.  
bACES: Adverse Childhood Experiences Scale.  
cDES-II: Dissociative Experiences Scale.  
dBSS: Beck Scale for Suicide Ideation.  
eCSSRS: Columbia Suicide Severity Rating Scale.  
fBDI-II: Beck Depression Inventory-II.  
gPHQ-9: Patient Health Questionnaire-9.  
hGAD-7: Generalized Anxiety Disorder-7.  
iIES-R: Impact of Events Scale Revised.  
jDERS: 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).
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].

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 [67].

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) [68].

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≤.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**

https://www.researchprotocols.org/2021/11/e30711 JMIR Res Protoc 2021 | vol. 10 | iss. 11 | e30711 | p.12 (page number not for citation purposes)


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.

Trial Registration: ClinicalTrials.gov NCT04176666; https://clinicaltrials.gov/ct2/show/NCT04176666
International Registered Report Identifier (IRRID): PRR1-10.2196/31789

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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.
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 Dalglish [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 Dalglish [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 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 statements. 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 (T1, preintervention) and after approximately 2 weeks of the intervention (T2, postintervention) through self-report measures that the adolescents fill in using Nettskjema, a secure online tool to conduct surveys [45]. A follow-up evaluation (T3) 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.

**Acknowledgments**

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References


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 (#I8-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.

Trial Registration: ClinicalTrials.gov NCT04810455; http://clinicaltrials.gov/ct2/show/NCT04810455

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

**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.

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Baseline</th>
<th>Deployment</th>
<th>Follow-up</th>
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<tr>
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<td>Week 1</td>
<td>Week 2</td>
<td>Week 3</td>
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<tr>
<td>Perceived child ER ability</td>
<td>Collected daily</td>
<td>Collected daily</td>
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<tr>
<td>Daily parent report ecological momentary assessment (modified differential emotions scale)</td>
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<td>Daily parent report ecological momentary assessment (reaction to triggers)</td>
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<td>Weekly parent questionnaire (ER Checklist)</td>
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<td>Weekly parent questionnaire (Twente Engagement With eHealth Technologies Scale)</td>
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<tr>
<td>Interviews with families</td>
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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 overwwhelmed 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 at all and extremely 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 liability 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 Liability 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 $\alpha$ 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.
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 presumed 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.

References


33. Sproutel. URL: http://www.sproutel.com [accessed 2020-12-29]
34. Purrble. URL: http://www.purrble.com [accessed 2020-12-29]

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

https://www.researchprotocols.org/2021/11/e28914
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
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 men 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]:

https://www.researchprotocols.org/2021/11/e25099
- 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 $\alpha$ 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).

![Cluster randomized trial flow diagram. HIVST: HIV self-testing; RDT: rapid diagnostic test.](https://www.researchprotocols.org/2021/11/e25099)
**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.

![HIVST Pathway Diagram](https://www.researchprotocols.org/2021/11/e25099)

**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.

Acknowledgments

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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


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
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.
**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 fulfill 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).

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

<sup>a</sup>LDL: low-density lipoprotein.<br>
<sup>b</sup>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.

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

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% HRR) [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%,
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.

Acknowledgments

This work is supported by the Portuguese Foundation for Science and Technology, grant number SFRH/BD/136702/2018.

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.
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

References


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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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, referrals 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

(JMIR Res Protoc 2021;10(11):e31951) doi:10.2196/31951

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 included in this 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
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:

\[
\text{Sample size} = \frac{(1.96^2 \times \text{Variance})}{d^2}
\]

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-COVID-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.

<table>
<thead>
<tr>
<th>Serial number</th>
<th>Activity</th>
<th>Intervention arm</th>
<th>Control arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>• Meeting with key stakeholders</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>• Health talk sessions in community</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>• Refer patients to VC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>• Awareness activity through IEC distribution</td>
<td>Yes (door-to-door)</td>
<td>Yes (cluster meeting in village during visits)</td>
</tr>
<tr>
<td>4</td>
<td>• Permission for door-to-door survey intervention</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>• Door-to-door screening</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>• Refer patients to VC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.
the work in this initiative. The Operational Research Capacity Building Study Group mentored the authors and was funded by the Seva Foundation in this endeavor. A funding source was not sought for the preparation of the article or implementation of the project on which this research is based. The Operational Research Capacity Building Group consists of the following authors, who contributed equally to the paper: Gudlavalleti VS Murthy, Rajan Shukla, Samiksha Singh, Shailaja Tetali, Suresh K Rathi, Hemant Mahajan, Melissa G Lewis, Hira Pant, Tripura Batchu, Anirudh G Gaurang, Suzanne Gilbert, Ken Bassett, Priya A Reddy, Parami Dhakhwa, Ram P Kandel, Kuldeep Singh, and Prasanna Sharma.

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.

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


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

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 $d_{\text{ePREP}}=0.42$) and emotional support (Cohen $d_{\text{OurRelationship}}=0.46$; Cohen $d_{\text{ePREP}}=0.36$), along with decreases in breakup potential (Cohen $d_{\text{OurRelationship}}=0.53$; Cohen $d_{\text{ePREP}}=0.43$), communication conflict (Cohen $d_{\text{OurRelationship}}=0.78$; Cohen $d_{\text{ePREP}}=0.54$), and intimate partner violence (IPV; Cohen $d_{\text{OurRelationship}}=0.10$; Cohen $d_{\text{ePREP}}=−0.08$) [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 $\alpha$=.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 $\alpha$=.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 $\alpha$=.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 $\alpha$=.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 (page number not for citation purposes)* [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 $\alpha$=.86) [48]. Furthermore, this scale has excellent discrimination when attempting to detect severe cases of psychopathology, providing evidence of its validity [47].

**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, *My partner/spouse was rude or mean to me when we disagreed*. Past RCTs using this item have reported good internal consistency (Cronbach $\alpha$=.83) [17].

**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 Predictors × Treatment × Coaching interactions. However, the second model will maintain all predictors by coaching interactions but drop all program assignment interactions (ie, resulting in only Predictors × Coaching interactions). Next, the root mean square error (RMSE) between the 2 models will be compared. If the null hypothesis does not get rejected (H0: 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 (H1: RMSE Model 1 ≠ 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 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.
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:

\[ \hat{Y}(x, \text{Contingent Coach}) - \hat{Y}(x, \text{Full Coach}) \]

where \( \hat{Y} \) is the between-group likelihood of treatment adherence or gains for couple \( x \), \( \text{Full Coach} \) is the within-group likelihood of treatment adherence or gains for couple \( x \) in the full-coach condition, and \( \text{Contingent Coach} \) 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**


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

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VIMP: variable importance
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 reinstalment 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), Django (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 $\alpha=0.05$.

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 (e.g., 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 (e.g., 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.

<table>
<thead>
<tr>
<th>Potential event and consequences</th>
<th>Type of harm</th>
<th>Severity (1-5)</th>
<th>Likelihood (1-5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reidentification of a participant</td>
<td>Psychological</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Participants can feel betrayed by the data controller and lose trust in the research or society</td>
<td>Economical</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Participants with controversial opinions could lose their jobs if these views are considered particularly dangerous by their employers</td>
<td>Social</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Participants with controversial opinions could be rejected and isolated from the societies they belong to</td>
<td>Physical</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Participants with controversial opinions could be physically assaulted because of their opinions</td>
<td>Psychological</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

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.

Acknowledgments

The authors would like to acknowledge Samuel Giacomelli, Luca Fedrizzi, Claudio Postinghel, Luca d’Incà, Giulio Michelon, and the whole Belka team for their fundamental contribution to the development of the project’s software.

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https://www.researchprotocols.org/2021/11/e33653
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


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
National Disability Insurance Scheme and the Lived Experience of Psychosocial Disability for 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 intervention 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 continuity of care with this population group.

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 potential indicators 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 this vulnerable group of people, while also informing health policy.

International Registered Report Identifier (IRRID): PRR1-10.2196/33268
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%) presentations classified as “Mental and Behavioural Disorders,” 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 the inability to navigate access across multiple services [9]. Those 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].

Those in a mental health crisis periodically have the longest wait times in the ED and, at times, leave before treatment is completed [12]. Alternatively, they could 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], possibly due to inadequate or a rationing of care [18]. Conversely, positive experiences of continuity of care practices contribute to favorable patient outcomes [19].

Lack of psychiatric beds in hospitals can also be a cause for delayed treatment. 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 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.

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 outcomes for patients [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 those 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 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, 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 at transfer of care for those 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 those 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 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?

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 phenomena to be discovered and interpreted for this study are: (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 discover 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, the lived experience voice will be captured and augmented by the voice of carers (participant group 1) with interviews and of 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.

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**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.

**Table 1.** Characteristics and inclusion/exclusion criteria for each participant group.

<table>
<thead>
<tr>
<th>Participant group</th>
<th>Sample and sample size</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;20 (lived experience: n=14; carers: n=7)</td>
<td>Aged &gt;18 years; have lived experience and a psychosocial disability NDIS plan; not in acute care at the time of the interview; presented to the ED 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</td>
<td>Anyone that is unwell and unable to give informed consent; anyone that does not have a psychosocial disability NDIS plan; anyone that has not presented to the ED</td>
</tr>
<tr>
<td>2</td>
<td>&gt;20 NDIS support workers</td>
<td>Aged &gt;18 years; NDIS support workers and support coordinators with experience of intervention with people who have presented to the ED</td>
<td>Anyone who is not an NDIS support coordinator or support worker</td>
</tr>
<tr>
<td>3</td>
<td>&gt;50 individuals on a psychosocial disability NDIS plan</td>
<td>Same as participant group 1</td>
<td>Same as participant group 1</td>
</tr>
<tr>
<td>4</td>
<td>&gt;50 clinicians (including doctors, nurses, psychiatrists, social workers)</td>
<td>Aged &gt;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</td>
<td>Clinicians (including doctors, nurses, psychiatrists, social workers) who have not worked in the ED within the last 2 years</td>
</tr>
</tbody>
</table>

aNDIS: National Disability Insurance Scheme.
bED: 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 to enhance continuity of care to improve connection with community mental health services and outcomes for patients [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.

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.

**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 stay well and to inform health policy.

Acknowledgments
This research project is funded by MIND Australia Inc.

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
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]


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]


Abbreviations

ED: emergency department
NDIS: National Disability Insurance Scheme
PSD: psychosocial disability
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 (427/545, 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.
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 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 (StatCorp 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.

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:

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 during 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.
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
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.

Trial Registration: ISRCTN registry ISRCTN38472626; https://www.isrctn.com/ISRCTN38472626

International Registered Report Identifier (IRRID): DERR1-10.2196/28191

(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 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
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).

**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 Malcantone 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-I 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 include 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.
Due to some recruitment issues, the COVID-19 pandemic, and analyzed for the qualitative study and economic evaluation. 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.

### Direct costs

<table>
<thead>
<tr>
<th>Cost type</th>
<th>Intervention group (CRHT)</th>
<th>Control group (hospitalization)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment phase</td>
<td>Sum of direct medical and nonmedical costs. 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.</td>
<td>Total bed cost per day \times total number of inpatient days \begin{align*} \text{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.} \end{align*}</td>
</tr>
<tr>
<td>Follow-up phase</td>
<td>Direct costs in the follow-up phase correspond to direct medical costs, including the costs of medical consultations, medical emergencies, hospitalizations, pharmaceutical therapies, etc</td>
<td>Same costs for the intervention group</td>
</tr>
</tbody>
</table>

### Indirect costs

<table>
<thead>
<tr>
<th>Cost type</th>
<th>Intervention group (CRHT)</th>
<th>Control group (hospitalization)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment and follow-up phases</td>
<td>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.</td>
<td>Same costs for the intervention group</td>
</tr>
</tbody>
</table>

\textsuperscript{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


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.

Trial Registration: International Clinical Trials Registry Platform DRKS00023806; https://trialsearch.who.int/Trial2.aspx?TrialID=DRKS00023806

International Registered Report Identifier (IRRID): DERR1-10.2196/30259

(JMIR Res Protoc 2021;10(11):e30259) doi:10.2196/30259

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 Health Toolbox 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-Barre 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.

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.

<table>
<thead>
<tr>
<th>Disease</th>
<th>CNS complication base rate (%) [10]</th>
<th>Extrapolated CNS complications from COVID-19, n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>World a</td>
<td>Europe b</td>
</tr>
<tr>
<td>SARS</td>
<td>0.04</td>
<td>79,335</td>
</tr>
<tr>
<td>MERS</td>
<td>0.20</td>
<td>396,673</td>
</tr>
</tbody>
</table>

bBased 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].

<table>
<thead>
<tr>
<th>Population</th>
<th>Population size (millions), n&lt;sup&gt;a&lt;/sup&gt;</th>
<th>CNS complications based on hypothetical saturation rates, n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>30% saturation</td>
</tr>
<tr>
<td>Global</td>
<td>7794.80</td>
<td>93,537,600</td>
</tr>
<tr>
<td></td>
<td>SARS (0.04%)</td>
<td>467,688,000</td>
</tr>
<tr>
<td></td>
<td>MERS (0.20%)</td>
<td>8,971,632</td>
</tr>
<tr>
<td>Europe</td>
<td>747.636</td>
<td>44,858,160</td>
</tr>
<tr>
<td></td>
<td>SARS (0.04%)</td>
<td>1,005,406</td>
</tr>
<tr>
<td></td>
<td>MERS (0.20%)</td>
<td>5,027,034</td>
</tr>
<tr>
<td>Germany</td>
<td>83.7839</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SARS (0.04%)</td>
<td>39,720,000</td>
</tr>
<tr>
<td></td>
<td>MERS (0.20%)</td>
<td>198,600,000</td>
</tr>
<tr>
<td>United States</td>
<td>331.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SARS (0.04%)</td>
<td>16,560,000</td>
</tr>
<tr>
<td></td>
<td>MERS (0.20%)</td>
<td>82,800,000</td>
</tr>
<tr>
<td>India</td>
<td>1380.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SARS (0.04%)</td>
<td>2,550,720</td>
</tr>
<tr>
<td></td>
<td>MERS (0.20%)</td>
<td>12,753,600</td>
</tr>
<tr>
<td>Brazil</td>
<td>1380.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SARS (0.04%)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>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.<sup>a</sup>

<table>
<thead>
<tr>
<th>Neurological and psychiatric outcomes</th>
<th>Base rates (%) [9]</th>
<th>Case counts, n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>World&lt;sup&gt;b&lt;/sup&gt; (N=198,336,258)</td>
<td>Germany&lt;sup&gt;b&lt;/sup&gt; (N=3,778,277)</td>
</tr>
<tr>
<td>Neurological</td>
<td>2.10</td>
<td>41,150,061</td>
</tr>
<tr>
<td>Any psychiatric disorder</td>
<td>6.03</td>
<td>17,116,419</td>
</tr>
<tr>
<td>(mood, anxiety, psychotic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substance misuse</td>
<td>1.92</td>
<td>3,808,056</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2.53</td>
<td>5,017,907</td>
</tr>
<tr>
<td>Any first outcome</td>
<td>12.84</td>
<td>25,466,376</td>
</tr>
</tbody>
</table>

<sup>a</sup>This table is for illustrative purposes only and is neither exhaustive nor necessarily reflective of the future outcomes in any given country or region.  
<sup>c</sup>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.

<table>
<thead>
<tr>
<th>General inclusion criteria</th>
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<tbody>
<tr>
<td>• written informed consent</td>
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<tr>
<td>• aged 25 to 75 years</td>
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<tr>
<td>• able and willing to participate throughout the study</td>
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<tr>
<td>• fluent German language abilities</td>
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<tr>
<th>Cohort-specific inclusion criteria</th>
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<tr>
<td>Cohort I: Asymptomatic course of COVID-19 (SARS-CoV-2–positive) or mild course (ie, no symptoms other than anosmia and/or ageusia)</td>
</tr>
<tr>
<td>Cohort II: severely affected course of COVID-19 (SARS-CoV-2–positive) (ie, requiring hospital stay)</td>
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<tr>
<td>Cohort III: Healthy controls will only be included in the study if they also meet all of the following criteria:</td>
</tr>
<tr>
<td>• must perform &gt;−1.0 SD on the Hopkins Verbal Learning Test</td>
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<tr>
<td>• no substance abuse</td>
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<tr>
<td>• no known history of or current diagnosed psychiatric illness</td>
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<tr>
<td>• negative SARS-CoV-2 rapid antibody test at baseline</td>
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<table>
<thead>
<tr>
<th>General exclusion criteria</th>
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<tr>
<td>• inability to give informed consent</td>
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<tr>
<td>• any condition that clearly interferes with participation in the study</td>
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<tr>
<td>• any condition that interferes with the clinical or neuropsychological study procedures</td>
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<tr>
<td>• sensory impairment that prevents or significantly interferes with neuropsychological testing</td>
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<tr>
<td>• contraindication for magnetic resonance imaging</td>
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<td>• severe or unstable medical condition</td>
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<tr>
<td>• current major depressive episode</td>
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<tr>
<td>• psychotic disorder, bipolar disorder, substance abuse at present or in the past</td>
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<tr>
<td>• known neurodegenerative disorder (Alzheimer disease, Parkinson disease, frontotemporal dementia, Huntington disease, amyotrophic lateral sclerosis)</td>
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<tr>
<td>• vascular dementia, history of stroke</td>
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<td>• history of malignant disease</td>
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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
analyses 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 “close” 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 (postinfecitious) 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, patients who recovered from COVID-19 have employed such comprehensive neurocognitive testing in 

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 can 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, pulmonological, 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 it...
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


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
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, socioeconomic, 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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KEYWORDS
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% CO2 (Heracell Vios 160, 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 depend 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 log2 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 (|z|)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 operator 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, 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.](https://www.researchprotocols.org/2021/11/e32395/fig1.png)
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 ($\chi^2$ test: $P=0.28$), whereas participating cancer-free controls were slightly younger than participants with childhood cancer ($\chi^2$ test: $P<0.001$). 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.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Participants</th>
<th>Nonparticipants$^a$</th>
<th>Controls (n=150)</th>
<th>Total (n=591)</th>
<th>SPNs (n=146)</th>
<th>FPNs (n=1389)</th>
<th>Controls (n=96)</th>
<th>Total (n=1631)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>50 (49.5)</td>
<td>189 (55.6)</td>
<td>62 (41.3)</td>
<td>301 (50.9)</td>
<td>71 (48.6)</td>
<td>606 (43.6)</td>
<td>42 (43.8)</td>
<td>719 (44.1)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>51 (50.5)</td>
<td>151 (44.4)</td>
<td>88 (58.7)</td>
<td>290 (49.1)</td>
<td>65 (44.5)</td>
<td>657 (47.3)</td>
<td>54 (56.2)</td>
<td>776 (47.6)</td>
</tr>
<tr>
<td>Sex missing, n (%)</td>
<td>N/A$^d$</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Age at recruitment (years), mean (range)</td>
<td>32 (19-51)</td>
<td>34 (19-53)</td>
<td>29 (18-48)</td>
<td>32 (19-53)</td>
<td>34 (18-49)</td>
<td>34 (18-51)</td>
<td>31 (18-51)</td>
<td>33 (18-51)</td>
</tr>
<tr>
<td>&lt;25 years old, n (%)</td>
<td>19 (18.8)</td>
<td>44 (12.9)</td>
<td>57 (38.0)</td>
<td>120 (20.3)</td>
<td>18 (12.3)</td>
<td>111 (8.0)</td>
<td>17 (17.7)</td>
<td>146 (9.0)</td>
</tr>
<tr>
<td>25-29 years old, n (%)</td>
<td>25 (24.8)</td>
<td>69 (20.3)</td>
<td>40 (26.7)</td>
<td>134 (22.7)</td>
<td>18 (12.3)</td>
<td>234 (16.8)</td>
<td>25 (26.0)</td>
<td>277 (17.0)</td>
</tr>
<tr>
<td>30-34 years old, n (%)</td>
<td>19 (18.8)</td>
<td>78 (22.9)</td>
<td>20 (13.2)</td>
<td>117 (19.8)</td>
<td>24 (16.4)</td>
<td>245 (17.6)</td>
<td>19 (29.8)</td>
<td>288 (17.7)</td>
</tr>
<tr>
<td>≥35 years old, n (%)</td>
<td>38 (37.6)</td>
<td>149 (43.8)</td>
<td>33 (22.0)</td>
<td>220 (37.2)</td>
<td>75 (51.4)</td>
<td>672 (48.4)</td>
<td>30 (31.3)</td>
<td>777 (47.6)</td>
</tr>
<tr>
<td>Age missing, n (%)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>11 (7.5)</td>
<td>127 (9.1)</td>
<td>5 (5.2)</td>
<td>143 (8.8)</td>
</tr>
<tr>
<td>Age at 1st diagnosis (years), mean (range)</td>
<td>7 (0-14)</td>
<td>8 (0-16)</td>
<td>N/A</td>
<td>N/A</td>
<td>8 (0-14)</td>
<td>7 (0-15)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Year of 1st diagnosis</td>
<td>1980-2011</td>
<td>1980-2012</td>
<td>N/A</td>
<td>N/A</td>
<td>1980-2005</td>
<td>1980-2012</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Years between 1st and 2nd diagnoses, mean (range)</td>
<td>16 (2-35)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>16 (1-30)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Age at 2nd diagnosis (years), mean (range)</td>
<td>23 (5-46)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>24 (5-41)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Year of 2nd diagnosis</td>
<td>1986-2018</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>1989-2014</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

$^a$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.

<table>
<thead>
<tr>
<th>Cancer site (International Classification of Childhood Cancer 3rd Edition)</th>
<th>Participants</th>
<th>Nonparticipants&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SPNs&lt;sup&gt;b&lt;/sup&gt; (n=101)</td>
</tr>
<tr>
<td>1st neoplasm, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia (I(a), I(b), I(c), I(d))</td>
<td>41 (40.6)</td>
<td>166 (48.8)</td>
</tr>
<tr>
<td>Lymphoma (II(a), II(b), II(c))</td>
<td>41 (40.6)</td>
<td>135 (39.7)</td>
</tr>
<tr>
<td>Central/peripheral nervous system (III(a), III(b), III(c), III(d), IV(a))</td>
<td>15 (14.9)</td>
<td>35 (10.3)</td>
</tr>
<tr>
<td>Other tumors V, VI(a), IX(a), IX(e)</td>
<td>4 (4.0)</td>
<td>4 (1.2)</td>
</tr>
<tr>
<td>2nd neoplasm, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid cancer (XI(b))</td>
<td>30 (29.7)</td>
<td>N/A&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Skin carcinoma (XI(e))</td>
<td>32 (31.7)</td>
<td>N/A</td>
</tr>
<tr>
<td>Malignant melanoma (XI(d))</td>
<td>4 (4.0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Leukemia (I(a), I(b), I(d))</td>
<td>9 (8.9)</td>
<td>N/A</td>
</tr>
<tr>
<td>Lymphoma (II(a), II(b))</td>
<td>6 (5.9)</td>
<td>N/A</td>
</tr>
<tr>
<td>Central nervous system (III(a), III(b), III(c))</td>
<td>9 (8.9)</td>
<td>N/A</td>
</tr>
<tr>
<td>Breast cancer (XI(f))</td>
<td>3 (3.0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Other unspecified carcinoma (XI(f))</td>
<td>6 (5.9)</td>
<td>N/A</td>
</tr>
<tr>
<td>Sarcoma (IX(d), IX(e))</td>
<td>2 (2.0)</td>
<td>N/A</td>
</tr>
<tr>
<td>3rd neoplasm, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal carcinomas (VI(b))</td>
<td>1 (1.0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Skin carcinoma (XI(e))</td>
<td>2 (2.0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Breast cancer (XI(f))</td>
<td>1 (1.0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Other and unspecified carcinomas (XI(f))</td>
<td>2 (2.0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Other specified intracranial and intraspinal neoplasms (III(e))</td>
<td>2 (2.0)</td>
<td>N/A</td>
</tr>
<tr>
<td>4th neoplasm, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid cancer (XI(b))</td>
<td>1 (1.0)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

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 | — | — |

<sup>a</sup>Information available only for nonparticipants from the main study.

<sup>b</sup>SPNs: second primary neoplasms.

<sup>c</sup>FPNs: first primary neoplasms.

https://www.researchprotocols.org/2021/11/e32395
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 (90.3% of 340 participating FPN), and 100 cancer-free controls (66.7% 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.

<table>
<thead>
<tr>
<th>Type of data</th>
<th>SPNs (n=101)</th>
<th>FPNs (n=340)</th>
<th>Controls (n=150)</th>
<th>Total (n=591)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questionnaire data, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participant information</td>
<td>85 (84.2)</td>
<td>325 (95.6)</td>
<td>144 (96.0)</td>
<td>554 (93.7)</td>
</tr>
<tr>
<td>Family history of diseases</td>
<td>85 (84.2)</td>
<td>325 (95.6)</td>
<td>146 (97.3)</td>
<td>556 (94.1)</td>
</tr>
<tr>
<td>Both questionnaires</td>
<td>85 (84.2)</td>
<td>325 (95.6)</td>
<td>144 (96.0)</td>
<td>554 (93.7)</td>
</tr>
<tr>
<td>Biosamples, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy</td>
<td>92 (91.1)</td>
<td>307 (90.3)</td>
<td>100 (66.7)</td>
<td>499 (84.4)</td>
</tr>
<tr>
<td>Saliva</td>
<td>84 (83.2)</td>
<td>319 (93.8)</td>
<td>108 (72.0)</td>
<td>511 (86.5)</td>
</tr>
<tr>
<td>Biopsy and saliva</td>
<td>77 (76.2)</td>
<td>291 (85.6)</td>
<td>71 (47.3)</td>
<td>439 (74.3)</td>
</tr>
<tr>
<td>Biopsy or saliva</td>
<td>99 (98.0)</td>
<td>335 (98.5)</td>
<td>137 (91.3)</td>
<td>571 (96.6)</td>
</tr>
<tr>
<td>No bio-samples</td>
<td>2 (2.0)</td>
<td>5 (1.5)</td>
<td>13 (8.7)</td>
<td>20 (3.4)</td>
</tr>
<tr>
<td>Cryopreserved tubes of fibroblasts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total, n</td>
<td>757</td>
<td>2179</td>
<td>950</td>
<td>3886</td>
</tr>
<tr>
<td>Tubes per participant, mean (SD)</td>
<td>7.7 (4.3)</td>
<td>6.5 (3.1)</td>
<td>6.9 (5.9)</td>
<td>6.8 (4.2)</td>
</tr>
<tr>
<td>Tubes per participant, minimum</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tubes per participant, maximum</td>
<td>20</td>
<td>16</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>DNA extracts, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From fibroblasts</td>
<td>90 (89.1)</td>
<td>301 (88.5)</td>
<td>97 (64.7)</td>
<td>488 (82.6)</td>
</tr>
<tr>
<td>From saliva</td>
<td>84 (83.2)</td>
<td>319 (93.8)</td>
<td>107 (71.3)</td>
<td>510 (86.3)</td>
</tr>
</tbody>
</table>

aSPNs: second primary neoplasms.
bFPNs: 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 (e.g., 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 (e.g., 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 of 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.

Acknowledgments
The authors especially thank Claudia Spix from the German Childhood Cancer Registry for her assistance in developing strategies and materials for the recruitment of former childhood cancer patients with her long-standing experience in conducting register-based studies in Germany. In addition, we gratefully acknowledge the assistance from Franziska Himmelsbach, Cornelia Becker, Ilona Kerenyi, and Marianne Brömmel from the German Childhood Cancer Registry who identified, matched, and made the first contact with former childhood cancer patients. We are thankful for the local support of all participating dermatologists in Germany, Austria, and Switzerland, for the central support of Patricia Sadre Fischer during the start of the recruitment, as well as for the excellent laboratory assistance of Ursula Disque-Kaiser. We further thank Caine Lucas Grandt, Claas Sontag, Katharina Musiolik, and Christin Goldbaum for their meticulous work on the databases and Heiko Karle for his tireless work to establish the method for fibroblast irradiation. The authors acknowledge resources and support from the Bioinformatics Core Facility at the University Medical Center Mainz.

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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.

References


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]


84. Li X, Yin 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/NGHRI, NIH/NIMH, NIH/NIDA, Biospecimen Collection Source Site—NDRI, Biospecimen Collection Source Site—RPCI, Biospecimen Core Resource—VAR1, 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]


Abbreviations

CMMC: combined multivariate and collapsing expression quantitative trait loci (eQTLs)
FDR: false discovery rate
FPN: first primary neoplasm
GTEx: genotype-tissue expression database
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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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

Rachel Engler-Stringer¹, PhD; Jennifer Black², PhD; Nazeem Muhajarine¹, PhD; Wanda Martin³, PhD; Jason Gilliland⁴, PhD; Janet McVittie⁵, PhD; Sara Kirk⁶, PhD; Hannah Wittman⁷, PhD; Amin Mousavi⁸, PhD; Sylvana Tu⁹, MPH; Brent Hills¹⁰, MEd; Gordon Androsoff¹¹, MSc; Debbie Field¹², MA; Brit Macdonald¹³, BA; Chelsea Belt¹⁴, MSc; Hassan Vatanparast¹⁵, PhD

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Related Article:
Correction of: https://www.researchprotocols.org/2021/9/e30899
doi:10.2196/34393

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:
Rachel Engler-Stringer1, PhD; Jennifer Black2, PhD; Nazeem Muhajarine1, PhD; Wanda Martin1, PhD; Jason Gilliland3, PhD; Janet McVittie3, PhD; Sara Kirk4, PhD; Hannah Wittman5, PhD; Amin Mousavi7, PhD; Sinikka Elliott8, PhD; Sylvania Tu9, MPH; Brent Hills10, MED; Gordon Androsoff11, MSc; Debbie Field12, MA; Brit Macdonald13, BA; Chelsea Belt14, MSc; Hassan Vatanparast15, PhD

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This has been corrected to:

Rachel Engler-Stringer1, PhD; Jennifer Black2, PhD; Nazeem Muhajarine1, PhD; Wanda Martin1, PhD; Jason Gilliland3, PhD; Janet McVittie3, PhD; Sara Kirk4, PhD; Hannah Wittman5, PhD; Amin Mousavi7, PhD; Sinikka Elliott8, PhD; Sylvania Tu9, MPH; Brent Hills10, MED; Gordon Androsoff11, MSc; Debbie Field12, MA; Brit Macdonald13, BA; Chelsea Belt14, MSc; Hassan Vatanparast15, PhD

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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.
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
doi:10.2196/34515

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.

This has been corrected to the following:

Medard Kofi Adu1*, BSc, MSc; Reham Shalaby1*, MD; Ejemai Eboreime1, MD, PhD; Adegboyega Sapara1, PhD, FRCP; Nnamdi Nkire1, MD, MBBS, DHSM, DCP, FRAMI; Rajan Chawla1, MBBS, CCT, MSC, MRCPych; Chidi Chima1, MBBS, MPH, PhD; Michael Achor1, MD, MSc, FRCP; Felix Osiogo1*, FRCPC, FWACS, CCT-UK, MBBS; Pierre Chue1, MD, DABPN, MRCPych, FRCP; Andrew J Greenshaw1, PhD, FRSA; Vincent Israel Agyapong1,2, MD, PhD, FRCPC, FRCPych

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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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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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