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Optimizing the Context of Support to Improve Outcomes of Internet-Based Self-help in Individuals With Depressive Symptoms: Protocol for a Randomized Factorial Trial

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Abstract

Background: Internet-based self-help interventions for individuals with depressive symptoms, in which the main component is often a web-based self-help program, have been shown to be efficacious in many controlled trials. However, there are also trials on self-help programs showing no significant effect when delivered in routine care, and some studies report high dropout and low adherence rates. Research suggests that these findings do not emerge primarily due to the specific content of a self-help program. It seems more important how a program is embedded in the context of human and automated support before and during the use of a self-help program.

Objective: This study aims to better understand the effects of 4 supportive contextual factors on outcomes of and adherence to a web-based self-help program for depressive symptoms. In a factorial experiment, 2 of 4 supportive factors, for which there is evidence for their role on outcomes and adherence, are realized during the intervention—personal guidance and automated email reminders. The other 2 factors are realized before the intervention—a diagnostic interview and a preintervention module aimed at increasing the motivation to use the program with motivational interviewing techniques.

Methods: The study is a full factorial randomized trial. Adults with mild to moderate depressive symptoms (Patient Health Questionnaire–9 score: 5-14) are recruited from the community through the internet and conventional media. All participants receive access to a web-based self-help program based on problem-solving therapy. They are randomized across 4 experimental factors, each reflecting the presence versus absence of a supportive factor (guidance, automated reminders, diagnostic interview, preintervention module) resulting in a 16-condition balanced factorial design. The primary outcome is depressive symptoms at 10 weeks post assessment. Secondary outcomes include adherence to the program, anxiety, stress, health-related quality of life, possible negative effects, and treatment satisfaction. Potential moderators and mediators (eg, treatment expectancy, problem-solving skills, working alliance with the study team) will also be investigated.

Results: Ethical approval was received on January 20, 2020. The study was initiated in February 2020, and 240 participants have been enrolled in the study as of November 1, 2020. Recruitment for a total of 255 participants is ongoing. Data collection is expected to be completed by May 2021.

Conclusions: A better understanding of relevant supportive factors in the dissemination of web-based interventions is necessary to improve outcomes of and adherence to web-based self-help programs. This study may inform health care systems and guide decisions to optimize the implementation context of web-based self-help programs for depressive symptoms.

Trial Registration: ClinicalTrials.gov NCT04318236; https://clinicaltrials.gov/ct2/show/NCT04318236

International Registered Report Identifier (IRRID): DERR1-10.2196/21207
Introduction

Depression is one of the most common mental disorders that burdens society and individuals psychologically and financially [1,2]. Psychological consequences of depression include lower quality of life and more years lived with disability [3,4]. Although psychotherapy is an established evidence-based treatment option for depression [5], people often do not receive adequate care [6-8]. Internet-based self-help interventions are promising to reduce the burden of depression. During the last two decades, several research groups intensively studied the efficacy of internet-based self-help interventions and concluded that they effectively reduce depression [9-12].

Internet-based self-help interventions complement existing interventions in health care, addressing some of their limitations. Potential advantages of internet-based self-help interventions include that they are easily accessible, provide a high degree of anonymity, can be used independently of time and place, and can be provided to many people simultaneously. Hence, many authors suggest internet-based self-help interventions as a possibility to complement face-to-face psychotherapy to improve mental health care [13].

Although internet-based self-help interventions effectively reduce depressive symptoms, their potential might not be fully exploited. For example, studies [10] about internet-based self-help interventions for depression report a wide range of effect sizes (Hedges g=0.02-1.56). One study [14] that investigated widely used internet-based self-help interventions for depression failed to transfer the established effects into other settings, such as primary care. Further challenges of internet-based self-help interventions are low uptake rates (ie, logging into an intervention) and low levels of adherence (eg, completing modules of an intervention) [15,16].

One reason for diverging outcomes and adherence seems to be the degree of human support and guidance provided before and during the use of a self-help program. Current literature suggests that unguided internet interventions without human support at any stage tend to be associated with high dropout rates [17], lower adherence [18], and lower effects [11]. In a review [19], the authors suggested there were positive effects from guidance during the treatment on outcome in depressive patients. Additionally, several meta-analyses [9,12,20,21] report larger symptom reductions in guided self-help interventions with therapist support during the treatment compared to unguided self-help interventions without therapist support during the treatment. However, the differences between guided and unguided interventions may also be related to other factors such as the scope of diagnostic assessments or the length and content of a self-help program. These and other factors may confound the association between guidance, adherence, and outcomes. It is worth mentioning that in some studies [22,23] directly comparing self-help interventions with and without guidance, no significant differences were reported about the outcomes and number of modules completed.

In the review [19], the authors propose that other forms of human interaction (such as pretreatment contact) might also be beneficial for the treatment with internet-based self-help interventions. In a study [24] with patients that have social anxiety disorder, a diagnostic telephone interview conducted before an internet-based intervention significantly improved adherence to treatment and secondary outcomes of depression and stress.

Other aspects that potentially improve internet-based self-help intervention outcomes and adherence can be automated and realized without human contact. There is limited evidence that automated email reminders may improve adherence and outcomes of internet interventions. For example, a study [25] that compared semistandardized email feedback with fully standardized email feedback did not find a difference in the 2 conditions indicating that fully automated emails may be as effective as semistandardized feedback. Furthermore, in a transdiagnostic intervention, email reminders resulted in better outcomes for participants who had elevated co-occurring symptoms of anxiety and depression [26]. However, this did not apply to participants with elevated symptoms of either just anxiety or depression. In the same study [26], the reminders increased the number of people completing the intervention. Consistent with this finding, some participants mentioned that they experience email reminders helpful for adhering to the intervention [27].

Another possibility for increasing outcomes of and adherence to internet-based self-help interventions is to enhance the motivation of participants. A well-known method in face-to-face treatments to address ambivalence and enhance motivation is motivational interviewing [28]. High effect sizes and increased adherence were observed in a study [29] with motivational interviewing prior face-to-face psychotherapy treatment. A study [30] on an internet-based self-help intervention for social phobia was able to replicate these findings for internet-based self-help interventions to some extent—whereas participants of the group that received an additional motivational interviewing–based intervention did not show a higher magnitude of improvement, these participants were more likely to complete the treatment. Furthermore, for patients with depressive symptoms, a brief informational video about internet-based self-help interventions significantly increased the acceptance of internet-based self-help interventions [31].

Thus, several supportive contextual factors have been associated with better outcomes and increased adherence. Yet, it is not entirely clear which factors are crucial for a significant enhancement of internet-based self-help interventions. Consequently, clear guidelines for how to optimally embed...
internet-based self-help interventions into a context of supportive factors are missing. To fully exploit the potential of internet-based self-help interventions, dismantling studies are needed to understand how and which supportive factors are essential when disseminating internet-based self-help interventions. Often, studies that investigated the influence of a specific supportive factor such as guidance had other factors in their study design that potentially confounded the effect of guidance (eg, a diagnostic interview). Therefore, only conclusions about the whole treatment package (eg, internet-based self-help intervention, diagnostic interview, and guidance combined) and not about individual supportive factors (eg, either diagnostic interview or guidance) were possible. This entanglement limits insight into both the main effect of a given factor and possible interactions with other factors.

One reason for limited insight into essential supportive factors may be reliance upon RCTs in internet-based self-help intervention research. Although RCTs are the gold standard for establishing the efficacy or effectiveness of an intervention, they are not suited for investigating the effects of single supportive factors or specific treatment components. Because RCTs only compare the whole multifactorial intervention (treatment package) with another intervention or a control group, specific mechanisms are confounded with one another. Therefore, it is only possible to draw conclusions about the whole treatment package and not about the main and interactive effects of specific factors [32].

A new approach to getting more insight into how treatments work is the multiphase optimization strategy, which integrates perspectives, approaches, and concepts of various sciences [33]. Collins and Kugler [33] suggest that behavioral intervention research has focused too much on establishing the efficacy of treatments rather than understanding how treatments work and how they could be optimized. The multiphase optimization strategy’s fundamental idea is to optimize interventions to meet specific criteria such as effectiveness, economy, or scalability. Interventions can be optimized by making decisions based on findings about which intervention components work and which intervention components do not work, which ones work well together, or which ones adversely affect each other.

The multiphase optimization strategy presents several experimental designs to optimize interventions. The most frequently used in behavioral sciences is the factorial design [34-36]. This design allows investigating multiple factors simultaneously within one trial. It can reveal which factors are active or inactive in influencing the desired outcomes. More specifically, factorial experiments allow exploring the main effects of and possible interactions between factors. Consequently, the findings of a factorial design study are suited to optimize a given intervention because they provide information about which factors can be kept and which factors can be omitted. Note that Collins and Kugler [33] do not claim that RCTs can be replaced with factorial designs. Rather, they suggest an integrative strategy that focuses both on optimizing interventions (for which there are better designs than RCTs) and establishing efficacy or superiority of interventions (for which RCTs are still the best option).

This study aims to further clarify the optimal context of support of internet-based self-help interventions for depressive symptoms. It uses a factorial design to test the impact of 4 factors and their combinations. These factors are (1) a diagnostic interview conducted before the intervention, (2) a preintervention module using techniques of motivational interviewing accessible before the intervention, (3) human guidance during the intervention, and (4) automated email reminders during the intervention.

Methods

Study Design

The study, including assessments and the self-help intervention, will be conducted online. Participants will not receive any financial reimbursement for taking part in the study. The study consists of a full factorial trial that includes 4 experimental factors. Each factor will be evaluated at 2 levels (either present or absent), resulting in a 16-condition (2 × 2 × 2 × 2) balanced full factorial design (Table 1). Factorial designs allow for reliably estimating all main effects and 2-factor interactions. To do so, the full sample (ie, participants from all 16 conditions) are used. Thereby, power remains associated with all participants as half of the participants are in a condition with a specific factor active, and half of the participants are in a condition with a specific factor inactive. This makes the factorial design efficient with respect to sample size and power.
Table 1. Overview of the 16 experimental conditions of the full factorial design—every factor is balanced; therefore, each is present and absent an equal number of times.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diagnostic interview</th>
<th>Preintervention motivational interviewing module</th>
<th>Guidance</th>
<th>Email reminders</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>✓✓✓✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>2</td>
<td>✓✓</td>
<td>✓</td>
<td>✓</td>
<td>_b</td>
</tr>
<tr>
<td>3</td>
<td>✓</td>
<td>_</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>4</td>
<td>✓✓</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>5</td>
<td>✓✓</td>
<td>_</td>
<td>✓✓</td>
<td>_</td>
</tr>
<tr>
<td>6</td>
<td>✓</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>7</td>
<td>✓</td>
<td>_</td>
<td>_</td>
<td>✓</td>
</tr>
<tr>
<td>8</td>
<td>✓</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>9</td>
<td>✓</td>
<td>_</td>
<td>✓✓</td>
<td>_</td>
</tr>
<tr>
<td>10</td>
<td>✓</td>
<td>_</td>
<td>✓</td>
<td>_</td>
</tr>
<tr>
<td>11</td>
<td>✓</td>
<td>_</td>
<td>_</td>
<td>✓</td>
</tr>
<tr>
<td>12</td>
<td>✓</td>
<td>_</td>
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</tr>
<tr>
<td>13</td>
<td>✓</td>
<td>_</td>
<td>_</td>
<td>✓</td>
</tr>
<tr>
<td>14</td>
<td>✓</td>
<td>_</td>
<td>✓</td>
<td>_</td>
</tr>
<tr>
<td>15</td>
<td>✓</td>
<td>_</td>
<td>_</td>
<td>✓</td>
</tr>
<tr>
<td>16</td>
<td>✓</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
</tbody>
</table>

aFactor is present.
bFactor is absent.

Participant Eligibility

Eligible participants are German-speaking residents of Switzerland, Germany, Austria, and Lichtenstein. Inclusion criteria are (1) being at least 18 years of age; (2) meeting criteria for mild to moderate depression (score between 5 to 14 on the Patient Health Questionnaire–9) [37]; (3) providing written informed consent; (4) having access to the internet as well as an email account; and (5) providing an emergency contact before treatment. The study allows participants to take part even if they currently receive constant antidepressant medication or psychotherapy treatment. Exclusion criteria are (1) having a history of a psychotic or a bipolar disorder and (2) having increased suicidal tendencies (a score >7 on the Suicide Behaviors Questionnaire-Revised)[38,39].

Study Procedure

Interested participants can leave an email address on our study website [40]. Participants will automatically receive study information and an informed consent sheet (by email). After providing informed consent, participants are invited to complete the baseline assessment. Study eligibility is assessed and if included in the study, participants must wait 2 weeks before they can start with the intervention. Depending on which condition participants are randomized to, during these 2 weeks, participants either wait, are diagnostically interviewed, receive access to the preintervention motivational interviewing module, or receive both the interview and the preintervention motivational interviewing module (see Table 2).
Table 2. Study flow and overview of study variables.

<table>
<thead>
<tr>
<th>Study activity</th>
<th>Study period and timepoint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocation</td>
</tr>
<tr>
<td></td>
<td>Week 0, T0</td>
</tr>
<tr>
<td>Enrollment</td>
<td></td>
</tr>
<tr>
<td>Registration</td>
<td>✓</td>
</tr>
<tr>
<td>Informed consent</td>
<td>✓</td>
</tr>
<tr>
<td>Eligibility screening</td>
<td>✓</td>
</tr>
<tr>
<td>Randomization</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Internet intervention</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Factors</td>
<td></td>
</tr>
<tr>
<td>Diagnostic interview</td>
<td></td>
</tr>
<tr>
<td>Motivational interviewing module</td>
<td></td>
</tr>
<tr>
<td>Guidance</td>
<td></td>
</tr>
<tr>
<td>Automated emails</td>
<td></td>
</tr>
<tr>
<td>Surveys</td>
<td></td>
</tr>
<tr>
<td>Patient Health Questionnaire–9</td>
<td>✓</td>
</tr>
<tr>
<td>Generalized Anxiety Disorder–7</td>
<td>✓</td>
</tr>
<tr>
<td>Patient Health Questionnaire–Stress</td>
<td>✓</td>
</tr>
<tr>
<td>Short Form health survey–12</td>
<td></td>
</tr>
<tr>
<td>Suicide Behaviors Questionnaire–Revised</td>
<td>✓</td>
</tr>
<tr>
<td>Social Problem-Solving Inventory–Revised</td>
<td>✓</td>
</tr>
<tr>
<td>Client Satisfaction Questionnaire</td>
<td></td>
</tr>
<tr>
<td>Working Alliance Inventory for Guided Internet Interventions</td>
<td></td>
</tr>
<tr>
<td>Credibility/Expectancy Questionnaire</td>
<td></td>
</tr>
<tr>
<td>Inventory for the Assessment of Negative Effects of Psychotherapy</td>
<td></td>
</tr>
<tr>
<td>System Usability Scale</td>
<td></td>
</tr>
</tbody>
</table>

*aThe study activity was not applied at this point.
*bParentheses indicate that factors apply to half of the participants.
*cPrimary outcome.

If individuals are excluded, they can make use of the intervention outside of the study. However, participants reporting suicidal ideation first need to confirm that they are in touch with their emergency contact or a psychotherapist. We offer to provide a contact for professional psychological help in case participants are severely depressed.

**Recruitment**

Participants are recruited through depression-related websites, radio interviews, self-help groups, Facebook groups, Google ads, and the website of the University of Bern (Switzerland). The description of our study includes a link to the study website. Written informed consent to participate in the study is obtained from all participants.

**Intervention**

The web-based self-help program *Herausforderungen meistern (overcoming challenges)* (HERMES) is based on problem-solving therapy [41]. The first, second, and last author developed the online program at the University of Bern. The problem-solving therapy intervention includes an introductory module and 3 toolkits: (1) Feeling, (2) Thinking, and (3) Acting. Problem-solving therapy shares various assumptions of cognitive behavioral therapy but focuses more explicitly on problems causing distress and problem-solving skills. We recommend that participants use the intervention approximately 1 hour per week and complete each module or toolkit within 2 weeks. This results in 8 weeks of recommended program use. An online problem-solving therapy intervention has previously been
investigated in a 3-arm RCT [42]. Results indicated that, compared to a waiting list control group, the online problem-solving therapy intervention was as effective as an online cognitive behavioral therapy intervention in reducing symptoms of anxiety and depression [42].

Within the factorial design, 4 factors are realized. The first factor consists of a diagnostic telephone interview conducted before the self-help program. The second factor is a preintervention module based on motivational interviewing presented before the self-help program. The module aims at initiating a reflection process about one’s motivation for using the intervention [29]. The third factor is human support during the self-help program with personalized weekly emails. Guidance contains answering questions from participants within 3 working days and giving regular feedback on progress once a week. It is carried out by trained Master and PhD students who are supervised by licensed psychotherapists. The fourth factor is a set of weekly automatically sent emails during the self-help program. The emails inform participants on how far they should be in the program approximately, suggest content to work on next, and remind participants that they take part in a study. In contrast to human support (guidance), these emails are not individualized and contain the same information for all participants. In addition to these emails, prompts are sent to participants who have not logged in for 1 week. Our research focuses on investigating the context of human and automated support when providing web-based interventions. This implies that all participants receive the same main intervention with all program components of HERMES and that the main intervention is not changed throughout the whole study.

Study Outcome Measures

All outcome measures will be assessed online with validated German versions of the original questionnaires.

Primary Outcome Measure

Symptoms of depression will be assessed with the self-reported measure Patient Health Questionnaire–9 [37]. The Patient Health Questionnaire–9 has good diagnostic validity, sensitivity, and specificity and is a commonly used measure to assess and monitor depression severity [43].

Secondary Outcome Measures

Adherence is defined as the extent to which participants use the intervention. Following the suggestion of Donkin et al [44], a composite score encompassing time spent in the intervention, number of modules completed, number of exercises completed, number of log-ins, and number of clicks in the intervention will be used to measure adherence to the intervention. The composite score will be created by averaging the z scores of these indicators. Furthermore, and for exploratory purposes, we will also run the analyses with each of these indicators of adherence.

Symptoms of anxiety will be assessed with the Generalized Anxiety Disorder–7 [45]. Symptoms of stress will be assessed with the stress subscale of the Patient Health Questionnaire [45]. Health-related quality of life will be assessed with the Short Form Health Survey–12 [46,47]. Suicidal ideation will be assessed with the Suicide Behaviors Questionnaire–Revised [38,39]. Problem solving will be assessed with the Social Problem Solving Inventory-Revised [48,49].

Treatment Characteristics

Possible adverse effects of the intervention will be assessed with the Inventory for the Assessment of Negative Effects of Psychotherapy [50]. Client satisfaction will be measured with the Client Satisfaction Questionnaire [51,52]. System usability will be assessed with the System Usability Scale [53,54].

Moderators and Mediators

Demographic information about participants will be assessed at baseline. Treatment expectancy will be assessed with the Credibility/Expectancy Questionnaire [55]. Working alliance with the online coaches will be assessed with the Working Alliance Inventory for Guided Internet Interventions [56].

Randomization

The online platform Qualtrics (Qualtrics XM) randomizes participants in 2 steps. First, after T0 and before any contact with the study team, participants are randomized automatically to 1 of 4 groups (1, diagnostic interview and motivational interviewing module; 2, diagnostic interview; 3, motivational interviewing module; 4, no factor). The first randomization is stratified (either mild or moderate depressive symptoms). Second, after 2 weeks and completing T1, participants are randomized to 1 of 4 groups (1, guidance and email reminders; 2, guidance; 3, email reminders; 4, no factor). Both times, block randomization ensures a balance in sample size across groups over time. A schedule of enrollment and participation is shown in Table 2.

Data Collection, Management, and Analysis

Participants complete questionnaires at all 5 time points online via Qualtrics. We manually invite participants to complete the baseline questionnaire (T0). The 4 subsequent time points (after 2, 4, 10, and 16 weeks) are automatically triggered once T0 is completed. We try to limit the amount of missing data from survey attrition by reminding participants after 5 and 10 days to complete the questionnaires.

Statistical Analysis

Statistical reporting will follow CONSORT [57] and CONSORT-EHEALTH standards [58]. We will conduct primary analyses using intention-to-treat. The primary outcome is the change in Patient Health Questionnaire–9 score from baseline to 10 weeks and 16 weeks. Dropout rates are examined per condition. Before the analysis, we will examine baseline predictors of attrition. If it appears that attrition is related to measured aspects of the participants, we will include those measures as covariates in the models.

To test for the main and interaction effects of treatment components on primary and secondary outcomes, linear mixed model analysis of variance will be used. This approach uses all available data on each subject and does not involve the substitution of missing values but estimates parameters about missing values. However, sensitivity analyses will explore the impact of the imputation of missing values before computing the mixed models. The main effects and interactions will be
Based on aggregates across experimental conditions. The purpose of the factorial experiment is not to compare the 16 conditions to each other but to estimate the main effects of the 4 factors and interactions between the factors. For example, the main effect of the diagnostic interview will be estimated by comparing the mean of the experimental conditions in which this factor is present (conditions 1-8 in Table 1) versus the mean of the experimental conditions in which this factor is not present (conditions 9-16 in Table 1). No adjustment for multiple testing will be applied in the estimation of statistical significance because, in the optimization phase of the multiphase optimization strategy framework, the emphasis is on deciding what components will make up the optimized intervention [33]. Only a future RCT can then establish the superiority of the optimized intervention over other conditions.

Power Analysis
We conducted an a priori power analysis for small-to-medium effect sizes (Cohen $d=0.35$) for main effects and interactions between 2 factors (eg, guidance and diagnostic interview) on change in depressive symptoms (G-Power 3.1). From a clinical perspective, smaller effects are considered to be less relevant [59]. For type I error $\alpha=0.05$, with a common power of .80 to detect effects. Based on previous studies, we assume that our measurements regarding pre, post, and follow-up correlate at approximately $r=0.60$. For a factorial design, this signifies a sample of $n=204$ to detect effects. Because we expect a dropout rate of about $20\%$, the planned sample size is $n=255$. For every condition, roughly 15 participants are required.

Results
The study was registered at ClinicalTrials.gov (NCT04318236). The ethics committee of the canton of Bern (Kantonale Ethikkommission Bern) approved the study on January 20, 2020 (2019-01795). Recruitment started in February 2020. As of November 1, 2020, out of 1480 interested individuals, 409 individuals have completed T0, and 240 participants have been enrolled in the study.

Discussion
Overview
The primary outcome is depressive symptoms 10 weeks after baseline. Several secondary outcomes will be measured, such as symptoms of anxiety and stress, health-related quality of life, suicidal ideation, and problem solving. Possible moderating (age, gender, and adherence) and mediating (treatment expectancy, therapeutic alliance) effects will be tested. Furthermore, negative effects of psychotherapy, treatment satisfaction, system usability, and dropout rates will also be measured and inspected. This study builds on a wealth of encouraging efficacy studies of internet-based self-help. It promises to provide a more detailed insight into which supportive context factors enhance outcomes of and adherence to internet-based self-help interventions for depressive symptoms. Furthermore, the study may also inform about possible mediation and moderation effects that could provide more information about how or why internet-based self-help interventions for depressive symptoms work.

Strengths and Limitations
Our study has been designed to shed more light on the supportive context of internet-based self-help interventions. It deconstructs a treatment package and explores active and inactive supportive factors. Understanding which factors do and do not work will help us get closer to the goal of delivering internet-based self-help interventions optimally. According to the guidelines of multiphase optimization strategy, a future RCT should test an intervention providing an optimal supportive context based on our findings, against an intervention providing a context that is usual in studies about internet-based self-help interventions (eg, an intervention with guidance). With such a study, the possible superiority of the optimized context could be established.

Limitations of this study are comparable to those of the majority of studies about internet-based self-help interventions. The sample of this study is self-selected and participants become aware of our study through the internet. This limits the generalizability of possible findings to regular clinical settings or individuals that rarely use the internet.

Conclusion
To improve outcomes to future internet-based self-help interventions for depression, this study could provide recommendations on how to optimize the context of human and automated support. Based on findings of active and inactive factors and the interactions thereof, recommendations could be made for future research and the implementation and dissemination of internet-based self-help interventions in routine care.

Acknowledgments
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Authors’ Contributions
OTB and TB designed the study. OTB is responsible for the data collection. OTB wrote the first version of the manuscript. TK, SM, JPK, and TB read the manuscript and provided suggestions for improvements. All authors approved the final version of the manuscript.

http://www.researchprotocols.org/2021/2/e21207/
Conflicts of Interest

JPK received funding for clinical trials (German Federal Ministry of Health, Servier), payments for presentations on internet interventions (Servier), payments for workshops and books (Beltz, Elsevier, Hogrefe, and Springer) on psychotherapy for chronic depression and on psychiatric emergencies. Other authors declare no conflicts.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials

CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth

HERMES: Herausforderungen meistern (overcoming challenges)

RCT: randomized controlled trial
Protocol

A Brief Mobile-Augmented Suicide Prevention Intervention for People With Psychotic Disorders in Transition From Acute to Ongoing Care: Protocol for a Pilot Trial

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Abstract

Background: People with serious mental illnesses (SMIs) are at exceptionally high risk for lifetime suicidal ideation and behavior compared with the general population. The transition period between urgent evaluation and ongoing care could provide an important setting for brief suicide-specific interventions for SMIs. To address this concern, this trial, SafeTy and Recovery Therapy (START), involves a brief suicide-specific cognitive behavioral intervention for SMIs that is augmented with mobile phone interactions.

Objective: The primary aim of this pilot trial is to evaluate the feasibility, acceptability, and preliminary effectiveness of the intervention.

Methods: A 6-month pilot trial with 70 participants with a diagnosis of bipolar disorder, schizophrenia or schizoaffective disorder, and current active suicidal ideation were randomized to START or START with mobile augmentation. START consists of 4 weekly sessions addressing early warning signs and triggers, symptoms influencing suicidal thinking, and social relationships. Recovery planning is followed by biweekly telephone coaching. START with mobile augmentation includes personalized automated cognitive behavioral therapy scripts that build from in-person content. Participants were evaluated at baseline, 4 weeks (end of in-person sessions), 12 weeks (end of telephone coaching), and 24 weeks. In addition to providing point estimates of feasibility and acceptability, the primary outcome of the trial was the change in severity of suicidal ideation as measured with the Scale for Suicide Ideation (SSI) and secondary outcome included the rate of outpatient engagement.

Results: The trial is ongoing. Feasibility and acceptability across conditions will be assessed using t tests or Mann-Whitney tests or chi-square tests. The reduction of SSI over time will be assessed using hierarchical linear models.

Conclusions: The design considerations and results of this trial may be informative for adapted suicide prevention in psychotic disorders in applied community settings.

Trial Registration: ClinicalTrials.gov NCT03198364; http://clinicaltrials.gov/ct2/show/NCT03198364

International Registered Report Identifier (IRRID): DERR1-10.2196/14378

KEYWORDS

prevention; mental health services; psychosis; technology
Introduction

Suicide in Serious Mental Illnesses

The burden of suicide is exceptionally high in serious mental illnesses (SMIs) such as bipolar disorder and schizophrenia. The lifetime risk of suicide in people with SMIs is 5% to 10% [1,2], which is 12 times the rate in the general population [3]. Recent evidence indicates that direct interventions (ie, those that target suicidal thoughts, such as cognitive behavioral therapy [CBT] techniques) are more effective in reducing suicide risk than indirect interventions (eg, those that target depressive symptoms and promote treatment engagement) [4,5]. Unfortunately, most clinical trials of direct interventions exclude patients with psychotic symptoms or disorders [4,6]. Only a handful of trials of psychosocial interventions have been evaluated for their impact on suicidal ideation or behavior in schizophrenia (some of which are suicide-specific CBT [7,8]), and data on psychosocial interventions in suicide prevention are virtually nonexistent in bipolar disorder [9].

Intervention Targets for Suicide Prevention in People With SMIs

To address these gaps, the 2 key questions are as follows: (1) How might the content of suicide prevention interventions be adapted for people with SMIs? (2) Where and when would such interventions fit within the care continuum? One adaptation consideration is that people with SMIs appear to have some unique characteristics of suicidal ideation and behavior as well as the transition between them. For example, in psychotic disorders, suicidal ideation may be intertwined with hallucinations, suicidal ideation appears to be less transient [10], and suicidal ideation is more likely to be associated with suicide attempts than in people without psychosis [11]. The means used to attempt suicide are also different, and a history of psychosis is overrepresented in those with severe attempts [12]. Moreover, social support is frequently limited in SMIs [13], and people with SMIs may be less likely to self-initiate the use of suicide prevention services such as crisis lines [14]. Finally, although psychotherapeutic interventions such as CBT are effective for SMIs, they are typically adapted to accommodate aspects of these illnesses that may interfere with skill acquisition, such as cognitive impairments [15,16].

There are also unique considerations for fitting suicide prevention interventions into the care continuum in SMIs. A higher proportion of service use is in acute and outpatient specialty mental health services compared with primary care. Furthermore, services tailored to people with SMIs are increasingly tailored to reduce barriers to access given the high rates of disengagement from care. One emerging site of potential deployment for brief suicide prevention interventions for people with SMI is walk-in or same-day clinics. Walk-in clinics provide access to immediate unscheduled psychiatric evaluation and are the best practice in both the Zero Suicide framework [17] and for service engagement of people with SMIs [18]. These clinics aim to increase access to mental health care and provide an access point to initiate ongoing psychiatric outpatient care [19,20]. However, only a minority of patients seen in urgent care for suicidal ideation actually go on to engage in follow-up outpatient care [21].

SafeTy and Recovery Therapy

To address the gaps described earlier, we developed a brief suicide-specific intervention adapted for SMIs called SafeTy and Recovery Therapy (START). The intervention builds from prior work in CBT for suicide and SMIs. START consists of 4 sessions intended to fit within a typical gap period between urgent and ongoing care and to successively build suicide-specific skills. Furthermore, this brief in-person individual psychotherapeutic intervention is integrated with an automated mobile intervention. Emerging research has examined mobile health and telemonitoring interventions in suicide prevention [22-24], although less so in SMIs. Ecological momentary interventions (EMIs) couple brief in-person CBT with automated mobile assessment linked with personalized intervention content in SMIs [25-28] and deliver automated therapeutic content that extends the content of in-person CBT to everyday life. The role of EMIs in START is to promote recall and engagement in personalized, adaptive thoughts and behaviors aimed at suicide prevention by employing content collaboratively developed during in-person sessions.

To evaluate the START intervention, we developed a pilot clinical trial using a deployment-focused approach. The goals of this pilot trial were to evaluate the feasibility, acceptability, and preliminary effectiveness of the intervention. Here, we report our study design, intervention approach, and related considerations, which we hope will be informative for research on suicide-specific interventions for SMIs. Of particular interest, may be, design decisions in suicide-specific intervention clinical trials on SMIs, informed by guidance from the National Institute of Mental Health [29]. This study has the following aims:

- **Aim 1:** to refine intervention content and safety protocol with input from community stakeholders.
- **Aim 2:** to evaluate feasibility, engagement, impact, and preliminary comparison of START with Mobile Augmentation versus START alone.

Methods

Study Deployment Planning

This study is deployed in the public mental health system in San Diego, California. Study deployment relied on collaborative meetings with leadership, triage, and outpatient clinicians. Key components of these meetings included (1) a review of the draft manuals, study materials, and mobile app; (2) specifications of research team community communication plans, roles, documentation, and reporting protocols; and (3) emergency and safety planning for participants, research staff, and clinicians delivering the intervention. Front-line staff were afforded the opportunity to suggest and improve the approach, for example, where same-day clinics were in separate locations from outpatient centers, a suggestion was to split the sessions across these sites to allow participants the opportunity to transition sites and become comfortable with the outpatient clinic. To reduce the burden on sites and to increase the likelihood of consistent appropriate referrals, we held additional meetings.
with triage providers during in-services and created a pocket guide detailing the study inclusion or exclusion criteria and procedures.

**Recruitment Sites and Screening**

Usual care in walk-in settings involves a diagnostic interview or intake with a triage provider (typically a social worker) and a psychiatric evaluation, which includes a standardized screening for suicidal thoughts and behavior. The outcome of these evaluations may include acute stabilization or hospitalization but is most frequently the initiation of medication treatment, linkage to resources, and an outpatient follow-up appointment for psychosocial care. The focal population of these clinics is people with SMIs, and individuals who do not meet the criteria for SMIs are referred to as primary care. To fit within these high acuity settings, our research screening is kept minimal and includes only the basic eligibility criteria, diagnostic screen, and recent and lifetime suicide history screening with the Columbia Suicide Severity Rating Scale (CSSR-S), lifetime version [30].

**Eligibility**

Participant inclusion criteria are as follows: (1) aged 18-65 years, (2) Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition diagnoses of bipolar disorder, schizoaffective disorder, or schizophrenia (confirmed by the Mini International Neuropsychiatric Interview [31]), and (3) suicidal ideation, defined as CSSR-S ≥2 in the past 1 month and/or a suicide attempt in the past 3 months as identified by the CSSR-S. Additional inclusion criteria are as follows: (1) plans to remain in the region for ≥6 months and pending appointment for outpatient mental health treatment initiation and (2) capable of informed consent. Exclusion criteria are as follows: (1) not English speaking, (2) inability to complete the assessment battery, (3) insufficient visual acuity or manual dexterity to navigate a touch screen, (4) current intoxication requiring immediate detoxification or an outpatient plan directed to substance use disorder (not mental health) services, and (5) under conservatorship requiring proxy consent. Given that the population is vulnerable to impaired decisional capacity, we confirm the capacity to consent with a brief measure [32].

A key consideration for inclusion criteria was the floor and ceiling for suicide risk. We selected a floor for our suicidal ideation measure at active thoughts or higher (≥2 on CSSR-S), consistent with a recent clinical trial [33]. As our study is embedded in an urgent screening setting, triage provides a ceiling which is voluntary or involuntary hospitalization on the day of evaluation. Finally, due to high base rates in the population, we included people with active substance use disorder, provided that they do not require acute detoxification as a next step following triage, and we also included those with unstable housing.

**Therapist Training**

Therapists for the study are employees of the San Diego County mental health system and include triage evaluators and case managers. Therapists complete a 4-hour training with 5 components: (1) intervention model and rationale, (2) safety procedures, (3) trial protocol, (4) fidelity monitoring procedures, and (5) mobile intervention deployment. Embedded in the training are role-plays of specific skills, including redirecting sessions to suicide-specific concerns and conducting risk assessments or documentation of adverse events. Therapists are required to complete role-plays concerning safety assessment, describing the treatment model, and re-establishing focus on suicide-related concerns in sessions.

**Randomization, Masking, and Trial Design Considerations**

Participants are randomized to START with mobile augmentation or START alone. Randomization schedules are compiled by an independent statistician, and research assessors are kept masked to the assignment. Participants and the study therapists are not blinded to the assignment. Several factors led to our decision to include 2 active conditions in this pilot trial. First, we were encouraged by our prior trial that identified a statistically significant augmentative benefit of a mobile intervention immediately posttreatment with a comparable sample size, albeit in a somewhat different population. Second, we considered the primary success criteria for this pilot phase to start the absence of sustained changes in suicidal ideation (in aggregate) and secondary comparisons across the mobile-augmented and nonaugmented conditions were designed to yield information about preliminary differences in feasibility, acceptability, and hypothesized mediators of change (eg, recall of safety plans). Third, we considered a no-treatment control condition, but this design was not preferred by our stakeholder community partners. Moreover, due to the timing of the intervention to the gap period between urgent and ongoing care, a waitlist control would be impossible.

The primary success criteria for this pilot trial of START are sustained changes in suicidal ideation (in aggregate), and secondary comparisons across the mobile-augmented and nonaugmented conditions were designed to yield information about preliminary differences in feasibility, acceptability, outcomes, or hypothesized mediators of change (eg, outpatient engagement, recall of safety plans). Owing to the pilot nature of the trial, we may not have adequate power to detect modest differences between START and START with mobile augmentation conditions; however, we considered that the absence of detectable differences between conditions on any of the dimensions of feasibility, acceptability, mediators, and preliminary outcomes in the presence of sustained improvement in the primary outcome (suicidal ideation) would indicate that mobile augmentation may not be warranted in future deployment of START.

**Interventions**

After baseline assessment, participants were scheduled for 4 consecutive weekly sessions with a study therapist in the walk-in facility. We opted for individual sessions (vs group) to enhance the likelihood of personalization and to reduce the potential for wait times to reach group capacity. Each session is structured with a demonstration and practice of a coping skill (10 min), skill focus on 1 of 4 topics (20 min), and personalization of implementation intentions surrounding a topic area (30 min). The structure of sessions is highly comparable between START with mobile augmentation and START-alone conditions, as...
both conditions involve compiling implementation intention statements in a workbook. Participants in the START-alone condition are instructed to record homework completion, and those in the mobile augmentation condition are instructed to respond to queries on the mobile app as described below. Figure 1 outlines the study flow.

**Figure 1. Study flow.**

**Session 1: Content (Early Warning Signs and Triggers, 90 Min)**

After establishing the ground rules, participants are led through a brief grounding technique called *look, point, name*. Then, an interactive description of the generic cognitive model is provided (ie, that thoughts, feelings, and behaviors are related), thoughts and feelings are identified and labeled, and patients complete exercises demonstrating how dysfunctional beliefs can impact feelings and behavior. Suicidal thoughts are discussed in this framework, and education is provided about the high frequency of such thoughts among people with SMI diagnoses. The concept of early warning signs (internal experiences) and triggers (external factors) are introduced in relation to suicidal thoughts. Participants are also presented with the idea of adaptive versus unhelpful responses; participants then form implementation intention statements based on adaptive responses. The session concludes with an agreement regarding the focus of work together in diminishing vulnerabilities to suicidal thinking, with parameters around safety planning, crisis contacts, and one commitment to reduce access to means. In the START with mobile augmentation condition, participants were provided with a 15- to 20-minute overview of interactive responding on the phone, and in the START-alone condition, the session concludes (see below for mobile content).

**Session 2: Content (Symptom Actuators and Treatment Engagement, 60 Minutes)**

In this session, the therapist first elects from 1 of the 2 symptom actuators of suicidal thoughts from early warning signs (mood or psychotic symptoms), with modules focused on these symptom clusters as they create vulnerabilities to suicidal thoughts. Evidence is used to challenge unhelpful beliefs, such as the uncontrollability or permanence of symptoms, and each is coupled with a behavioral suggestion or experiment that can be employed to test assumptions. The therapist and participant decide to focus on mood symptoms or voices, depending upon which is most associated with suicidal thinking. Participants delineate portable coping strategies for 3 levels of severity of depressed mood (and manic symptoms, if present) or for common dysfunctional beliefs about voices (eg, uncontrollability). In addition, the role of treatment in managing these symptoms is discussed, which is linked with intentional (eg, treatment won’t work) and unintentional (eg, forgetting) barriers and facilitators to treatment adherence.

**Session 3: Content (Social Relationships, 60 Min)**

This session begins with progressive muscle relaxation. Content then addresses the role of social relationships and beliefs about others as factors in coping with or exacerbating suicidal thinking. Unhelpful, generalized, or extreme beliefs about social interactions are reappraised (eg, *there are some people who are on my side*), and the role of social isolation in suicidal thinking is discussed. Potential behaviors that promote social contact are elicited, including the use of crisis-oriented resources. Barriers to asking for help are elicited, including appraisals and predictions about disclosing suicidal thoughts to others and behaviors that are linked with help-seeking that resulted in benefits.

**Session 4: Content (Recovery Plan and Goals, 60 Min)**

This session begins with a Loving Kindness meditation to increase positive affect and addresses recovery goals and future-oriented thinking; a recovery plan is developed around
personal values and a linked single, attainable short-term goal consistent with personal values. Participants and the therapist worked within the START goal framework and delineated 2 relevant goals and steps aligned with the selected goals. Next, the therapist and participants reviewed the topics and content generated in sessions 1 to 4 and revised and added to statements that were previously generated. Plans for subsequent contacts were made for follow-up phone contacts.

**Rationale for START Foci**

The therapeutic targets were selected to address short-term risk and protective factors in a brief intervention format, and as such, do not directly address all of the risk factors for suicide in SMIs. For example, we do not directly target substance abuse, although participants do have the freedom to select substance use as a trigger or unhelpful coping strategy. We also do not directly involve caregivers, such as family members. We will use postintervention follow-up satisfaction data to identify potential modifications to the protocol.

**Follow-Up Telephone Coaching**

Participants are contacted via phone by the study therapist every at weeks 6, 8, and 10 or until they are established in outpatient care (ie, attend an intake appointment). Follow-up telephone coaching consists of a concise scripted interaction to briefly check in (target 10 min) with a focus on the following: (1) safety and utilization of strategies developed in the 4 in-person sessions; (2) assessing and problem solving around barriers to outpatient engagement; and (3) in the mobile augmentation condition, troubleshooting, and requests for adapting any elements of the device interaction [34-36].

**Mobile Augmentation Procedures**

**Mobile Devices and Training**

Participants can opt to either use their mobile phone device or, if they do not use a personal mobile phone device, obtain a provisional one during the 12-week period with support for accessing free or low-cost mobile devices. In either case, the interactive content is delivered through an EMI app called Illumivu. Personalized content is delivered through this app, and deidentification is made possible by a mobile code that is unique to each participant. In Session 1, participants receive training that is individually tailored to their learning needs on how to respond to questions and response choices, procedures for charging the device, and responding to outreach.

**Mobile Intervention Content**

Surveys scaffold onto in-person content and successively add modules according to the following schedule—**Session 1**: Early Warning/Triggers; **Session 2**: Symptom Actuators and Treatment Engagement; **Session 3**: Social Relationships; and **Session 4**: Recovery Plan/Goal tracking. In each survey, participants are asked whether they practiced relaxation skills. They are then asked to respond to first-layer ecological momentary assessment (EMA) questions that assess current state (eg, past 24-hour presence of triggers or early warning signs, severity of depressed mood). In the second layer, content is branched to address endorsement of maladaptive beliefs pertaining to first-layer questions, and the third layer contains 2 questions on participants’ adaptive cognitions or behaviors developed in session and their implementation intentions for these. Each of these layers contains a set of possible responses derived from content that was personalized in the in-person sessions. If no triggers or early warning signs or symptoms are endorsed, participants select from personalized adaptive beliefs and actions pertinent to the maintenance of wellness. Participants are then queried about their intention to engage in the behavior and the survey concludes with a quote on recovery, adapted from public sources or from anonymous prior participants. See Figure 2 for a sample mobile session. During in-person contact with study therapists, participants can request to alter content, add, remove, and/or update their responses. In addition to the pushed surveys, participants can access content (eg, recovery goals) on demand.
Figure 2. Sample mobile session for early warning signs and triggers.

Rationale for Mobile Augmentation

Our group and others have completed trials that indicate that patients will use mobile devices for EMIs up to 12 weeks or more when coupled with in-person therapies [26,37]. On the basis of prior research suggesting that only 50% of participants initially engaged with outpatient care, there is reasonable concern that without additional intervention, participants may disengage from this care during the 6-month period of this study [38]. Given that there is no staff cost to continue an automated mobile intervention through 6 months after establishment in outpatient care and the content reinforces ongoing participation in care, the automated intervention is available in perpetuity.

Safety Procedures

In collaboration with stakeholders, plans have been developed to systematically monitor and address safety. At screening, participants are seen on the same day as the triage assessment, in which plans for outpatient follow-up are set by the triage provider. Our research screening included crisis resources for all screened participants. If screening cannot occur on the same day as triage, we follow the protocol for baseline assessments. At baseline and follow-up assessments, we developed a suicide safety monitoring protocol that uses the CSSR-S to identify increases in ideation or new interim behavior since the time of screening (or in case of delay, urgent evaluation is initiated if CSSR-S scores are >2). During in-person START sessions and telephone contacts, the study therapist administers the CSSR-S at the end of each session. If an increase in ideation or new interim suicide behavior is identified, it activates urgent evaluation, connection with resources, and arrangement of notification of providers and hospitalization. We also elected not to directly query about suicidal ideation via the device, as the understanding of the use of remote technologies in querying suicidal risk and safety response is in its infancy [39,40].

Measures

The measurement battery for this pilot trial was brief and restricted to study constructs related to acceptability and preliminary outcomes (Table 1).
### Table 1. Study measures.

<table>
<thead>
<tr>
<th>Timing and measure</th>
<th>Specific aim</th>
<th>Construct assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening</strong></td>
<td></td>
<td></td>
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<tr>
<td>MINI&lt;sup&gt;a&lt;/sup&gt; DSM-5&lt;sup&gt;b&lt;/sup&gt; interview</td>
<td>Inclusion</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>CSSR-S&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Inclusion</td>
<td>Suicide risk inclusion</td>
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<tr>
<td><strong>Baseline and follow-ups</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scale for Suicide Ideation or CSSR-S Interval</td>
<td>Primary outcome</td>
<td>Suicidal ideation severity</td>
</tr>
<tr>
<td>Outpatient follow-up</td>
<td>Secondary outcome</td>
<td>Treatment engagement post-triage</td>
</tr>
<tr>
<td>Composite suicide-related crises</td>
<td>Secondary outcome</td>
<td>Suicidal behavior or psychiatric hospitalization for suicidal ideation</td>
</tr>
<tr>
<td>Beck Hopelessness Scale</td>
<td>Mechanism</td>
<td>Hopelessness</td>
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<tr>
<td>Coping Self-Efficacy Scale</td>
<td>Mechanism</td>
<td>Self-efficacy</td>
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<tr>
<td>EMA&lt;sup&gt;d&lt;/sup&gt; Adherence or Outcomes</td>
<td>Acceptability: secondary outcome</td>
<td>Response rate to mobile surveys: mood or psychotic symptoms</td>
</tr>
<tr>
<td>Tablet routines questionnaire</td>
<td>Secondary outcome</td>
<td>Medication adherence</td>
</tr>
<tr>
<td>BPRS-24&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Secondary outcome</td>
<td>Global psychopathology</td>
</tr>
<tr>
<td>Treatment Rationale Scale</td>
<td>Acceptability</td>
<td>Treatment expectancy</td>
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<tr>
<td>Timeline Followback Scale</td>
<td>Moderator</td>
<td>Substance abuse</td>
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<tr>
<td><strong>Follow-ups only</strong></td>
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<tr>
<td>Intervention Satisfaction Questionnaire</td>
<td>Acceptability</td>
<td>Satisfaction with intervention</td>
</tr>
<tr>
<td>Recovery plan and safety plan recall</td>
<td>Mechanism</td>
<td>Accuracy of recall</td>
</tr>
</tbody>
</table>

<sup>a</sup>MINI: Mini International Neuropsychiatric Interview.
<sup>b</sup>DSM-V: Diagnostic and Statistical Manual of Mental Disorders Fifth Edition.
<sup>c</sup>CSSR-S: Columbia Suicide Severity Rating Scale.
<sup>d</sup>EMA: ecological momentary assessment.
<sup>e</sup>BPRS-24: Brief Psychiatric Rating Scale–24 item.

**Suicidal Ideation Severity and Behavior (Primary Outcome)**

We administer the interview-rated version of the Scale for Suicide Ideation, a 21-item widely used measure that predicts completed suicide [41,42] in addition to the interval CSSR-S, which queries the timing, severity, and characteristics of suicidal ideation and behavior [30].

Our study addresses changes in suicidal ideation and is underpowered to detect the impact on the risk of suicidal behaviors. Our rationale for change in suicidal ideation as our primary outcome was that for a suicide-specific intervention to be potentially effective, it must be feasible, acceptable, and associated with significant and sustained reductions in suicidal ideation to move on to a confirmatory trial. If the target of suicidal ideation was not moved, then we would not proceed to a confirmatory trial. We recognize that people may experience a reduction in suicidal ideation severity as part of natural regression to baseline. However, we note that people with SMIs are more likely to have chronic ideation than people without psychosis and therefore would be less likely to experience natural reductions in ideation [43]. Moreover, people with SMIs are more likely to have recurrent suicidal ideation, and as such, we added follow-up assessments at 12 and 24 weeks. Finally, we used the minimally important clinical difference of 0.5 SD as a threshold for meaningful reduction and power analyses. We will investigate whether the SSI score is skewed or kurtotic using the convention of +3 investigate skew and, if evident, will dichotomize the variable.

**Outpatient and Crisis Service Utilization (Secondary Outcome)**

We extracted electronic medical record (EMR) encounter data regarding attendance at the first follow-up appointment and rate of follow-up outpatient contacts. It is possible that participants may use out-of-county institutions not captured in the EMR; therefore, the Cornell Service Use Index [44] is administered for service use not recorded in the EMR to facilitate a comparison of augmented and nonaugmented arms.

**Global Psychopathology (Secondary Outcome)**

Global psychopathologic severity is evaluated using the Brief Psychiatric Rating Scale–24-item expanded version 4.0 (BPRS-24) [45], a clinician-rated measure with 24 items that
cover depression, anxiety, mania, suicidality, delusions or hallucinations, and unusual behavior.

**Medication Adherence (Secondary Outcome)**
Self-reported adherence is assessed with the Tablet Routine Questionnaire [46], which asks about the proportion of psychotropic medication taken over the past week and month.

**Electronic Adherence and Targets (Secondary Outcome)**
A wealth of EMA data will be generated, including adherence data (eg, response rate=the number of responses/number of queries) and patterns of adherence over time. In our completed trial, treatment response was associated with greater adherence; thus, we will also explore this association. We structured the EMA protocol to provide day-to-day data on the early warning signs or triggers, symptoms, medication use, socialization, and contextual influences. These data will inform hypotheses about determinants or contexts of suicidal thoughts in SMIs [47].

**Substance Use Frequency or Intensity (Moderator)**
We assessed substance abuse as an exploratory moderator of attrition, adherence, and response. To quantify alcohol and drug use, we selected the 30-day Timeline Followback Scale [48].

**Therapeutic Mechanisms Variables**
We examined mechanistic targets for the START intervention that map on to therapeutic content: Treatment Engagement, Coping Self-Efficacy (CSE) Scale [49] and Beck Hopelessness Scale [50].

**Safety and Recovery Plan Recall (4, 12, and 24 weeks only)**
Modeled after recent research on recall of elements of CBT for bipolar disorder [51] and our research in schizophrenia [15], we administer a knowledge or recall measure that corresponds to elements in the safety plan generated in Session 1 as well as the recovery plan in Session 4. Participants are asked to recall broad elements discussed (eg, responding to early warning signals) and the individual responses of their own plan once prompted (eg, specific responses to early warning signs). Participants’ written responses are coded as fully accurate, partially accurate, or not accurate in regard to recalled elements of the safety and recovery plans.

**Acceptability Measures**
At baseline, participants are administered the Treatment Rationale Scale [52], a 3-item self-report that garners perceived credibility and anticipated benefit. Participants also completed seven 5-point Likert-type and 4 open-ended questions (modified from Kimhy et al [53] and used in our prior research [54]) focused on greater intervention satisfaction, barriers and suggestions concerning the intervention, the therapist, and the manual, and for the mobile health condition, experiences with the device and suggestions for future usability.

**Fidelity**
We systematically address the relevant components of treatment integrity: Competence, Therapist and Participant Adherence, and Treatment Differentiation [55]. Competence is addressed by initial training of the study therapists who meet minimum competence standards (see above) and in an ongoing fashion by audiotaape-rated delivery of the intervention, supported by weekly supervision. Therapist Fidelity to the manualized protocol is assessed via 100% of session recordings rated by the therapist and research team on an adapted version of the Cognitive Therapy Rating Scale for Psychosis (CTS-Psy) [56]. Participant adherence is assessed by session attendance or telephone contacts and objectively via device-obtained data. Treatment differentiation is assessed by blinded random selection of 25% of audio-taped sessions rated by masked raters, with a running quarterly calculation of discrepancies between conditions evaluated to determine if content delivered varies between the 2 conditions; retraining occurs if differences in CTS-Psy scores are >0.5 SD.

**Sample Size Determination**
Our pilot trial’s sample size is derived based on the nexus of 3 goals, guided by work on optimization of pilot studies [57]: (1) to obtain point estimates of feasibility, acceptability, and test the impact of the intervention compared with population base rates for engagement and crisis service utilization; (2) to be powered to test a clinically significant within-subjects reduction (d>0.5) in the SSI score; and (3) to evaluate the preliminary impact of augmentation. Intent-to-treat analyses with 70 patients, with an alpha of .05, will have 95% power to evaluate whether the sample estimates differ from population estimates (eg, 50% no-show rates) [58] and 77% power for each of the individual arms. On the basis of the General Linear Multivariate Model Power and Sample Size program [59], there is >0.80 power across 24 weeks to detect a 0.5 SD pre-post change in SSI score. We have considerably less power to detect augmentation effects, but following recent research on sample size estimation in pilot trials and confidence intervals [60,61], the preliminary impact of augmentation will be assessed by defining a minimally clinically significant augmentative effect for a future trial.

**Analysis of Feasibility and Acceptability**
Point estimates of feasibility and acceptability included the following: (1) triage clients screened, (2) screened clients eligible, (3) eligible clients enrolled, (4) enrolled clients completing 4 sessions and follow-up calls, and (5) percentage of participants reporting being somewhat or very satisfied with the overall intervention. Comparative data regarding feasibility and acceptability are our completed trials, which enable us to examine whether indicators of feasibility in the triage setting are similar to general outpatient populations. Each of these estimates, in addition to Treatment Rationale and Satisfaction scores, will be contrasted across conditions with t tests or Mann-Whitney tests or chi-square tests.

**Analysis of Within-Person Changes**
Distributions for the SSI score may be skewed (with overdispersion due to persons with no present ideation) and, if so, zero-inflated negative binomial models will be employed. We will use hierarchical linear models (HLMs) in which time will be tested as a categorical time-varying predictor of SSI score and subjects are a random effect, with significant reduction in SSI over time indicated by a statistically significant time effect. We expect that by the 24-week time-point, SSI will have
at least a medium effect size decrease ($d$≥0.5) as measured by HLM linear-estimated change. To evaluate augmentation, we will examine grouptime interactions, with estimated standardized differences considered supportive of the augmentation inclusive of minimal clinical significance CI$>0.80$. We will evaluate secondary continuous outcomes (eg, BPRS) variables in the same way.

**Analysis of Mechanisms**

For analysis of binary mechanisms (outpatient engagement) and outcomes (crisis service use), we will use chi-square analyses to examine associations at 24 weeks. For the continuous time-varying mechanism (CSE), we will examine a mechanistic association between changes in CSE and SSI scores using the Macarthur framework [61]. We will use generalized estimating equations to evaluate the prediction of crisis service use by within-subjects change in CSE and then repeat these analyses within mobile-augmented and nonaugmented arms. We will also contrast the Safety or Recovery Plan recall at weeks 4, 12, and 24 using $t$ tests or Mann-Whitney U tests.

**Results**

The trial is ongoing and recruitment is active, with anticipated completion of the baseline sample randomization target of 70 participants by the close of 2020.

**Discussion**

**Principal Findings**

This trial focuses on evaluating a novel brief suicide prevention intervention for SMI, addressing the imbalance between the low number of empirically supported interventions for SMI and the high rates of suicide in people with bipolar disorder and psychotic disorders. Key considerations in developing and deploying an intervention to fit the needs of people with SMI were in the design of the intervention content and the setting and timing of the intervention within the typical American community mental health care continuum. This approach could yield potential benefits to both suicide prevention and operational efficiency by improving follow-through with scheduled outpatient appointments and reducing lost productivity due to no shows at follow-up appointments. This experimental treatment approach is an augmentation of the standard transition from a walk-in clinic to outpatient care follow-up and is not fully integrated into care. The likelihood of future adoption may depend upon a demonstrated reduction of suicide and cost recovery due to the reduced rate of missed appointments.

A trial focus is also on the relative additional value of integrating mobile interventions with in-person appointments. The additional mobile intervention content is meant to augment the recall and implementation of personalized intervention content derived from in-person sessions. In this community-based trial of a suicide-specific intervention, we did not have a no-treatment control condition, and this trial design decision was due in part to the community partner’s preference against a no-treatment condition. We note that future developmental trials of suicide-specific interventions may face a similar dilemma and alternative designs (eg, SMART designs) may provide useful means of detecting mobile augmentation effects.

**Lessons Learned**

Key lessons learned to date include the importance of frequent deployment meetings that emphasized co-design among staff training and leadership to enable referral, recruitment, and safety protocol refinement. We also based our safety protocol on published guides [29]; these guides have yet to be specifically adapted for SMIs but provide a reasonable starting point for clinical trials in suicide prevention in SMIs. We also opted not to include direct questions about suicidal ideation or behavior during automated mobile communications that augment in-person appointments, due to the lack of specific evidence of acceptability in SMI to date. The trial is currently ongoing, and we anticipate that data collected will further inform research and practice in suicide prevention interventions adapted for SMIs.

**Acknowledgments**

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**Conflicts of Interest**

EG reported consulting fees from Otsuka America Pharmaceutical, Inc.

**References**


Abbreviations

BPRS-24: Brief Psychiatric Rating Scale—24 item
CBT: cognitive behavioral therapy
CSE: coping self-efficacy
CSSR-S: Columbia Suicide Severity Rating Scale
CTS-Psy: cognitive therapy rating scale for psychosis
EMA: ecological momentary assessment
EMI: ecological momentary interventions
EMR: electronic medical record
HLM: hierarchical linear model
SMI: serious mental illnesses
SSI: Scale for Suicide Ideation
START: SafeTy and Recovery Therapy
Protocol

Comparison of Endoscopy First and Laparoscopic Cholecystectomy First Strategies for Patients With Gallstone Disease and Intermediate Risk of Choledocholithiasis: Protocol for a Clinical Randomized Controlled Trial

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Abstract

Background: The optimal approach for patients with gallbladder stones and intermediate risk of choledocholithiasis remains undetermined. The use of endoscopic retrograde cholangiopancreatography for diagnosis should be minimized as it carries considerable risk of postprocedural complications, and nowadays, less invasive and safer techniques are available.

Objective: This study compares the two management strategies of endoscopic ultrasound before laparoscopic cholecystectomy and intraoperative cholangiography for patients with symptomatic choledocholithiasis and intermediate risk of choledocholithiasis.

Methods: This is a randomized, active-controlled, single-center clinical trial enrolling adult patients undergoing laparoscopic cholecystectomy for symptomatic gallbladder stones with intermediate risk of choledocholithiasis. The risk of choledocholithiasis is calculated using an original prognostic score (the Vilnius University Hospital Index). This index in a retrospective evaluation showed better prognostic performance than the score proposed by the American Society for Gastrointestinal Endoscopy in 2010. A total of 106 participants will be included and randomized into two groups. Evaluation of bile ducts using endoscopic ultrasound and endoscopic retrograde cholangiography on demand will be performed before laparoscopic cholecystectomy for one arm (“endoscopy first”). Intraoperative cholangiography during laparoscopic cholecystectomy and postoperative endoscopic retrograde cholangiopancreatography on demand will be performed in another arm (“cholecystectomy first”). Postoperative follow-up is 6 months. The primary endpoint is the length of hospital stay. The secondary endpoints are accuracy of the different management strategies, adverse events of the interventions, duct clearance and technical success of the interventions (intraoperative cholangiography, endoscopic ultrasound, and endoscopic retrograde cholangiography), and cost of treatment.

Results: The trial protocol was approved by the Vilnius Regional Biomedical Research Ethics Committee in December 2017. Enrollment of patients was started in January 2018. As of June 2020, 66 patients have been enrolled.

Conclusions: This trial is planned to determine the superior strategy for patients with intermediate risk of common bile duct stones and to define a simple and safe algorithm for managing choledocholithiasis.

Trial Registration: ClinicalTrials.gov NCT03658863; https://clinicaltrials.gov/ct2/show/NCT03658863.

International Registered Report Identifier (IRRID): DERR1-10.2196/18837

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KEYWORDS
choledocholithiasis; endoscopic ultrasound; intraoperative cholangiography; common bile duct stone; endoscopic retrograde cholangiopancreatography; laparoscopic cholecystectomy

Introduction

Gallbladder stones can be silent or symptomatic. This statement is also valid when speaking about choledocholithiasis, which involves stones situated in the common bile duct (CBD). About 10% to 18% of people undergoing cholecystectomy for gallstones have concomitant CBD stones [1]. Untreated choledocholithiasis can lead to acute biliary pancreatitis, acute ascending cholangitis, and secondary sclerosing cholangitis; thus, it is essential to diagnose and treat it on time. Endoscopic retrograde cholangiopancreatography (ERCP) became a prominent diagnostic method for CBD stones since its introduction to clinical practice in the 1970s [2]. Later on, it was agreed that use of ERCP for diagnostic reasons should be minimized and that it should not be used for first-line diagnostics as it carries a considerable risk (5% to 10%) of postprocedural complications [3]. It has been noticed that adverse events occur more often in patients with low risk of choledocholithiasis [4]. The possibility to avoid using ERCP for diagnostic purposes came with the introduction of new less invasive diagnostic procedures, such as magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), and intraoperative cholangiography (IOC) during cholecystectomy. Therefore, in the 2000s, a discussion about more careful patient selection for ERCP began, as it should be considered only in those with high probability of demand for therapeutic interventions (ie, stone removal), and patients with intermediate risk for choledocholithiasis should undergo additional investigation.

The most frequently used system to evaluate the risk of choledocholithiasis was proposed in 2010 by the American Society for Gastrointestinal Endoscopy (ASGE) [5]. It already stratifies the probability of CBD stones into low, intermediate, and high risk groups, and it suggests noninvasive investigations for the intermediate risk group, although its predictive value is not completely satisfying [6-10]. These results encourage the development of more accurate prognostic systems.

At the Center of Abdominal Surgery of Vilnius University Hospital Santaros Klinikos, an original prognostic index (Vilnius University Hospital Index [VUHI]) is being used for the prediction of choledocholithiasis risk before laparoscopic cholecystectomy (LC). Recently, we evaluated its accuracy and determined new threshold values for low, intermediate, and high risk groups [11]. The intermediate risk group (risk for choledocholithiasis of 25%-75%) would benefit from additional examination before ERCP. EUS and IOC are less invasive procedures with high accuracy for identifying CBD stones. These procedures will be applied for patients with intermediate risk of CBD stones and will help to decide if ERCP is indicated.

We aim to compare EUS as the first diagnostic biliary intervention to LC with IOC in patients with intermediate risk of choledocholithiasis in order to evaluate the accuracy, technical success, and safety of these two management strategies.

The hypothesis is that LC with IOC ("cholecystectomy first" strategy) will decrease both the length of hospital stay and morbidity by lessening the number of endoscopic investigations (EUS and ERCP) and thus the number of possible complications of ERCP, as well as decreasing the complications related to delayed cholecystectomy.

Methods

Recruitment
This study is a single-center, randomized, active-controlled trial comparing EUS and IOC for finding CBD stones in patients with intermediate risk of choledocholithiasis. Participants will be enrolled and the trial will be carried out at Vilnius University Hospital Santaros Klinikos, a tertiary referral center. All patients with planned LC due to gallstone disease will be evaluated for trial eligibility.

Ethical approval has been obtained from the Vilnius Regional Biomedical Research Ethics Committee (approval protocol number 158200-17-978-473).

The eligibility criteria are listed inTextbox 1 [12-14]. The trial will enroll patients with cholecystolithiasis aged 18 to 80 years, for whom LC is indicated and who have intermediate risk of choledocholithiasis. We will not include patients who are pregnant, morbidly obese (BMI >40), or severely ill (IV-VI class of the American Society of Anesthesiologists physical status classification, contraindications for general anesthesia or surgery). Additionally, patients with anastomosis in the upper gastrointestinal tract, known or suspected hepatitis of another origin (viral, toxic, etc), and other known cholestatic hepatopancreatobiliary disease will be excluded. We will rule out patients with known complications of gallstone disease, such as biliary pancreatitis, acute cholangitis, and acute cholecystitis (degree II-III, as defined in the Tokyo guidelines) [12,13].
Textbox 1. Eligibility criteria.

### Inclusion Criteria

- Age 18-80 years
- Symptomatic cholecystolithiasis (stones in the gallbladder seen on imaging studies and causing episodes of biliary colic)
- Intermediate risk of choledocholithiasis (Vilnius University Hospital Index 2.6-6.9 and one of the following predictors: dilated common bile duct >6 mm, elevated total bilirubin >21 µmol/L, or suspected stone in the common bile duct [CBD] on ultrasound)

### Exclusion Criteria

- Acute cholangitis, as defined in the Tokyo guidelines 2013 [12]
- Moderately severe or severe biliary pancreatitis, as defined in the revised Atlanta classification [14]
- Acute cholecystitis (degree II-III), as defined in the Tokyo guidelines 2013 [13]
- Anastomosis in the upper gastrointestinal tract
- Known cholestatic hepatopancreatobiliary disease (primary biliary cholangitis, primary sclerosing cholangitis, secondary biliopathy, tumor of the head of the pancreas or major papilla, or benign or malignant CBD stricture)
- Known or suspected hepatitis (viral, toxic, alcoholic, etc) or liver cirrhosis
- Contraindications for general anesthesia or surgery
- IV-VI class of the American Society of Anesthesiologists physical status classification
- Morbid obesity (BMI > 40)
- Pregnancy
- Patient refusal to participate in the study

### Elimination From the Trial

Patients will be omitted from the trial if the situation changes to incompatible with the trial protocol. This can happen because of the following reasons: a neoplastic condition is found at the time of management; the general status of the patient worsens owing to other health issues not related to cholelithiasis (eg, myocardial infarction) and the patient needs urgent interventions not included in the trial protocol; and LC is converted to open cholecystectomy before IOC in the “cholecystectomy first” arm. Additionally, if the patient refuses to further participate in the trial, all the patient’s data are eliminated and further follow-up is not carried out. Informed consent will be obtained from all study participants.

### Randomization and Data Protection

Eligible patients who provide informed consent will be assigned to the groups “endoscopy first” or “cholecystectomy first” randomly, according to a premade sequence. The sequence is generated by a randomization website [15]. The sequence is created using block randomization of two elements A and B (“endoscopy first” and “cholecystectomy first”) in a ratio of 1:1. According to the sequence, sheets with group names are enclosed in opaque envelopes. Envelopes are numbered, and the envelope number is the patient number in the trial. When a new participant is enrolled, the topmost envelope is opened by one of the investigators and the participant is randomized into the specified group.

All collected data are coded, that is, every case receives an individual number. Only coded data will be employed for statistical analysis and publishing. Uncoded data are available only for researchers of the trial and, on special and reasonable request, for the coordination center for biomedical research of the institution and Biomedical Research Ethics Committee.

Data are processed and stored in an electronic database, and physical (“paper”) copies are stored at the trial center in accordance with procedures established by law.

### Procedure

The participants of the trial will undergo CBD evaluation depending on the group assignment. For the group “endoscopy first,” EUS is used to evaluate bile ducts. If stones are seen in the extrahepatic bile ducts, ERCP and CBD stone removal are performed during the same general endotracheal anesthesia. LC is performed after endoscopic procedures as soon as possible. In the group “cholecystectomy first,” LC with IOC is performed. If stones are found, postoperative ERCP with CBD stone removal is applied (during cholecystectomy if the CBD is completely blocked or as soon as possible).

EUS is performed with linear or radial Olympus ultrasound endoscopes. The CBD, pancreatic head, and adjacent structures are visualized from the duodenal bulb and descending duodenum. EUS is considered positive for a CBD stone when a constant hyperechogenic lesion with acoustic shadowing is seen in CBD projection.

ERCP procedures are performed by experienced endoscopists (each has more than 5 years of experience in ERCP and has done more than 500 procedures). Olympus side-viewing endoscopes (TJF-160VR) are used. Primary deep selective cannulation of the CBD is performed with a sphincterotome or cannula and guidewire technique. Diatrizoate (Urografin, Bayer) and iohexol (Omnipaque, GE Healthcare) are used as contrast media. Endoscopic sphincterotomy is performed over a
guidewire technique with an Olympus pull-type sphincterotome. Papillary balloon dilation using a through-the-scope balloon catheter is applied when a stricture is indicated. Stones are removed using a retrieval balloon catheter and/or a Dormia basket. Complete clearance of the CBD is documented with a balloon catheter cholangiogram at the end of the procedure. ERCP is considered positive when a filling defect is seen in the cholangiogram and/or a stone is evacuated from the CBD. ERCP is considered unsuccessful when cannulation of bile ducts is technically impossible.

All patients will undergo a standard four-port LC (a 10-mm port at the umbilicus, a 10-mm port at the subxiphoid, a 5-mm port at the bottom of the gallbladder, and a 5-mm port at the right epigastrium). A 30-degree laparoscope is used for intra-abdominal visualization. After exposure and identification of the elements of the hepatocystic triangle, a small transverse cut is made in the cystic duct close to the gallbladder infundibulum with laparoscopic scissors. A 4-French cholangiogram catheter is placed in a 5-mm cholangiography fixation clamp and then inserted into the cystic duct. After verifying the absence of leakage at the catheter insertion site, contrast medium (Urografin) diluted in NaCl 0.9% solution (1:1 ratio) in a 20-mL syringe is injected under fluoroscopic vision (C-arm, Siemens GmbH). Cholangiograms are assessed by the operating surgeon and radiologist. IOC is considered positive when there is a filling defect or lack of contrast evacuation to the duodenum.

Blinding
As both management strategies (endoscopic evaluation and intraoperative examination) differ in nature and postprocedure effect on the patient, complete blinding of participants is not possible. Before enrollment in the trial, the participant, treating clinician, and investigator will not know to which group the participant is assigned.

Follow-Up
Participants are followed as treated inpatients after LC (short-term surveillance) and for 6 months after hospitalization (long-term surveillance). In the short-term surveillance period, postprocedural adverse events, signs of cholestasis, and need for repeated procedures are recorded. In the long-term surveillance period, participants are encouraged to contact the investigators if any symptoms of recurrent cholelithiasis are suspected. Participants will be contacted via phone or email 6 to 12 months later. Their health status will be evaluated using a questionnaire on the possible symptoms of cholecystolithiasis (Multimedia Appendix 1). If any symptoms of possible gallstone disease are observed, the participant is invited for additional investigation (biochemical blood tests, transabdominal ultrasound, and MRCP on demand). All the enrollment, intervention, and surveillance procedures are listed in Multimedia Appendix 2.

Statistical Analysis
The sample size was calculated in reference to collected data on the management of cholecystolithiasis in the trial center Vilnius University Hospital Santaros Klinikos [11]. In our previous study, the mean treatment durations for different management strategy groups (LC-IOC first and ERCP first) were 5.37 and 7.13 days, with SDs of 2.5 and 2.8, respectively, and these findings were used to calculate the requested sample size. The program G*Power version 3.1.9.2 was used for calculations. It was calculated for a two-tailed t test for means of two independent groups. The significance level was selected to be .05, with a power of 0.8. The required sample size is 74 (37 valid participants in each of the two groups).

The endpoints in different management groups will be analyzed using the chi-square test or t test for independent means. Two-sided hypotheses are to be checked, and a P value <.05 will be considered statistically significant. If the distribution is nonnormal, a transformation, such as the logarithm or square root function, can be applied to obtain a normal distribution or nonparametric tests, such as the Mann-Whitney test, can be used. To evaluate the achieved power, a post-hoc power analysis calculation will be performed. As for the primary outcome, a difference of 2 days of hospital stay will be considered clinically meaningful.

Outcomes
The primary endpoint is the length of hospital stay (duration from enrollment into the trial to discharge, in days).

The secondary endpoints are as follows:
1. Diagnostic accuracy of the different management strategies (proportion of correctly diagnosed [true positive and true negative] cases in the entire sample; time frame: 6 to 12 months).
2. Technical success of diagnostic and therapeutic biliary procedures (IOC, EUS, ERCP) (during the active treatment period). For IOC, successful cannulation and contrast media injection into the CBD are considered. For EUS, successful visualization of the CBD is considered. For ERCP, successful cannulation and contrast media injection into the CBD are considered. Successful CBD clearance is also considered.
3. Postoperative course and possible complications of treatment (time frame: up to 1 month). With regard to adverse events of endoscopic interventions and IOC, we consider (1) bleeding, hematemesis and/or melena, or hemoglobin drop >20 g/L; (2) perforation, evidence of air or luminal contents outside the gastrointestinal tract; (3) post-ERCP pancreatitis, new or worsening abdominal pain persisting for at least 24 h and requiring analgesics after ERCP in conjunction with an elevation in serum amylase or lipase levels greater than three times the normal upper limit [16,17]. We also consider assessment of the postoperative course by the Clavien-Dindo classification of surgical complications [18].
4. Cost of treatment (charges for diagnostic procedures, invasive procedures, surgery, and antibacterial treatment, if needed, as well as hospital charges).

Results
The trial protocol was approved by the Vilnius Regional Biomedical Research Ethics Committee in December 2017.
Enrollment of patients was started in January 2018. As of June 2020, 66 patients have been enrolled.

**Discussion**

In the era of minimally invasive surgery and personalized medical care, the optimal cost-effective strategy for the management of patients with symptomatic gallstones and suspected cholecodolithiasis has not been categorically defined yet.

The whole approach to patients with gallbladder stones consists of the following steps: evaluation of the probability of stones in the CBD, visualization, and evacuation of the stones when present along with treatment of cholecystolithiasis itself [19]. There are a few main clinical dilemmas in the management of cholecodolithiasis, including which patients should be investigated for CBD stones and what is the optimal way to treat it (single-stage technique [LC with intraoperative CBD evaluation] or two-stage technique [preoperative ERCP followed by LC]).

First, it is essential to define the criteria for different risk groups. While the majority of recent trials evaluating the accuracy of cholecodolithiasis prediction refer to ASGE guidelines, we performed an analysis of seven different studies on this prognostic system, and the predictive values of high-risk criteria were quite mediocre. The general sensitivity was 52.4%, specificity was 60.8%, positive-predictive value was 65.6%, negative-predictive value was 47.4%, and accuracy was 55.9% [11]. At the center of this trial, an original prognostic index (VUHI) has been used for the prediction of cholecodolithiasis risk before LC since 1999. It is calculated by the following formula: VUHI = A / 30 + 0.4 × B, where A is the total bilirubin concentration (µmol/L) and B is the CBD diameter measured by ultrasound. The results of our previous study showed that the VUHI had comparable and, for some parameters, superior performance than the prognostic system of the ASGE guidelines [11]. The most modest measure was the specificity of VUHI (54%), while the sensitivity was 80.5%. This implied that earlier threshold of the index was kind of a weak spot in the evaluation system. The newly generated model for predicted probability of cholecodolithiasis sets limits for the intermediate risk group, that is, it determines which patients should undergo additional noninterventional investigation. We chose thresholds for the intermediate risk group of 25% and 75% of the probability for CBD stones considering that the upper limit of 50% in the ASGE guidelines would still leave a certain number of patients for unnecessary ERCP. Latest European Association for the Study of the Liver (EASL) guidelines also state that patients with intermediate probability should undergo further evaluation with EUS or MRCP, but do not define what this intermediate probability is [20]. Meta-analyses showed that these two diagnostic procedures are quite comparable, but EUS has better diagnostic accuracy [21,22]. Just one trial comparing EUS and IOC was found in the PubMed database, and it showed better predictive values of IOC [23]. Considering that this study was performed 20 years ago and imaging technologies have advanced since then, it is worth comparing these two methods again. When comparing IOC with ERCP as a diagnostic procedure, a systematic review of 10 trials by Gurusamy et al showed slightly higher sensitivity for IOC with no difference in specificity [24].

All imaging methods are somehow operator dependent (or assessor dependent). EUS can have higher operator dependency as agreed by experts in the field because it requires not only evaluation of images but also proper positioning of the scope [25]. On the other hand, EUS is considered to be able to detect smaller CBD stones, which increases its value. Overall, this potentially is reflected in meta-analyses when evaluating not common specificity or sensitivity but the range in different studies. For example, Meeralam et al presented a pooled sensitivity and specificity of 0.97 (range 0.91-0.99) and 0.90 (range 0.83-0.94) for EUS and 0.87 (range 0.80-0.93) and 0.92 (range 0.87-0.96) for MRCP, respectively [21].

In terms of the level of “invasiveness” of these diagnostic methods, MRCP can be considered the least invasive; however, it has its own disadvantages, such as possible reaction to the contrast material and contraindications for the procedure (claustrophobia and ferromagnetic foreign objects). Additionally, EUS can be compared to conventional upper endoscopy, and the main possible complication is injury of the gastrointestinal tract wall with the scope, which is extremely rare. However, this procedure requires sedation or general anesthesia. IOC could seem to be the most invasive option because it is performed during operation, but it is just an additional step in an already ongoing surgery.

Determination of the best exploration method greatly depends on local expertise and availability of certain procedures. At our institution, availability of magnetic resonance imaging is limited because of the lack of equipment, so we decided to choose investigational procedures performed by surgeons and endoscopists themselves to compare.

The next step is to choose the optimal management strategy. In the aforementioned study, we assessed the effectiveness of different approaches (LC with IOC and ERCP “on demand” versus preoperative ERCP with sphincterotomy and necessary therapeutic interventions followed by LC). Some advantages in both strategies were found. There were less missed stones and false-positive cholangiographies in the ERCP first group. On the other hand, the LC-IOC group had less ERCP-related complications, and the mean length of hospital stay in this group was shorter, reflecting no need to wait for another procedure in most cases [11]. Barreras González et al also found these two strategies comparable in efficacy [26]. Moreover, meta-analyses of various different trials showed that there is no difference in the mortality, morbidity, retained stones, and failure rate between single-stage and two-stage cholecodolithiasis management [1,27]. The main drawback of the preoperative ERCP plus LC strategy compared with various single-session approaches (intraoperative ERCP, LC with laparoscopic bile duct clearance, and open bile duct clearance) is higher time. Usually, there is a waiting period between the two procedures, which prolongs the duration of hospital stay and slightly increases the risk of developing recurrent biliary events and cholecystitis [20,28,29]. The reduced length of hospital stay (mean difference ~3.01 days, 95% CI ~3.51 to ~2.50; P=12%)
was the only significant advantage of intraoperative ERCP found by a Cochrane systematic review when comparing single-stage and two-stage approaches in another way (laparoscopic endoscopic rendezvous versus preoperative endoscopic sphincterotomy) [30]. A recent meta-analysis by Ricci et al of four laparoscopic and endoscopic techniques for managing gallstone disease with biliary duct calculi showed that the safest and most successful approach is LC combined with intraoperative ERCP [31]. However, one of the biggest limitations of single-session ERCP and LC is difficult coordination of medical personnel, equipment, and location of the procedure [32,33]. Despite these restraints, a large survey of general surgeons in the United States showed that the majority of respondents preferred ERCP to laparoscopic CBD exploration for the management of choledocholithiasis if CBD stones were diagnosed preoperatively or intraoperatively [34]. IOC followed by laparoscopic CBD exploration is another possible single-stage strategy. This method appeared to be the safest for avoiding bleeding, took the shortest operative time, and was the least costly in the review by Ricci et al [31]. Unfortunately, this method is not usually applied in our institution, so we decided not to involve it in the trial owing to lack of local expertise.

CBD clearance was found to be alleviated by flushing saline after anterograde balloon dilatation of the Oddi sphincter or after glucagon injection, but these methods are described in singular trials and confirmatory studies are needed [35-37].

This trial is aimed to clarify which one of the two strategies (preoperative EUS or LC with IOC) is the optimal solution for patients with intermediate risk of CBD stones. We intend to compare various aspects of the two approaches of choledocholithiasis management, ranging from accuracy to cost and time efficiency. The thresholds of different risk groups according to the VUHI (original prognostic index) will also be verified prospectively. The index was designed to evaluate the risk for CBD stones in patients with gallbladder stones and an intact gallbladder [38]. Symptomatic cholelithiasis is the main inclusion criterion because it is a major indication for cholecystectomy. We will include adult subjects under 80 years of age as the CBD diameter tends to increase with age [39].

Individuals with other diseases that can cause cholestasis or abnormal liver function test results will be excluded. The diseases include parenchymal disease and mechanical obstruction (from primary sclerosing cholangitis to tumor of the pancreas), as well as biliary pancreatitis, which has been found to not be associated with the risk of choledocholithiasis [10,40,41]. Additionally, we chose to exclude patients with severe acute cholecystitis or cholangitis, as these cases must receive immediate intervention. Finally, patients with absolute or conditional contraindications or burdensome factors for surgery or ERCP (eg, morbid obesity, Billroth II type resection, and severe general condition) are ruled out. We presume that LC with IOC could be the preferred management strategy because of saved time compared with a two-stage strategy, so the study is planned as a superiority trial. We chose to designate hospital stay of 2 days as the minimal important difference between the two groups because it causes a considerable increase in management cost and is barely influenced by nonmedical reasons, which can happen when the difference is chosen to be 1 day. If the difference in inpatient treatment duration is not statistically significant, there are yet other outcomes to be evaluated to compare these two strategies. Overall, this trial is planned to define a simple and safe algorithm for managing choledocholithiasis.

Acknowledgments

This trial will be conducted with no external funding and will be performed with the resources of the hospital as it is a part of the PhD research of one of the investigators (AA) and the center of the trial is a university hospital. Approval to carry out the trial with the resources of the hospital has been obtained, and a contract has been signed between the hospital and the investigators.

Authors’ Contributions

GS and AA conceived the project, designed the study, drafted the manuscript, and approved the final submission. GS, AA, JS, TJ, and MD created the inclusion criteria, and will participate in patient selection and enrollment. AA performed sample size calculation. KS and JV helped design the study, revised the manuscript, and approved the final submission. All authors read and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Possible symptoms of choledocholithiasis.
[DOCX File, 13 KB - resprot_v10i2e18837_app1.docx ]

Multimedia Appendix 2
Enrollment, intervention, and surveillance procedures.
[DOCX File, 14 KB - resprot_v10i2e18837_app2.docx ]

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Abbreviations

- **ASGE:** American Society for Gastrointestinal Endoscopy
- **CBD:** common bile duct
- **ERCP:** endoscopic retrograde cholangiopancreatography
- **EUS:** endoscopic ultrasound
- **IOC:** intraoperative cholangiography
- **LC:** laparoscopic cholecystectomy
- **MRCP:** magnetic resonance cholangiopancreatography
- **VUHI:** Vilnius University Hospital Index

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Mobile Health–Supported HIV Self-Testing Strategy Among Urban Refugee and Displaced Youth in Kampala, Uganda: Protocol for a Cluster Randomized Trial (Tushirikiane, Supporting Each Other)

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Abstract

Background: HIV is the leading cause of mortality among youth in sub-Saharan Africa. Uganda hosts over 1.43 million refugees, and more than 83,000 live in Kampala, largely in informal settlements. There is limited information about HIV testing uptake and preferences among urban refugee and displaced youth. HIV self-testing is a promising method for increasing testing uptake. Further, mobile health (mHealth) interventions have been effective in increasing HIV testing uptake and could be particularly useful among youth.

Objective: This study aims to evaluate the feasibility and effectiveness of two HIV self-testing implementation strategies (HIV self-testing intervention alone and HIV self-testing combined with an mHealth intervention) in comparison with the HIV testing standard of care in terms of HIV testing outcomes among refugee/displaced youth aged 16 to 24 years in Kampala, Uganda.

Methods: A three-arm cluster randomized controlled trial will be implemented across five informal settlements grouped into three sites, based on proximity, and randomization will be performed with a 1:1:1 method. Approximately 450 adolescents (150 per cluster) will be enrolled and followed for 12 months. Data will be collected at the following three time points: baseline enrollment, 8 months after enrollment, and 12 months after enrollment. Primary outcomes (HIV testing frequency, HIV status knowledge, linkage to confirmatory testing, and linkage to HIV care) and secondary outcomes (depression, condom use efficacy, consistent condom use, sexual relationship power, HIV stigma, and adolescent sexual and reproductive health stigma) will be evaluated.
**Results:** The study has been conducted in accordance with CONSORT (Consolidated Standards of Reporting Trials) guidelines. The study has received ethical approval from the University of Toronto (June 14, 2019), Mildmay Uganda (November 11, 2019), and the Uganda National Council for Science and Technology (August 3, 2020). The Tushirikiane trial launched in February 2020, recruiting a total of 452 participants. Data collection was paused for 8 months due to COVID-19. Data collection for wave 2 resumed in November 2020, and as of December 10, 2020, a total of 295 participants have been followed-up. The third, and final, wave of data collection will be conducted between February and March 2021.

**Conclusions:** This study will contribute to the knowledge of differentiated HIV testing implementation strategies for urban refugee and displaced youth living in informal settlements. We will share the findings in peer-reviewed manuscripts and conference presentations.

**Trial Registration:** ClinicalTrials.gov NCT04504097; https://clinicaltrials.gov/ct2/show/NCT04504097.

**International Registered Report Identifier (IRRID):** DERR1-10.2196/26192

**KEYWORDS**
adolescents and youth; implementation research; HIV testing; mobile health; refugee; Uganda

**Introduction**

HIV is the leading cause of death among young people globally and the main cause of death among adolescents and young people in sub-Saharan Africa [1]. In sub-Saharan Africa, half of newly infected adolescents and young people are girls [2,3]. Uganda’s 2018 HIV prevalence among adolescent girls was over double that of adolescent boys, with 14,000 young women aged 15 to 24 reporting new HIV infections compared with 5000 young men [4]. Only 53.6% of adolescent girls in Uganda know their HIV status, and this is far below the Joint United Nations Program on HIV/AIDS (UNAIDS) goal of 90% of persons living with HIV knowing their status by 2020 to achieve an AIDS-free generation [5,6]. HIV testing is a critical entry point for access to HIV prevention and control solutions, specifically access to antiretroviral therapy, which is vital for preventing onward HIV transmission [7,8].

There are more than 79.5 million forcibly displaced persons worldwide [9], and refugee and displaced persons are largely underserved by current HIV prevention strategies [10]. HIV vulnerabilities among displaced/refugee adolescents are shaped by a complex interplay of factors, including poverty, violence, host community HIV prevalence, urbanization, HIV testing and care access, and living conditions [10-12]. Uganda hosts more than 1.4 million refugees [13], with 62% aged below 18 years [14]. Kampala, Uganda’s capital city, hosts over 83,000 refugees [13], and 27% are aged 15 to 24 years [15]. It is important to explore HIV testing needs among urban refugees. There is a global trend of refugee urbanization, with refugees increasingly moving from refugee settlements to urban areas for employment and education opportunities [16-19]. Urban refugees and displaced adolescents and young people are at the nexus of HIV disparities among adolescents, displaced persons, and slum dwellers, and yet, there are knowledge gaps in the optimal HIV prevention for these groups [20,21].

HIV self-testing is a promising strategy to engage marginalized populations [20]. HIV self-testing can represent a convenient and private option, and may reduce stigma compared with clinic-based testing [21]. HIV self-testing has demonstrated acceptability, feasibility, and usability, with minimal harm, and is associated with increased HIV testing among individuals, including adolescents across Southern Africa and Malawi [20,22,23]. Mobile health (mHealth) strategies (digital media on mobile devices) have been efficacious in improving antiretroviral therapy adherence and HIV and sexually transmitted infection testing, and are relevant for the way youth learn and socialize [24-26]. In particular, two-way SMS-based mHealth interventions that are interactive and supportive have been found to be more efficacious in increasing adherence than one-way messages/reminders [27,28]. However, few studies have integrated mHealth into HIV self-testing delivery with adolescents or focused on optimal HIV self-testing delivery strategies with displaced/refugee youth.

Global HIV self-testing knowledge gaps include strategies to facilitate linkage to confirmatory testing and HIV care for persons testing positive [29]. Identifying strategies to promote linkage to HIV care is essential to realize the public health impact of HIV self-testing [30]. A recent systematic review reported a dearth of evidence-based strategies for linkage to HIV care following positive HIV self-testing results among adolescents [31]. This is an urgent knowledge gap that we aim to address with bidirectional text messaging strategies. We also aim to address the lack of evidence regarding the acceptability and feasibility of HIV self-testing among refugee and displaced persons [32]. In Uganda, HIV self-testing was feasible and acceptable; demonstrated the ability to identify new HIV diagnoses among men who have sex with men [33]; and was associated with increased recent and frequent testing among sex workers [34].

Tushirikiane, roughly translating to supporting each other in Swahili, aims to address these knowledge gaps among displaced and refugee adolescent youth in Uganda by testing a mHealth support strategy alongside HIV self-testing delivery to increase routine HIV testing uptake. The findings can be used to inform the implementation and scale-up of HIV self-testing programs with displaced and refugee adolescents across Uganda, sub-Saharan Africa, and other humanitarian contexts.
Methods

Study Aim and Objectives

This study aims to evaluate the feasibility and clinical effectiveness of two HIV self-testing delivery approaches (HIV self-testing intervention alone and HIV self-testing combined with a two-way supportive SMS mHealth intervention) in comparison with the standard of care in terms of HIV testing uptake among refugee and displaced youth aged 16 to 24 years in Kampala, Uganda. The specific objectives of this study are to determine the effectiveness of the interventions on the following criteria: (1) increased frequency of HIV testing; (2) increased knowledge of HIV status; (3) increased linkage to confirmatory testing (for those with an HIV positive self-test); and (4) increased linkage to HIV care (for persons testing positive for HIV in HIV self-testing and confirmatory testing). Secondary outcomes include (1) depression, (2) condom use self-efficacy, (3) consistent condom use, (4) sexual relationship power, (5) HIV stigma, and (6) adolescent sexual and reproductive health (SRH) stigma.

Study Design

To evaluate the intervention effectiveness, we will conduct a cluster randomized controlled trial (cRCT), where informal settlements are randomized. The clusters include five informal settlements grouped into three sites that are randomized in a 1:1:1 method to one of three study arms. Although outcome data will be collected at the level of the individual, we selected cluster randomization over individual randomization because the intervention is implemented at the settlement level. A cluster randomized design addresses threats of internal validity. It reduces the possibility of experimental contamination due to the shared social and physical environments between youth in the same or nearby informal settlements [35]. Data will be collected at the following three time points: baseline enrollment into the intervention, 8 months after enrollment, and 12 months after enrollment.

Study Setting

This trial is being conducted in Kampala, which is the capital of Uganda. Uganda’s progressive refugee policies provide refugees and displaced persons in refugee settlements a plot of land. Yet, with the 2006 Uganda Refugee Law, refugees forgo rights to humanitarian assistance if they leave these refugee settlements [16,17]. The convergence of this law with refugee urbanization contributes to extreme poverty among Kampala’s urban refugees, creating slum environments [16,36,37]. Among Ugandan youth aged 15 to 19 years, the HIV prevalence is estimated at 4% [38]. However, among vulnerable youth living in Kampala’s informal settlements, this is estimated at 37.2% [39]. The five informal settlements selected for this study are grouped into three sites based on their proximity to one another (Kabalagala/Kansanga, Katwe/Nsambya, and Rubaga) and have been purposively chosen because these communities host many displaced/refugee persons in Kampala [16,18,36,37]. We focused on these refugee communities, largely from the Democratic Republic of Congo, Rwanda, and Burundi [13], where refugees continue to arrive, owing to similarities in socioeconomic status and living conditions, health care access, and shared languages (French and Swahili).

Study Population and Eligibility Criteria

A minimum of 432 youth (144 per cluster) between the ages of 16 and 24 years will be enrolled into this study and followed for 12 months. Individuals are eligible for inclusion if they meet the following criteria: (1) currently live in one of the following five informal settlements in Kampala: Kabalagala, Kansanga, Katwe, Nsambya, and Rubaga; (2) identify as a refugee/displaced person or have refugee/displaced parents; (3) are aged 16 to 24 years; (4) speak English, Swahili, Luganda, French, Kinyarwanda, or Kirundi; and (5) own a mobile phone. A brief eligibility screening (via phone, in person, or via WhatsApp) with interested participants will be conducted, asking self-reported HIV serostatus. Only participants reporting an HIV-negative status (baseline serostatus) will be eligible to participate.

Participant Recruitment and Retention

The project team includes a refugee youth-focused community-based nongovernment organization that implements economic empowerment programs for refugee youth and holds expertise on youth engagement. The team also involves academics and practitioners from the Ministry of Health and HIV clinics. Additionally, this project engages peer navigators who identify as refugees or displaced persons (aged 18-24 years) to help with participant recruitment and to provide feedback on the study design and survey. Twelve peer navigators (six young women and six young men) recruited for this study have been identified by community-based collaborators, have experience working in the various study communities as health or peer educators, and are deeply respected and connected in their communities.

Participants will be recruited within each settlement using purposive methods, including word-of-mouth and venue-based sampling at refugee agencies and community events. Peer navigators will conduct peer-driven recruitment at each site, sharing youth-designed flyers for potential participants to contact (via email and mobile number) peer navigators to join the study. Community collaborators and peer navigators will facilitate participant retention. Specifically, peer navigators will use multiple study reminder strategies (eg, social media and texts) to maintain engagement. We will utilize existing outreach and services by local refugee agencies and community partners.

Patient and Public Involvement in Research

Study collaborators at Young African Refugees for Integral Development (YARID) have been involved in the research from the initial stage of developing the research question and focus. We conducted a preliminary exploration of the needs and priorities of refugees and youth with YARID prior to developing this study, and those findings indicated a low prevalence of lifetime HIV testing, which reinforced the importance of this study. Peer navigators, who themselves are urban refugee youth living in Kampala’s informal settlements, provided feedback for the study design and outcomes; conducted recruitment and active engagement with study participants for retention; supported study implementation by facilitating linkages between...
participants and data collectors; pilot tested the survey to assess the time required to participate in the research; and will engage in multiple dissemination strategies for community members (eg, providing input for infographic design and sharing community reports with community stakeholders including the Ministry of Health).

**Intervention Description**

The study has been designed as a three-arm cRCT consisting of two treatment arms and one control arm. Clusters will be randomized to one of the following three arms: (1) HIV self-testing, (2) HIV self-testing plus mHealth strategies (supportive text messages), and (3) standard of care (clinic-based HIV testing). The trial arms and interventions are described below and summarized in Figure 1.

**Figure 1.** Study design for Tushirikiane, a cluster randomized trial of a mobile health (mHealth) HIV self-testing strategy among urban refugee and displaced youth in Kampala, Uganda. SRH: sexual and reproductive health.

<table>
<thead>
<tr>
<th>Treatment Arm 1: HIV Self-Testing Intervention</th>
<th>Time 1 (Baseline Enrollment)</th>
<th>Time 2 (8 months)</th>
<th>Time 3 (12 months)</th>
<th>Time 3 + 1 month</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arm 1</strong> (HIV Self-Testing)</td>
<td>Primary Outcomes - Frequency of HIV testing - Knowledge of HIV status</td>
<td>Primary Outcomes - Frequency of HIV testing - Knowledge of HIV status</td>
<td>Primary Outcomes - Frequency of HIV testing - Knowledge of HIV status - Linkage to HIV confirmatory testing - Linkage to HIV care</td>
<td>Primary Outcomes - HIV self-test kit use</td>
</tr>
<tr>
<td><strong>Arm 2</strong> (HIV Self-Testing + Bidirectional Supportive SMS mHealth Intervention)</td>
<td>Secondary Outcomes - Depression - Condom use self-efficacy - Consistent condom use - Sexual relationship power</td>
<td>Secondary Outcomes - Depression - Condom use self-efficacy</td>
<td>Secondary Outcomes - Depression - Condom use self-efficacy - Consistent condom use - Sexual relationship power - HIV-related stigma - Adolescent SRH stigma</td>
<td></td>
</tr>
<tr>
<td><strong>Arm 3</strong> (Standard of Care)</td>
<td>- HIV-related stigma - Adolescent SRH stigma</td>
<td>- HIV-related stigma - Adolescent SRH stigma</td>
<td>- HIV-related stigma - Adolescent SRH stigma</td>
<td>- HIV-related stigma - Adolescent SRH stigma</td>
</tr>
</tbody>
</table>

**Treatment Arm 1: HIV Self-Testing Intervention**

Participants in this arm will be enrolled into the HIV self-testing intervention group and will receive HIV self-testing kits so they can perform HIV testing. At baseline enrollment, the peer navigator will provide an HIV self-testing kit (OraQuick Rapid HIV-1/2 Antibody Test, OraSure Technologies), which includes an oral swab test stick and tube solutions, a written detailed step-by-step description of how to correctly use the HIV self-testing kit, pictorial and written guides for the HIV self-testing kit, condoms and lubricant, information booklets on HIV and testing, and referral cards with the addresses and phone numbers of local clinics for confirmatory testing. The cards will also have the peer navigator’s phone number to allow participants to contact the peer navigator if they need additional information on how to use the kit or need support to go for confirmatory tests at local clinics. Instructions for the kit are in French, Luganda, Swahili, Kirundi, Kinyarwanda, and English and have been pilot tested for clarity and comprehensiveness with peer navigators. A 24-hour contact number will be provided to participants to text if/when they have questions. At follow-up visits, peer navigators will check in with participants about the HIV self-testing kit, distribute another HIV self-testing kit and condoms/lubricant, and screen for adverse events (eg, negative HIV self-testing–related experiences).

**Treatment Arm 2: HIV Self-Testing Plus mHealth**

Participants in this arm will be enrolled into the HIV self-testing group (as above) and on a web-based SMS platform hosted by WelTel [40,41]. WelTel is a nonprofit agency developing the mHealth intervention, in which participants receive weekly supportive bidirectional text messages asking how they are doing [42]. Participants are requested to reply “fine” or “not fine,” and those responding “not fine” will be contacted with support by a peer navigator. Participants in this arm will discuss the weekly WelTel messages with peer navigators and respond to the “not fine” messages within 2 days. If they do not reply to the initial SMS message within the specified timeframe, a peer navigator will follow up with them during that week. The WelTel system will manage the SMS intervention on a structured mobile phone platform (all SMS interactions are logged). WelTel’s two-way texting mHealth intervention may prompt participants to engage in HIV self-testing and/or to engage peer navigator support in decision making regarding HIV self-testing practices.

**Arm 3: Standard of Care**

Participants in this arm will be enrolled into a standard of care group. Participants will receive information about HIV testing, care, and support services at local clinics. They will be provided a pamphlet of information about HIV and HIV prevention strategies (written in French, English, Luganda, Kirundi, Kinyarwanda, and Swahili).

**Outcomes**

**Primary Outcomes**

The primary outcomes measured in this trial are as follows:
1. Changes in HIV testing frequency: This is measured as participants’ self-reported last HIV test. To capture changes, this measure is assessed at all three study time points (baseline [Time 1], 8 months [Time 2], and 12 months [Time 3]).
2. Changes in knowledge of HIV status: To address social desirability bias challenges regarding self-reported HIV serostatus, multiple steps are employed. First, at each timepoint (Time 1, Time 2, and Time 3), participants are asked their current HIV status. At Time 3, participants are offered a completely voluntary rapid HIV test. Knowledge of HIV status will be assessed as correct for persons who agree to take the rapid test and correctly report their HIV status (prior to receiving the result).
3. Changes in linkage to confirmatory HIV testing: Participants in trial arms 1 and 2 (HIV self-testing and mHealth HIV self-testing intervention) are asked at Time 2 and Time 3 if they used their HIV self-testing kit. For those who respond affirmatively, they will be asked the result, and those who report a positive result will be asked if and where they received confirmatory testing.
4. Changes in linkage to HIV care: Participants who seroconvert during the study are asked the frequency of accessing HIV care service since diagnosis. This will be assessed at Time 2 and Time 3.
5. HIV self-testing kit use: To understand the frequency of HIV self-testing kit use and to reduce social desirability bias regarding HIV self-testing kit use, participants in trial arms 1 and 2 will be followed up 1 month after Time 3 to request for purchasing unused kits back. Participants will not be informed of this as an option prior to this time.

**Secondary Outcomes**

Secondary outcomes include changes in depression assessed using the Patient Health Questionnaire-9 items (PHQ-9) [43]; condom use self-efficacy measured with the Condom Use Efficacy Scale [44,45]; consistent condom use frequency assessed by asking participants if they used condoms every time (consistently) in the past 3 months; sexual relationship power assessed using the relationship control subscale from the Sexual and Reproductive Power Scale [46]; perceived HIV-related stigma with the perceived HIV-related stigma subscale of Steward et al [47]; and adolescent SRH stigma assessed with the Ugandan Adolescent SRH Stigma Scale [48] adapted from the Adolescent SRH scale by Hall et al [49].

**Sample Size and Power Analysis**

Cluster sizes of 130 per group (n=390) are required to have 80% power (P<.05) to detect a 25% difference (39% [5] vs 64% tested) in HIV testing between any two groups from three pairwise comparisons (control vs arm 1, control vs arm 2, and arm 1 vs arm 2) for an odds ratio of 1.66. We assume an intraclass correlation coefficient of 0.013 based on HIV research on condom use in sub-Saharan Africa [50]. With 10% attrition, 432 participants (144 per cluster) are required. Computations were performed using RStudio version 3.3.0 (RStudio Team), based on formulae for multiple comparisons of proportions, and adjusted for design effect [51].

**Data Collection and Management**

Outcome data will be collected at three time points as identified using a tablet-based survey application (QuickTapSurvey, Formstack for Time 1; SurveyCTO, Dobility for Time 2 and Time 3). Baseline data to characterize the study population include demographics and sexual history, which will be collected using these tools. Data will be automatically uploaded onto a secure password-protected server using an SSL certificate and will remain encrypted when not in use.

**Data Analysis Plan**

Analysis and reporting will be conducted in accordance with CONSORT (Consolidated Standards of Reporting Trials) guidelines [52] (Multimedia Appendix 1). The analyst will be blinded to group allocation. A flow diagram will be used to illustrate patient flow (screening, randomization, allocation, and follow-up). Baseline data will be reported for all three arms and summarized as mean (SD) or median (first quartile, third quartile) for continuous variables and as count and number (percentage) for categorical variables. Primary analysis will involve intention-to-treat analysis (data from participants will be analyzed according to their allocation, irrespective of whether they actually received that intervention). Between-group comparisons will be performed using multilevel mixed effect logistic or linear regression models (to account for clustering), depending on which outcome is being evaluated. For these models, the intervention group will be entered as a fixed effect. The level of significance will be set at α=.05, but adjusted using the Bonferroni method for secondary outcomes [53]. The results will be expressed as odds ratios or mean differences as appropriate, accompanied by 95% CIs and P values. We will conduct adjusted analysis for the primary outcome (changes in HIV testing frequency) to investigate the role of various covariates in the relative effect. We will build mixed effect multilevel logistic regression models with the intervention group as the independent variable and HIV testing uptake in the past 3 months (yes/no) as the dependent variable. Covariates (eg, age) will be entered as a block. We will explore gender differences in primary and secondary intervention outcomes.

**Results**

The Tushirikiane trial protocol has been approved by the Research Ethics Board of the University of Toronto (June 14, 2019), Mildmay Uganda Research Ethics Committee (November 11, 2019), and Uganda National Council for Science & Technology (August 3, 2020). The trial is registered at ClinicalTrials.gov (NCT04504097). The Tushirikiane trial launched on February 15, 2020, recruiting a total of 452 participants. Data collection was paused for 8 months owing to COVID-19. Data collection for wave 2 resumed on November 18, 2020, and as of December 10, 2020, a total of 295 participants have been followed up. Data collection for the third, and final, wave will be conducted between February and March 2021. The final follow-up to purchase back unused HIV self-testing kits will occur in June 2021.
Discussion

Study Implications

Although Uganda’s Ministry of Health currently recommends HIV self-testing, there are currently no national guidelines surrounding the optimal delivery of HIV self-testing for adolescents, young people, or refugees/displaced persons. This study is unique in Uganda and elsewhere [32] to outline a path to reducing the barriers to HIV testing faced by urban refugee and displaced youth living in slums and informal settlements. Refugee and displaced adolescents and youth are often not included in HIV and other SRH programs [54-56]. There is also a need for age and gender-disaggregated data to inform SRH programs with refugee and displaced youth, and our study will provide such data [57]. Our research has the potential to advance the HIV prevention and care cascade that involve the integration of social science, epidemiological, and health behavior theories in interventions to increase demand for (through HIV knowledge and peer support) and supply of HIV testing and linkage to HIV care and treatment among refugee and displaced youth [58-60]. Routine HIV testing is key to these cascades [61,62]. We address the World Health Organization (WHO) 2016-2021 HIV Global Health Sector Strategies to address youth key populations; low- and middle-income countries; and targeted HIV testing [58,59], Community partners and knowledge users will be involved in all stages of trial design, conduct, and analysis, as well as dissemination. Should findings indicate increased effectiveness of HIV self-testing over traditional HIV testing strategies, these partnerships will facilitate the scale-up of HIV self-testing implementation for marginalized communities in Uganda.

Ethics

The study population includes young adults (aged 16 years or above) capable of providing informed consent; Uganda’s HIV and AIDS Prevention and Control Act permits youth aged 12 years or above to independently access HIV testing and counselling without parental permission. All participants will receive information about the study before being enrolled to ensure understanding of rights for refusal/withdrawal, study processes, and expectations, and to provide written informed consent. At any time during the study data collection period, participants can withdraw from the study before completing the interview with no adverse consequences on the care or services they receive. All data will be stored on password-protected computers. To maintain confidentiality, all participants will be given a unique case ID, and no personal identifying information will be stored with the study data.

The risks associated with the Tushirikiane trial are reasonable. Physical risks exist for participants who conduct HIV testing (standard of care) and/or confirmatory testing (HIV self-testing and HIV self-testing plus mHealth). However, in all cases, HIV testing and confirmatory testing are optional. Further, the results will only be linked to participant ID. Second, an HIV diagnosis may cause stress, anxiety, and fear of stigmatization among participants. Such risks will be mitigated by the clinics conducting testing, which offer confidential pretest and posttest counselling, as well as HIV treatment. All participants will also be provided with a list of community resources regardless of HIV testing outcomes.

Any adverse event will be reported by the peer navigator to the research assistant, who will fill out an adverse event reporting form (Adverse Event Reporting Form) and adverse event narrative form if appropriate (Adverse Event Narrative Form). Adverse events can also be directly reported by study participants via a Tushirikiane hotline, which will be shared with the study participants at enrollment (Template HIV Counselor Hotline Card), can be called toll free, and will be monitored by trained HIV counselors throughout the duration of the study. Any adverse event requiring a narrative form will be reported to the principal investigators within 24 hours.

Dissemination

Regardless of the outcomes, trial results will be published in peer-reviewed scientific journals and disseminated via many methods. The findings will be disseminated (1) to academics and researchers in HIV, sexual health, social work, and adolescent health via presentations at key scientific conferences; (2) to international collaborating organizations, with executive summaries and reports disseminated to UNAIDS, WHO, and United Nations High Commissioner for Refugees; (3) to local organizations, with reports disseminated to the Ugandan National AIDS Control Program, Ministry of Health, and our collaborators; and (4) through a research brief with highlights of the findings in all five languages.

Data Sharing

The final data set will consist of self-reported demographic and social-ecological data from interviews with the participants and laboratory data from HIV confirmatory tests for HIV-positive individuals. Even though the final data set will be deidentified before release for sharing, it is possible to deductively disclose subjects using a combination of common characteristics.

Therefore, to access our data, users need to meet our data-sharing agreement that provides for (1) the ability to secure ethics approval from both the user’s institution and the University of Toronto research ethics board; (2) a commitment to use the data solely for research purposes and to not identify any individual participant; (3) a dedication to securing the data using appropriate computer technology such as encryption; and (4) a commitment to destroying or returning the data after analyses are completed.

Strengths and Limitations of This Study

The Tushirikiane study is unique in exploring HIV self-testing feasibility and uptake among urban refugee and displaced youth in Kampala, Uganda. Little is known about the preferred HIV testing strategies in this population.

Our three-arm cRCT longitudinal design will allow us to examine changes over time and assess if HIV self-testing alone or HIV self-testing alongside an mHealth component (bidirectional supportive SMS) increases HIV testing uptake and status awareness in comparison with the standard of care.

Our cluster randomization by informal settlements (“slums”) mitigates threats to internal validity and experimental contamination due to the shared social and physical
environments between youth in the same or nearby informal settlement. The primary study limitations are loss to follow-up, missing data points, and study delays due to COVID-19.

Our research will provide gender- and age-stratified analyses, as well as an understanding of the potential added benefits of SMS support strategies alongside HIV self-testing to inform differentiated HIV testing strategies among urban refugee and displaced youth, which can be adapted for diverse contexts.

Acknowledgments

We would like to acknowledge the support and contributions of Young African Refugees for Integral Development, Uganda Ministry of Health, Uganda National AIDS Control Program, Dr Gabby Serafini (WelTel), Interaid Uganda, Tomorrow Vijana, Mildmay Uganda, Organization for Gender Empowerment and Rights Advocacy (Uganda), Most At Risk Population Initiative, Uganda Office of the Prime Minister Department of Refugees, and Tushirikiane Peer Navigators (Gabriella Nzulungi, Sabrina Gamwanya, Hillary Nuwamanya, Nicole Muderhwa, Justin Paluku, Bella Nshimirimana, Claudine Noole, Priscilla Asimwe, Angeliqe Kipenda, Faith Musubaho, Phiona Nattabi, and Joyce Mugisho).

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Authors' Contributions


Conflicts of Interest

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

Multimedia Appendix 1
CONSORT-EHEALTH checklist (V.1.6.1).
[PDF File (Adobe PDF File), 416 KB - resprot_v10i2e26192_app1.pdf ]

Multimedia Appendix 2
CIHR Peer Reviews.
[PDF File (Adobe PDF File), 16 KB - resprot_v10i2e26192_app2.pdf ]

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https://www.researchprotocols.org/2021/2/e26192


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Protocol

mHealth-Supported Delivery of an Evidence-Based Family Home-Visiting Intervention in Sierra Leone: Protocol for a Pilot Randomized Controlled Trial

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Related Article:
This is a corrected version. See correction statement: https://www.researchprotocols.org/2021/2/e27711

Abstract

Background: Past trauma and exposure to violence have been related to poor emotion regulation and household violence, which can have persistent mental health effects across generations. The Family Strengthening Intervention for Early Childhood Development (FSI-ECD/called Sugira Muryango in Rwanda) is an evidence-based behavioral home-visiting intervention to promote caregiver mental health, positive parenting practices, and early childhood development among families facing adversity. In Sierra Leone and other lower- and middle-income countries, mobile health (mHealth) technology has the potential to improve health care delivery and health outcomes.

Objective: This study aims to (1) apply a user-centered design to develop and test mHealth tools to improve supervision and fidelity monitoring of community health workers (CHWs) delivering the FSI-ECD and (2) conduct a pilot randomized controlled trial of the FSI-ECD to assess feasibility, acceptability, and preliminary effects on caregiver mental health, emotion regulation, caregiving behaviors, and family violence in high-risk families with children aged 6-36 months in comparison with control families receiving standard care.

Methods: We will recruit and enroll CHWs, supervisors, and families with a child aged 6-36 months from community health clinics in Sierra Leone. CHWs and supervisors will participate in 1 problem analysis focus group and 2 user interface/user experience cycles to provide feedback on mHealth tool prototypes. Families will be randomized to mHealth-supported FSI-ECD or standard maternal and child health services. We will collect quantitative data on caregiver mental health, emotion regulation, caregiving behaviors, and family functioning at baseline, postintervention, and 3-month follow up. We will use a mixed methods approach to explore feasibility and acceptability of mHealth tools and the FSI-ECD. Mixed effects linear modeling will assess FSI-ECD effects on caregiver outcomes. Cost-effectiveness analysis will estimate costs across FSI-ECD versus standard care.

Results: Funding for this study was received from the National Institutes of Mental Health on August 17, 2020. Institutional Review Board approval was received on September 4, 2020. Data collection is projected to begin on December 15, 2020.

Conclusions: This study will provide important data on the feasibility, acceptability, and preliminary efficacy of mHealth-supported delivery of an evidence-based family home-visiting intervention in a postconflict LMIC.

Trial Registration: ClinicalTrials.gov NCT04481399; https://clinicaltrials.gov/ct2/show/NCT04481399.

International Registered Report Identifier (IRRID): PRR1-10.2196/25443
Introduction

Background
Exposure to war, trauma, and other humanitarian crises can have persistent mental health effects across generations, including intergenerational violence [1-3]. The World Health Organization (WHO) estimates that 35% of women globally report experiencing intimate partner violence in their lifetime, and 75% of children in lower- and middle-income countries (LMICs) experience some form of violent or psychologically damaging discipline at home. Experiencing or witnessing family violence during early childhood increases risks for poor emotion regulation and other psychological problems, including posttraumatic stress disorder, externalizing and internalizing behavioral difficulties, and school problems. In postconflict Sierra Leone, research on the intergenerational impact of the 11-year civil conflict has shown that exposure to violence is related to poor parent/caregiver mental health and harsh parenting practices, which adversely affect child development [4-8]. The 2017 Sierra Leone Multiple Indicator Cluster Survey found that 85% of children aged 3-4 and 67% of those aged 1-2 experience violent discipline [9]. Given that poor caregiver emotion regulation is related to family violence and poor child development outcomes [4,5], evidence-based interventions focused on enhancing caregiver–child interactions (including father/male caregiver involvement), improving caregiver emotion regulation and mental health, and promoting alternatives to harsh discipline practices are urgently needed.

Evidence-Based Family Strengthening
In prior research among families facing adversity in Rwanda, we developed and evaluated the Family Strengthening Intervention for Early Childhood Development (FSI-ECD/Sugira Muryango), a home-visiting behavioral intervention delivered by lay workers [10,11]. The FSI-ECD targets caregiver emotion regulation and caregiver–child interactions as major mechanisms to prevent the intergenerational transmission of emotional and behavioral difficulties related to past trauma. It has demonstrated effectiveness in improving caregiver emotion regulation, reducing family violence, and promoting healthy child development [7,11]. The FSI-ECD is a promising approach for targeting underlying mechanisms linked to poor child outcomes [6,7]. Vital for low-resource settings, it can be delivered feasibly by lay workers with strong supervision and quality improvement cycles. Given the limited health infrastructure in many LMICs, including Sierra Leone [12,13], behavioral interventions that can be delivered by well-trained and supervised lay workers, such as community health workers (CHWs), are a more viable option for implementation and sustainment of evidence-based practices.

To further address critical shortages in the mental health workforce in LMICs, intervention delivery strategies must innovate. In Sierra Leone, new government leadership is pursuing mobile health (mHealth) strategies as means to address significant health care workforce limitations that plague delivery of evidence-based behavioral interventions to vulnerable families. Mobile technology has the potential to transform health care delivery and improve health outcomes in Sierra Leone and other LMICs by providing training, supervision, and fidelity supports to enhance quality improvement while interventions are scaled out, but it has not been widely applied to mental health and family-based prevention, particularly in Sub-Saharan Africa [8,14,15]. mHealth supervision and fidelity monitoring tools could enhance quality of service delivery and expand the reach of evidence-based mental health services to vulnerable families by generating a rapid feedback loop between supervisors and facilitators unconstrained by geographical distances. However, successful implementation of mHealth tools in Sub-Saharan Africa has been limited by dependence on a reliable network connection and electricity [8]. Although 83% of adult Sierra Leoneans have access to a mobile phone, most lack internet access, particularly in rural areas [16]. In this context, innovative use of battery-powered tablets with offline functions and access to cloud storage are logistically feasible and could help improve delivery quality and supervision of CHWs.

Study Objectives
The current study aims to (1) pilot a culturally adapted version of the FSI-ECD delivered by CHWs to vulnerable Sierra Leonan families with children aged 6-36 months to assess feasibility, acceptability, and preliminary effects of mHealth-supported delivery of the FSI-ECD on caregiver mental health and emotion regulation, caregiver–child interactions, and family violence in comparison to control families who receive standard care with standard supervision; and (2) develop and pilot innovative and cost-effective mHealth tools to support CHW delivery of the FSI-ECD. Development of mHealth tools will employ a user-centered design approach to design, prototype, and test digital tools that incorporate user feedback from supervisors and CHWs at each stage of development. User-centered design grounds the tool/app development process in the needs and preferences of those who will use the tool to make it more user-friendly, acceptable, and suitable to the real-world needs of the user: it creates a sense of engagement and shared ownership that aids adoption of the innovation [17-19]. We will use participatory methods and best practices in the user interface/user experience (UI/UX) design to engage CHWs and supervisors in the iterative development process to ensure that our mHealth tools and strategies meet their needs, align with local technological capacity and health service priorities, and support sustained evidence-based practice. The objectives are to develop mHealth tools for supervision, fidelity monitoring, and training of CHWs in Sierra Leone and to provide supervisors with quick visual data displays on CHW performance to inform quality improvement cycles. We will also conduct a preliminary cost-effectiveness analysis to assess
the economic value of the mHealth-supported delivery of the FSI-ECD versus standard care with standard supervision.

Methods

Design

This study is approved by the Boston College Institutional Review Board (reference number 21.006.01; Multimedia Appendix 1) and the Sierra Leone Ethics and Scientific Review Committee. The reporting of the trial follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [20] (Figure 1). This trial is registered with the Clinical Trials Registry maintained by the National Library of Medicine at the National Institutes of Health (Trial ID NCT04481399, registered on July 22, 2020). Any subsequent modifications to the study protocol will be reviewed by the Boston College Institutional Review Board and Sierra Leone Ethics and Scientific Review Committee for approval and then submitted to the Clinical Trials Registry as an amendment.
Figure 1. SPIRIT Schedule of Enrollment, Interventions, and Assessments.

<table>
<thead>
<tr>
<th>TIMEPOINT</th>
<th>Enrollment</th>
<th>Allocation</th>
<th>Postallocation</th>
<th>Close-out</th>
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</thead>
<tbody>
<tr>
<td>ENROLLMENT:</td>
<td>Screening</td>
<td>0</td>
<td>Baseline</td>
<td>Post intervention</td>
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<tr>
<td>Eligibility screen</td>
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<tr>
<td>Informed consent</td>
<td>X</td>
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<td>X</td>
<td></td>
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<tr>
<td>Allocation</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>INTERVENTIONS:</td>
<td></td>
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<td></td>
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<tr>
<td>mHealth-Supported FSI-ECD</td>
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<tr>
<td>Standard Care</td>
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<tr>
<td>ASSESSMENTS:</td>
<td>Feasibility of mHealth-Supported FSI-ECD Implementation</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Emotion Regulation</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Home Observation</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Anxiety and Depression</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Intimate Partner Relationships</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Post-Traumatic Stress Symptoms</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>Caregiver-Child Interactions</td>
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<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Overview of Design

We will apply a 5-phase user-centered design approach [21] to develop and test mHealth supervision and fidelity monitoring tools (Figure 2). We will recruit CHWs delivering services to families with children aged 6-36 months (N=6; 3 male/3 female) and CHW supervisors (N=4; 2 male/2 female) to participate in end user focus group discussion sessions. We will hold 3 sessions: an initial problem analysis focus group session followed by 2 iterative cycles of UI/UX testing sessions. Problem analysis will seek to understand how CHWs and supervisors might use mHealth tools to enhance fidelity monitoring and supervision and what types of training resources might best support performance. Design of the mHealth tools will be informed by problem analysis findings. Development will test prototyped components of the mHealth tools to integrate audio, replay, visual displays of data, and summary features. UI/UX testing sessions will use Think Aloud Testing Protocols.
We will conduct a pilot randomized controlled trial to evaluate preliminary mental health benefits of the mHealth-supported FSI-ECD among vulnerable families (N=80) with children aged 6-36 months in the Makeni City region of Sierra Leone. Study research assistants will seek informed consent from families, CHWs, and supervisors for their participation. Families will be randomized to receive the FSI-ECD or standard maternal and child health services delivered by a CHW with standard supervision. To minimize contamination risk, we will use randomization rules developed in our prior work in Sierra Leone (eg, geographic information system mapping to ensure nonadjacency of control and FSI-ECD families). The randomization allocation sequence will be generated via computer-generated random number list in REDCap. Study research assistants and data analysts will be blinded to participant assignment and will assign participants to study condition based on the randomization allocation sequence. Different CHWs will provide the FSI-ECD and standard care to minimize contamination risks.

Setting and Participants

Makeni is the largest city in the Northern Province of Sierra Leone. The city is the capital of Bombali District, and is the economic center of the Northern Province. Makeni is the Provincial Headquarters of the Northern Province of Sierra Leone. The total population is 125,970, of which 124,634 live in urban areas and 1336 live in rural areas [24]. The most common forms of employment are agriculture and trade. Krio is the primary language.

Inclusion criteria for CHW participation in problem analysis and UI/UX testing are as follows: currently providing maternal and child health services to families with children aged 6-36 months in the Makeni region, aged 18 or older, and ability to attend three 90-minute sessions. Inclusion criteria for supervisors are as follows: currently providing supervision to CHWs delivering the aforementioned services in the Makeni region and aged 18 or older. We will exclude individuals who do not meet CHW or supervisor inclusion criteria.

Inclusion criteria for families are as follows: (1) a Sierra Leonean household with cohabitating caregivers (eg, father/mother, mother/grandmother, mother/partner) and child (aged 6-36 months) with both caregivers aged 18 or older; and (2) 1 caregiver scoring at least 62.5 on the Difficulties in Emotion Regulation Scale (DERS). Both caregivers must agree to attend FSI-ECD sessions; however, if 1 caregiver decides to withdraw, the family can still continue to participate. If enrolled families have more than 1 child aged 6-36 months, we will include all eligible children as study participants. We will exclude families who do not meet all inclusion criteria or who experience active family crises (eg, current suicidality or psychosis, serious medical condition, or cognitive impairment as assessed by a study social worker).

We will recruit families from 2 communities within the Makeni region in coordination with the CHW Focal Person, who is the Ministry of Health and Sanitation Community Health Worker Program official responsible for coordinating the work of CHWs and supervisors within peripheral health units. Peripheral health units are key units within the Sierra Leone health care system. They deliver “first-line” care, including prenatal care, routine deliveries, immediate postnatal and neonatal care, community outreach services, routine vaccination, and treatment of childhood illnesses and malnutrition. Peripheral health units maintain records of families in the community who have sought services and we will be able to identify families with a child aged 6-36 months by reviewing their records. We anticipate that engaging at the community level with the peripheral health units will facilitate recruitment and enrollment of our target sample size.

We will recruit CHWs (N=8) and supervisors (N=2) from the 2 identified peripheral health units to deliver the mHealth-supported FSI-ECD and provide weekly supervision. CHW is a volunteer position and there are no educational qualifications that must be met in order to be engaged as a CHW. CHWs and supervisors who participate in problem analysis and UI/UX sessions will be eligible to participate in the FSI-ECD pilot study. Inclusion criteria are CHWs assigned to the peripheral health unit that provides health services in 1 of the 2 communities and 18 years or older. We will exclude CHWs who do not meet inclusion criteria. Inclusion criteria for supervisors are currently overseeing CHWs providing maternal and child health services in 1 of the 2 communities and aged 18 or older.
18 or older. We will exclude supervisors who do not meet inclusion criteria.

**FSI-ECD**

The FSI-ECD is composed of 4 core components: (1) developing problem-solving, stress management, and emotion regulation skills; (2) cultivating positive parenting skills and fostering father/male co-caregiver engagement; (3) developing communication and conflict resolution skills; and (4) exploring alternatives to harsh punishment and practicing nonviolent child discipline. The FSI-ECD integrates key elements of the evidence-based Family-Based Prevention Intervention [25] and was culturally adapted to the Rwandan context through extensive community-based participatory research methods involving Rwandan community advisory boards. The FSI-ECD is delivered in 12 modules in the home via coaching by CHWs. Sessions are delivered once per week and last approximately 90 minutes. Prior to the trial, we will adapt the FSI-ECD to the cultural context of Sierra Leone. A Community Advisory Board will advise on local parenting and mental health terms and concepts drawing from previously collected qualitative data on parenting in Sierra Leone.

**Standard Services**

Standard CHW care involves 3 home-visiting, educational sessions delivered to families following childbirth, with weekly supervision via phone or face-to-face. Topics of home-visiting sessions include skilled postnatal care for mothers, early initiation of breastfeeding, nutrition, immunization services, handwashing and hygiene practices, building the capacity of family members to take care of newborns and children under age 5. CHWs also conduct screenings for acute malnutrition and growth monitoring to identify early referrals, and they can provide family planning methods; deworming tablets; and other vitamins for acute malnutrition, dehydration, and antimalaria treatment. Each home-visiting session lasts approximately 60 minutes.

**Training and Supervision**

CHWs and supervisors will be trained in the core components of the adapted FSI-ECD by FSI-ECD experts. Training will occur 5 days per week over the course of 3 weeks. At the conclusion of training, CHWs and supervisors will complete a competency assessment. CHWs and supervisors will also complete a 1-day technology training on use of the mHealth tools. During FSI-ECD delivery, CHWs and supervisors will participate in weekly 60-minute supervision sessions guided by mHealth tools to support delivery quality. CHWs and supervisors will complete fidelity monitoring checklists that are embedded in mHealth tools, and review of fidelity monitoring data will inform quality improvement feedback cycles during supervision.

**Measures**

**FSI-ECD Outcomes**

We will collect quantitative data on caregiver mental health and emotion regulation, harsh parenting practices, the home environment, and family functioning at baseline, postintervention, and 3-month follow-up. All quantitative measures have undergone a thorough development, translation, and validation process [26] in a prior randomized controlled trial in Sierra Leone. The following quantitative measures will be used: the DERS (α=.95) [27], WHO Disability Assessment Schedule (α=.91) [28], the Conflict Tactics Scale (α=.72-.86) [29], Hopkins Symptom Checklist (α=.92) [30], and Post-traumatic Stress Disorder Reaction Index (α=.93) [31]. To assess caregiver–child interactions, we will use the Home Observation for Measurement of the Environment (α=.73) [32] and the Observation of Mother–Child Interaction (α=.83) [33]. We will also collect qualitative data at postintervention via key informant interviews with randomly selected caregivers (4 males/4 females) to assess FSI-ECD feasibility, acceptability, and satisfaction.

**mHealth Outcomes**

We will collect quantitative data on mHealth tool feasibility, acceptability, adoption, and appropriateness with CHWs and supervisors at baseline and postintervention via quantitative scales developed by researchers at Johns Hopkins Bloomberg School of Health [34]. We will track length of time to deliver FSI-ECD content, use of embedded fidelity monitoring and tracking features, and amount of CHW–supervisor contact via tablet, phone, and face-to-face. Fidelity data will include a CHW-completed electronic fidelity checklist designed to support self-monitoring and performance review with supervisors as well as a supervisor-completed electronic fidelity checklist to be completed while reviewing audiotaped FSI-ECD sessions and discussed during supervision. We will also collect data on mHealth tools postintervention via key informant interviews with CHWs (n=8) and supervisors (n=4) to understand usability of audio/video functions for FSI-ECD delivery, supervision, and quality improvement cycles.

Participant diagnostic and assessment data will be collected via tablets and deidentified. All tablets will be encrypted and password protected using a password known only to the research team. All data on the tablet will remain on the tablet until it is connected to Wi-Fi and uploaded to a secure server. Daily quality assurance and data monitoring checks will determine successful upload of the data, which will be backed up to Box, a secure, HIPAA (Health Insurance Portability and Accountability Act)-compliant, cloud-based storage platform, before it is remotely wiped from the tablet.

**Data Analysis**

For quantitative data analysis, will use mixed effects linear models to assess the effects of the FSI-ECD on caregiver mental health and emotion regulation, caregiver–child interactions, and parenting practices. These models will account for clustering of families within CHWs delivering services and clustering of outcomes within families across time. If outcomes are skewed and violate the normality assumption for linear models, we will use generalized linear models with a Poisson distribution. We will track implementation of FSI-ECD by FSI-ECD experts. Training will be completed while reviewing audiotaped FSI-ECD sessions and discussed during supervision. We will also collect data on mHealth tools postintervention via key informant interviews with CHWs (n=8) and supervisors (n=4) to understand usability of audio/video functions for FSI-ECD delivery, supervision, and quality improvement cycles.

Participant diagnostic and assessment data will be collected via tablets and deidentified. All tablets will be encrypted and password protected using a password known only to the research team. All data on the tablet will remain on the tablet until it is connected to Wi-Fi and uploaded to a secure server. Daily quality assurance and data monitoring checks will determine successful upload of the data, which will be backed up to Box, a secure, HIPAA (Health Insurance Portability and Accountability Act)-compliant, cloud-based storage platform, before it is remotely wiped from the tablet.

**Data Analysis**

For quantitative data analysis, will use mixed effects linear models to assess the effects of the FSI-ECD on caregiver mental health and emotion regulation, caregiver–child interactions, and parenting practices. These models will account for clustering of families within CHWs delivering services and clustering of outcomes within families across time. If outcomes are skewed and violate the normality assumption for linear models, we will use generalized linear models with a Poisson distribution. We will conduct all analyses on an intent-to-treat basis. Paired t-tests (2-tailed) and Wilcoxon signed rank tests will examine postintervention change in quantitative implementation outcomes (ie, feasibility, acceptability, adoption, appropriateness), controlling for baseline scores.
Power calculations for sample size were calculated using the power command in STATA (StataCorp). The proposed pilot study is not powered to detect treatment effects of clinical significance. However, if we assume a standard $\alpha$ level of .05, 80 families with 2 eligible respondents per family on average, and 2 time points, with assumptions of moderate intraclass (within-family) correlation (approximately 0.5), this pilot randomized control trial has power of 0.80 to detect a standardized “medium” effect size of approximately 0.50 [35]. For outcomes with only 1 observation per time point, and using the same assumptions as above, this pilot randomized control trial has power of 0.80 to detect a standardized effect size of approximately 0.6. Multiple imputation will be used to deal with missing data.

Qualitative data analysis of key informant interviews will follow a 3-step analytical strategy derived from thematic content analysis and grounded theory [36,37]. We will use open coding to examine key interview themes (eg, barriers and facilitators to use, feasibility, and acceptability). We will iteratively develop a coding scheme organized by key themes. After we have identified major categories and established a codebook, we will conduct axial coding to link themes in terms of timing, context, and other dimensions. Poor agreement (ie, low $\kappa$ ratings as scored in MAXQDA [38]) will be grounds for refining the codebook. We will repeat reliability testing until coding is at >80% agreement for all data sources. We will code all data sets in MAXQDA. Mixed methods analysis will synthesize qualitative and quantitative data using embedded quotes and joint display tables [39]. This approach will also be used for qualitative data analysis of key informant interviews with caregivers.

Cost-effectiveness analysis will estimate costs across FSI-ECD versus standard care. We will use budget, expenditure, supervision, and fidelity data to collect implementation, health, and service costs using standard costing methodologies [40]. Costs will include implementation activities (eg, staff and CHW/supervisor trainings, session delivery, supervision) and directly related recurrent or capital items (eg, tablets, tech support, broadband access, travel supplies). Costs of digital tools will be included as a capital item and amortized based on project duration. Service delivery costs will rely on in-country data or standard costs provided by WHO-CHOosing Interventions that are Cost-Effective published costs data. Outcomes will include a functional impairment measure (WHO Disability Assessment Schedule) that can be converted to quality-adjusted life years [41]. We will use standard incremental cost-effectiveness analysis to compare mHealth-supported delivery of the FSI-ECD to standard care and capture marginal variations in costs and effectiveness using incremental cost-effectiveness ratios. Differences in intervention cost will be divided by differences in intervention effectiveness to calculate incremental cost-effectiveness ratios that can be used to understand the cost of the intervention per unit of outcome (cost per quality-adjusted life year). We can compare this to the standard willingness to pay threshold and to alternative programs to determine which programs are relatively more cost-effective.

Ethical Approval and Consent to Participate
This study received ethical approval from the relevant College Institutional Review Board and the Sierra Leone Scientific Review Committee (Multimedia Appendices 1 and 2). All participants provided verbal consent to participate due to low literacy levels. This procedure was approved by both ethics committees.

Availability of Data And Materials
Data sharing will be in accordance with the NIH Data Sharing Policy and Implementation Guidance and more specifically the “Data Sharing Expectations for National Institute of Mental Health (NIMH)-funded Clinical Trials.” The data generated in this study will be entered into the NIMH Data Archive as required as prescribed by the Notice of Award as well as presented at national or international conferences and published in a timely fashion. All final peer-reviewed manuscripts that arise from this proposal will be submitted to the digital archive PubMed Central. Published data will be available in print or electronically from publishers, subject to subscription or printing charges. Research data that document, support, and validate research findings will be made available after the main findings from the final research data set have been accepted for publication.

Results
Funding for this study was received from the National Institute of Mental Health on August 17, 2020 (Multimedia Appendix 1). Institutional Review Board approval was received on September 4, 2020. At the time of manuscript submission, the study has not yet initiated baseline data collection. Data collection is projected to begin on December 15, 2020. Table 1 presents information on the timeline of study activities across the 2 years of the project.
Table 1. Project activities and timeline.

<table>
<thead>
<tr>
<th>Quarter</th>
<th>Year 1</th>
<th>Year 2</th>
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<tbody>
<tr>
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<td>2</td>
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<tr>
<td><strong>AIM 1: mHealth tool/app development</strong></td>
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<tr>
<td>Focus group: UI(^a)/UX(^b) participant recruitment</td>
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<tr>
<td>Problem analysis</td>
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<tr>
<td>Design and development</td>
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<tr>
<td><strong>AIM 2: FSI-ECD(^c) adaptation and pilot study</strong></td>
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<td>CHW(^d) and supervisor recruitment</td>
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<tr>
<td>CHW and supervisor FSI-ECD training (3 weeks)</td>
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<td>Family recruitment, enrollment, and baseline diagnostics</td>
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<td>FSI-ECD implementation and postintervention evaluation</td>
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<tr>
<td>FSI-ECD 3-month follow-up</td>
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<td></td>
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<tr>
<td>Data analysis and dissemination</td>
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</tbody>
</table>

\(^a\)UI: user interface.  
\(^b\)UX: user experience.  
\(^c\)FSI-ECD: Family Strengthening Intervention for Early Childhood Development.  
\(^d\)CHW: community health worker.

**Discussion**

**Possible Challenges**

There are several potential challenges that may arise during study implementation. In Sierra Leone, many caregivers are involved in employment that requires a high level of daily mobility, such as trade and agriculture. Some caregivers travel across districts, regions, or to neighboring countries for several weeks in order to work. In this work context, we may experience some challenges recruiting and retaining caregivers because participation in the FSI-ECD requires caregivers to attend twelve 90-minute sessions delivered once per week. Although the FSI-ECD may provide long-term benefits for caregiver mental health and child development, these benefits may not be a sufficient incentive for study participation. To help address this challenge, we will encourage highly flexible scheduling to accommodate the working hours of caregivers. The home-visiting nature of the FSI-ECD is also intended to improve service access for families with young children and will relieve the burden of traveling to attend services.

Technology literacy levels and potential technical issues that may occur with the mHealth tools could also pose challenges to this study. To address this, we will provide a 1-day technology literacy training on the use of mHealth tools and basic skills with tablet use. We will also provide ongoing technical support to troubleshoot any technical issues. It is possible that poor connectivity may impede rapid resolution of technical issues, because technical assistance will be remote. However, given that CHWs and supervisors will not need to use mHealth tools on a daily basis, our team should be capable of reasonably resolving any issues with enough time to ensure study activities proceed as planned. We will also train the study data manager in use of the mHealth tools to support greater in-country expertise. We will document any technical issues and keep a log of the strategy to resolve them in the event that the same issue is encountered on a subsequent occasion. To address potential difficulties with internet connectivity, we will place a modem for CHWs and supervisors in the peripheral health unit where they are based. Battery-powered tablets with offline functions and access to cloud storage will also ensure that mHealth tools can be feasibly used and data securely stored until connectivity is available.

**Study Strengths**

This study has several strengths. We propose to recruit and enroll CHWs and supervisors, government health employees who work in the communities where they reside, to deliver the FSI-ECD. CHWs will likely already have familiarity with many families in their community before study recruitment and enrollment begins, which may facilitate recruitment and engagement of caregivers in study activities. CHWs will also be familiar with the social norms, typical work schedules, and family habits of their community members, which may also help increase engagement and retention of families in study activities.

**Conclusion**

This study has the potential to build urgently needed capacity for both delivery of evidence-based mental health services to reduce family violence and harsh parenting practices and for effective use of mHealth strategies to improve lay worker health service delivery. This study will provide important data on feasibility, acceptability, and cost of both mHealth tools and mHealth-supported FSI-ECD. If mHealth tools are feasible, acceptable, and support high-quality FSI-ECD delivery, this
platform could be used to improve efficiency and quality of service delivery for other CHW-delivered services in similar settings. The mHealth tools might also help expand the reach of evidence-based mental health services to vulnerable families in more rural areas by generating a more rapid feedback loop between supervisors and CHWs unconstrained by geographical distances. Finally, applying mHealth tools for supervision and quality improvement has the potential to reduce long-term costs associated with traditional modes of fidelity monitoring and supervision, thus enabling greater scalability in a setting with limited behavioral health professionals.

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Authors’ Contributions
AD contributed to conception and design of the work and to drafting and revising the manuscript. CS, RE, and MJ contributed to drafting the manuscript. TB contributed to conception and design of the work and revising the manuscript. All authors approved the submitted version of the manuscript and agree to be personally responsible for their own contributions.

Conflicts of Interest
None declared.

Multimedia Appendix 1
Boston College Institutional Review Board Approval.

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Abbreviations

CHW: community health worker
DERS: Difficulties in Emotion Regulation Scale
FSI-ECD: Family Strengthening Intervention for Early Childhood Development
LMIC: lower- and middle-income country
UI/UX: user interface/user experience
WHO: World Health Organization

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Protocol

An Asynchronous, Mobile Text-Based Platform (XatJove Anoia) for Providing Health Services to Teenagers: Protocol for a Quasiexperimental Study

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Abstract

Background: Due to the COVID-19 pandemic, it is more essential than ever to implement protective measures in primary care centers to ensure patients’ safety. This protocol describes a quasiexperimental study on the use of a mobile chat platform as a clinical consultation tool for adolescents and primary health care physicians.

Objective: The purpose of the quasiexperimental study is to demonstrate that the use of mobile phones and messaging apps increases the number of health consultations. The study will be performed as part of the Health in Schools program in the Anoia region.

Methods: The quasiexperimental study will compare the number of face-to-face consultations to the number of consultations conducted on XatJove Anoia, as part of the Health in Schools program in the Anoia region. The study will involve the use of a new communication platform (ie, XatJove Anoia) for health care professionals and adolescents, and data on the number of face-to-face consultations will be collected as part of the same program in another region. Data will be collected from secondary schools during the academic year 2020-2021. Statistical analyses will be performed on the data that users will enter in the registration form. These data will be collected by means of a questionnaire, which will be submitted once the questionnaire is closed. The questionnaire will consist of multiple-choice questions, which will allow numerical values to be assigned to various responses in order to carry out statistical analyses.

Results: The study is projected to start at the beginning of November 2020 and finish in June 2021, which is when data analysis is expected to start.

Conclusions: The results of the quasiexperimental study may assist in the development and planning of school health programs.

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KEYWORDS
mHealth; telehealth; teenager; health promotion and sexual health; health promotion; sexual health

Introduction

The World Health Organization defines “digital health” as the use of digital technologies for health purposes; digital health is a category that encompasses the increasing use of technologies for health services [1]. The internet has become an important tool for many people with health concerns, especially adolescents. Concerns regarding confidentiality, coupled with the stigma and shame associated with certain conditions, such as sexually transmitted infections and other health-related problems, make the internet an unsafe environment for adolescents who seek information.

Sex education is essential for the prevention of risky sexual behaviors, unwanted pregnancies, and the transmission of human immunodeficiency viruses and other sexually transmitted infections among adolescents. Young people receive sexual and reproductive health education from various sources, including formal education, school curricula, parents, fellow students, and media [2].

During the International Conference on Population and Development [2], several measures were established as a response to the need for providing relevant information that protects the sexual and reproductive lives of young people. Governments have been requested to provide sex education policies to promote the well-being of young people at a community level, especially in the school environment. Such policies will allow young people to make mature decisions regarding responsible sexual behavior much earlier than usual [3].

Finding information on health-related issues can be a major problem, as the underutilization of primary care services that provide information on certain topics and the untrustworthy nature of advice on the internet can subsequently lead to health-related complications that may require expensive and specialized medical interventions in the long term. These complications can ultimately lead to an increase in health care costs [4].

The Salut i Escola program (ie, the Health in Schools program) was launched by the Catalan Department of Health in the academic year 2004-2005. This program aims to improve the health of adolescents in Catalonia. The program involves health promotion, risk prevention, and early detection for problems related to mental health, emotional and sexual health, and drug, alcohol, and tobacco consumption. The program has been carried out in close collaboration with local schools and community health services.

This community-based outreach program requires intervention and cooperation from different professionals. One of the program’s main lines of activity is the open consultation service, in which a health care professional visits schools to facilitate primary care accessibility among adolescents and guarantee privacy, confidentiality, and proximity.

Patients—particularly adolescent patients—are often reluctant to seek counselling and health treatment for embarrassing or stigmatized conditions, which can result in the underutilization of primary care health services. In addition, searching for medical information on the internet (eg, searching via Google) is increasingly common. Primary care health services, which are often made for young people, include consultations for sexual and reproductive health problems [5] and mental health disorders [6]. Finding information on health-related issues can lead to serious problems; the underutilization of primary care services that provide information on certain issues and the untrustworthy nature of advice on the internet can subsequently lead to health complications that may require expensive and specialized medical interventions in the long run, which may result in increased care costs [4].

To avoid health complications and increased care costs, a tool that adolescents have easy, constant, and effective access to is required. Digital health interventions have been shown to minimize hesitancy in seeking health advice for stigmatized and embarrassing problems. The digital health innovations proposed by the company Abi Global Health (AGH) could provide a possible solution [7]. AGH has developed an asynchronous, mobile text-based communication platform that connects users to health care professionals. These professionals provide users with appropriate guidance to help them make informed decisions about their health. AGH operates in more than 10 countries and has a network of more than 300 health professionals. This preexisting tool will form the basis of XatJove Anoia (ie, YouthChat Anoia), which is a platform that attempts to provide resources for mobile communication and message exchanges between adolescents and primary care professionals. A quasi-experimental study on XatJove Anoia will take place in Anoia, which is a country in Central Catalonia.

According to a pilot study, cystitis and contraceptive problems are among the top 10 reasons why patients have used a web-based tool to conduct a consultation [8]. Although these conditions can be embarrassing and difficult to talk about, it is important that they are dealt with by health care professionals. If ignored, these conditions can lead to serious, unwanted, and costly complications (eg, a failure to use contraception can lead to unwanted pregnancies and sexually transmitted diseases) [9,10]. The fact that users have routinely reported these problems by means of digital health interventions, such as e-consulta (ie, an asynchronous teleconsulting service for primary care professionals and health service users that is connected to primary care electronic medical records), is a positive sign with regard to the greater use of health services for sensitive and serious conditions. As an anonymous digital health intervention,
XatJove has the potential to address the inefficient costs resulting from the underutilization of health services for embarrassing and stigmatized disorders.

Due to the current climate of the health crisis caused by the COVID-19 pandemic [11] and the need to reduce the risk of infection, it makes more sense than ever to avoid face-to-face consultations with nursing staff in schools and primary care center visits by young people. It should be noted that this does not mean that there will be a reduction in the number of consultations for health-related issues and the number of school programs. On the contrary, the health crisis is expected to generate an increase in the need for emotional support for young people, and such support requires tools that allow for the quick use of technology (ie, technology that adolescents and primary care center professionals are familiar with and use regularly).

The main objective of this protocol is to describe a quasiexperimental study that shows that the use of mobile phones and messaging apps leads to an increase in the number of health consultations for adolescents aged between 12 and 16 years, as part of the Health and School program in the Anoia region. The study also seeks to evaluate the degree of satisfaction among XatJove users via an electronic survey.

Our main hypothesis is that the use of XatJove will improve the early detection of health problems, the accessibility of reliable information for young people, and communication among nursing professionals in primary care centers, in terms of issues related to drugs, diet, emotional health, and sexuality. We also believe that XatJove can help with the detection of child abuse cases.

Methods

Study Design

A quasiexperimental study that compares the total number of face-to-face consultations and XatJove consultations will be conducted as part of the Health and School program in the Anoia region (ie, the intervention group) during the 2020-2021 academic year. Data on the number of face-to-face consultations will be collected from the same program in the Osona region (ie, the control group). Problems that affect adolescents and relate to mental health, emotional and sexual health, drug use, alcohol, and tobacco will be recorded. The study population will include adolescents aged between 12 and 16 years who attend secondary schools in the Anoia region. We will use a pragmatic sample of 100 XatJove consultations. The total number of visits (ie, face-to-face visits and XatJove visits) that relate to the Health and School program in the Anoia region during the 2020-2021 academic year will be recorded.

The following variables will be recorded: (1) universal variables, including gender and age; (2) dependent variables, including the total number of visits (ie, face-to-face visits and XatJove visits) that relate to the Health and School program; and (3) independent variables, including the topic of consultations (ie, consultations for sexual health, alcohol, drugs, eating disorders, bullying, domestic abuse, mental health, COVID-19, and other topics).

To learn more about the usefulness of XatJove, students will be asked to participate in a follow-up study that involves a focus group.

Data Collection and Sources of Information

Data regarding the total number of visits will be obtained from the Primary Care Services Information Technologies System (ie, Sistemes d’Informació dels Serveis d’Atenció Primària en Català), which belongs to the Catalan Institute of Health in Barcelona, Spain.

The asynchronous, mobile text-based communication platform that is made available by AGH makes it possible to collect information on cases that involve a written query. User data will be obtained from the platform’s database, and users will remain anonymous. The information collected will include age, gender, the date and time of the query, and the answer to the query. In addition, all the professionals involved in the study will sign a document, in which they will agree to respect data confidentiality.

After a response from a health care professional is received, users will be able to respond to a questionnaire, in which they can evaluate the quality of the service and their level of satisfaction (Multimedia Appendix 1). The data in this questionnaire will be collected and processed by AGH.

Statistical Analysis

Spreadsheets will be used to record the means and medians of various data. Statistical analyses will be performed on the data that users will enter in the registration form and the data collected from the questionnaire. The questionnaire will be sent to participants after their consultation concludes. The questionnaire consists of multiple-choice questions, which makes it possible to assign a numerical value to various responses. These values will be used in the corresponding statistical analyses.

Limitations of the Study

It is possible that an insufficient number of users will rate the service and respond to the questionnaire. If this happens, the deadline for collecting data will be extended.

Although it will be possible to send questions via XatJove 24 hours per day, answers will only be sent during specific time slots (ie, from 8 AM to 8 PM, including weekends). This may limit the accessibility of the service. However, any inquiries made outside of this time slot will be answered by medical professionals at the start of their next working day.

Since XatJove is an anonymized service, it will not be possible to verify whether users meet the inclusion criteria. Nevertheless, the service will only be offered to students who attend secondary schools in Anoia.

Ethical Considerations

The Institut Universitari d’Investigació en Atenció Primària Jordi Gol independent ethics committee in Barcelona, Spain approved the trial study protocol (code 20/137-P). Written informed consent will be requested from all patients who participate in the study. The study was registered on the...
ClinicalTrial.gov registry (NCT04562350) on September 24, 2020.

Availability of Data and Materials
All principal investigators of the study will have access to the complete dataset. The datasets generated and analyzed during the study will be made available by the corresponding author. The results generated during the study will be published in peer-reviewed journals and presented at national/international congresses.

The study has been designed in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines. The registration of the study on ClinicalTrials.gov is expected to facilitate transparency and reporting.

Results
The study is projected to start at the beginning of November 2020 and finish in June 2021, which is when data analysis is expected to start.

Discussion
This aim of the pilot quasiexperimental study is to investigate the use of a mobile phone health chat service for adolescents from secondary schools in Anoia and nursing professionals from primary care centers in the same region.

The various studies that we previously participated in have shown that the use of a web-based communication tool for patients and professionals reduces the number of face-to-face visits [12,13], which is a very positive aspect with regard to the COVID-19 pandemic. Furthermore, the results of the study and the long-term and short-term impacts of XatJove will be used to revise the Health and School program, which is offered by the Department of Health. In other words, XatJove is a tool that will serve in the review of existing protocols. Web-based visits and consultations are gaining in popularity in the new health care environment that has resulted from the COVID-19 pandemic.

Web-based consultations can help with avoiding self-diagnoses, as it is common for people to search for information on the internet, which is not always a reliable source. Current evidence points to the importance of innovating and improving the treatment processes offered by health and school programs. One of our study’s strengths is that the results will be obtained from usual clinical practices, without having to implement any considerable organizational or structural changes.

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Authors' Contributions
All authors contributed to the design and content of the study protocol. GSV, JVA, and VV, are responsible for the coordination of the study. More specifically, JVA, GSV, FS-R, GT, VV, and AE are responsible for designing the study, and GSV, JVA, VGF, KE, FS-R, and NC are responsible for writing the initial manuscript draft. GSV, JVA, VV, NC, KE, VGF, NC, AE, IS, and GT are responsible for data collection, fieldwork, and fundraising. VV, AE, and GT have epidemiological and statistical expertise. All authors read and approved the final version of the manuscript.

Conflicts of Interest
None declared.

Multimedia Appendix 1
Questionnaire for evaluating the quality of the service.
[DOCX File, 13 KB - resprot_v10i2e25062_app1.docx]

References


Abbreviations

AGH: Abi Global Health
CONSORT: Consolidated Standards of Reporting Trials
Protocol

Leadership in Digital Health Services: Protocol for a Concept Analysis

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Abstract

Background: Due to the rapid digitalization of health care, leadership is becoming more complex. Leadership in digital health services is a term that has been used in the literature with various meanings. Conceptualization of leadership in digital health services is needed to deliver higher quality digital health services, update existing leadership practices, and advance research.

Objective: The aim of this study is to outline a concept analysis that aims to clarify and define the concept of leadership in digital health services.

Methods: The concept analysis will be performed using the Walker and Avant model, which involves eight steps: concept selection, determination of aims, identification of uses, determination of defining attributes, construction of a model case, construction of additional cases, identification of antecedents and consequences, and definition of empirical referents. A scoping literature search will be performed following the search protocol for scoping reviews by the Joanna Briggs Institute to identify all relevant literature on leadership in digital health services. Searches will be conducted in 6 scientific databases (CINAHL, MEDLINE, Scopus, ProQuest, Web of Science, and the Finnish database Medic), and unpublished studies and gray literature will be searched using Google Scholar, EBSCO Open Dissertations, and MedNar.

Results: An initial limited search of MEDLINE was undertaken on October 19, 2020, resulting in 883 records. The results of the concept analysis will be submitted for publication by July 2021.

Conclusions: A robust conceptualization of leadership in digital health services is needed to support research, leadership, and education. The concept analysis model of Walker and Avant will be used to meet this need. As leadership in digital health services appears to be an interprofessional and intersectoral collaboration, defining this concept may also facilitate collaboration between professionals and sectors. The concept analysis to be conducted will also expand our understanding of leadership in digital health services.

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KEYWORDS
health care; leadership; health services; concept analysis; telehealth
Introduction

Background

Several health care programs and reforms introduced in recent years have highlighted the importance of digitalization and health information technology for solving problems in modern health care [1,2]. This importance has been increased further by the COVID-19 pandemic [3]. Health care digitalization, also referred to as digital transformation, means that health services and systems are undergoing a transition whereby increasing numbers of these services and systems are becoming digitalized [4]. Although there is a rapidly growing body of research on health care digitalization [5], the viewpoint of health care leadership in digital health services has been de-emphasized [6-9]. Health care leaders have traditionally been responsible for clinical health services and their management [10]; however, now they are also responsible for developing and managing health care organizations’ health information technologies (HITs) [11-13]. Nurse leaders seem to be particularly active in planning the implementation of digital health services and bear the chief responsibility for its use [14]. This may be because nurses are often more involved in the early-stage implementation of digital transformation projects, whereas physicians join during later phases [15]. It has, therefore, been suggested that more research should focus on how to develop continuously evolving health care leadership that is well placed to cope with changes such as the current rapid digital transformation [16].

However, the literature provides little clarity as to what leadership in digital health services means or entails [17,18]. Researchers have used terms such as e-leadership [6,8] and virtual leadership [19] in reference to nurse leaders; however, their definitions are inconsistent. For example, e-leadership has several different definitions; among other things, it has been understood as a process of social influence that takes place in the context of an organization where work is supported by information and communication technology (ICT) [20]. In contrast, virtual leadership has been defined as leading remotely working teams [21]. In addition to these terms, expressions such as physician leadership in eHealth have been used [6]. The existence of several inconsistently defined concepts and meanings relating to leadership in digital health services makes it difficult to hold dialogs about the phenomenon. A recent scoping review by Strudwick et al [22] concluded that it is essential to understand the informatics competencies of nurse leaders because nurse leaders play key roles in all issues relating to technology in health services.

What Is Known About Leadership in Digital Health Services?

Conceptualization of leadership and leadership-related issues is quite common in health care research. Previous concept analyses relating to health care leadership have focused on transformational leadership [24], staff nurse clinical leadership [25], nurse manager engagement [26], and nurse manager succession planning [27], among other things. As there has been limited research on leadership in digital health services [17,18], conceptualizing leadership in digital health services could provide important guidance for service development and future research. In this concept analysis, health care leadership will be considered to encompass both leading people and managing systems and structures [28]. The theory of transformational leadership, according to which leaders see change as an opportunity, has occasionally been linked to health care digitalization [17,29]. However, health care digitalization also seems to involve elements of management because implementing HITs requires decision making on various issues, including financial issues [30]. Health care organizations are among the most complex in society [31], and the increasing number of HITs makes them even more complex and challenging to manage for health care leaders [32-34].

Previous studies have mainly examined leadership in digital health services from the viewpoint of HIT implementation and adoption [7,13]. A recent scoping review by Laukka et al [13] found that roles adopted by health care leaders during HIT implementation include supporters, change managers, advocates, project managers, decision makers, facilitators, and champions. Another review by Ingebrigtsen et al [7] identified 7 leadership behaviors associated with successful outcomes in HIT adoption: communicating clearly about visions and goals, providing support, establishing a governance structure, establishing training, identifying and appointing champions, addressing work process change, and following up. These reviews synthesized leadership roles and behaviors important in HIT implementation and adoption. However, making the most of HIT also requires proper health care leadership in other processes [35]. For health care leaders, managing technology is also about the 3 Ps: people, processes, and (computer) programs [35]. The information age paradigm is transforming health care delivery and, in the process, may also shift leaders’ perspectives and shape their leadership responses [17].

Several studies have aimed to define the concept of e-leadership [36,37]; however, the definition has not been made in the context of health care, which is unique compared with other fields of businesses. According to Avolio and Kahai [36], “e-leadership takes place in a context where work is mediated by information technology.” Health care has lagged behind other areas of business in terms of the use of ICT [33,38,39], and efforts to implement HIT fail relatively frequently in health care settings [33,40]. This may be partly because of poor leadership in health care organizations [41,42].

To conclude, conceptualization of leadership in digital health services is needed to better understand how leadership can support health care digitalization and improve the likelihood of successful HIT implementation. For example, the integration of HIT is necessary for nurse leaders to lead effectively in the future [8]. Advancing digitalization and HIT implementation will enable the delivery of higher quality digital health services while also supporting health care professionals’ work related to HIT. In addition, a robust conceptualization will facilitate further research in this area and help reshape leadership models to establish digitalization as a core part of health care leaders’ core competency, thereby contributing to the provision of adequate education. Keijser et al [6] noted the importance of researching health care leadership in the context of digital health care and highlighted the importance of research in educating leaders.
Objectives
Precise conceptualization of leadership in digital health services is needed to support health care leaders working on digitalization on the frontline and at middle and senior management levels, to help create better digital health services, to facilitate continuously evolving leadership, and to advance research. To this end, the concept of leadership in digital health services was analyzed using the concept analysis model of Walker and Avant [23]. The use of a protocol based on this model was expected to increase the quality of the final concept analysis.

Methods

This Study

Aim
The protocol outlines a concept analysis procedure designed to clarify and define the concept of leadership in digital health services.

Design
The concept analysis model of Walker and Avant [23], which has become one of the most influential concept analysis models in health care [43], will be used. The strength of the model by Walker and Avant [23] is that it provides a structural guideline. Walker and Avant [23] define concept analysis as the process of defining a concept carefully by understanding and examining its basic elements and underlying attributes. The 8 steps of their concept analysis procedure are described in the following sections.

Step 1: Selecting a Concept
The concept analysis process starts with the selection of a concept to be analyzed [23]—in this case, leadership in digital health services. Analysis of this concept is needed to establish an up-to-date definition and framework of leadership for the era of health care digitalization.

Step 2: Defining the Aim of the Analysis
The next step is to define the aims or purpose of the study [23]. Our specific aims in this study are to clarify the concept of leadership in digital health services and develop a theoretical definition of leadership in digital health services. Conceptualization of the construct of leadership in the context of digital health services is needed to better understand the phenomenon of health care digitalization, to guide future research, and to construct a modern leadership framework for health services.

Step 3: Identifying All Uses of the Concept
The third step involves first identifying all previous uses of the concept when collecting material for analysis [23]. In this study, diverse sources will be used to identify different definitions of leadership in digital health services. These sources will then be subjected to critical analysis to identify different definitions, descriptions, and applications of leadership in digital health services. The reported ways of using and describing leadership in digital health services will finally be recorded for future reference.

Step 4: Determining the Defining Attributes of the Concept
After identifying the different uses of the concept under investigation, the uses will be read through to find the characteristics that appear repeatedly to define the key attributes of the studied concept (in this case, leadership in digital health services). This process will generate a cluster of attributes that are frequently associated with the concept [23].

Step 5: Constructing a Model Case
This step involves developing one or more model cases to represent a real-life example of the use of concept that includes all the critical attributes of the concept [23]. This will be done using data extracted during the earlier phases.

Step 6: Constructing Additional Cases
After identifying at least one model case, additional cases relating to the concept under investigation will be identified. This is necessary because it will not be possible to complete the concept analysis if there are overlaps between the identified attributes or contradictions between the defining attributes and the model case [23]. The purpose of this step is to determine which characteristics or attributes best fit with the concept under study and to identify the attributes that define the concept [43]. The additional cases should include examples that are (1) related, (2) borderline, (3) contrary, (4) invented, and (5) illegitimate [23]. Related cases closely resemble the model case but can be seen to lack at least some of the defining attributes when examined closely. Borderline cases display some of the defining attributes but lack several others. These 2 cases help to clarify the concept and to show what it is not. A contrary case is one that is clearly not an instance of the concept, whereas an invented case is used to illustrate the essential features of a concept. Finally, an illegitimate case illustrates improper use of the concept [43].

Step 7: Identifying Antecedents and Consequences of the Concept
Antecedents and consequences will be identified in the penultimate step. Walker and Avant [23] defined antecedents and consequences, respectively, as events or incidents that occur before or as a result of the occurrence of the concept.

Step 8: Defining Empirical Referents
The final step of the concept analysis will be to integrate the critical attributes with real-world empirical referents. According to Walker and Avant [23], empirical referents are measurable ways to demonstrate the occurrence of the concept.

Scoping Review
To identify all relevant literature on leadership in digital health services, a literature review will be conducted in accordance with the search protocol for scoping reviews by the Joanna Briggs Institute (JBI) [44]. Scoping reviews are useful for mapping the key concepts of a research topic and clarifying its working definitions and/or conceptual boundaries [45]. The search strategy used in a scoping review should be as comprehensive as possible [44]. This requirement aligns well with the principles of concept analysis, which call for the use...
of diverse sources to obtain varied definitions of the concept under investigation [43]. Unlike in a systematic review, quality assessment is not a necessary part of the scoping review process [44], and it is also not relevant in concept analysis [46,47]. Quality assessment is not needed in concept analysis because the data to be extracted relate to the definitions and attributes of leadership in digital health services, not the results of the study [46,47]. Therefore, all published uses of the concept under investigation are relevant, irrespective of the quality of the research in which they are used.

**Eligibility Criteria**

The Population, Concept, and Context (PCC) framework will be applied when defining eligibility criteria for the scoping review [44]. Initial inclusion and exclusion criteria relating to the PCC of studies considered for inclusion in the scoping review are presented in Textbox 1.

**Textbox 1.** Eligibility criteria based on the Population, Concept, and Context framework for publications included in the scoping review.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population: Studies on health care leaders regardless of their management position or health care field</td>
<td>Population: Studies on leaders working solely with information technology management</td>
</tr>
<tr>
<td>Concept: Health care or service leadership</td>
<td>Concept: Not related to health care or service leadership</td>
</tr>
<tr>
<td>Context: Digital health services</td>
<td>Context: Health services with no digitalization of any kind</td>
</tr>
</tbody>
</table>

Both peer-reviewed publications and papers from gray literature will be included in the review. The studied population will consist of health care leaders or managers regardless of their management position and health care field. Leaders working solely with information technology management will be excluded because they are not responsible for clinical health services and management. Publications eligible for inclusion in the review will be those that somehow define or clarify the concept of leadership in the context of digital health services.

**Search Strategy**

A 3-step search strategy [44] will be used to retrieve both published and unpublished studies. An initial limited search of MEDLINE was undertaken on October 19, 2020, as part of this study protocol, resulting in 883 papers (Table 1). Relevant papers were identified by analyzing their titles, abstracts, and index terms. MEDLINE was used in this preliminary search because its large database includes several papers relating to health care leadership; as such, the search was expected to provide a rough estimate of the number and availability of relevant papers. An information specialist was consulted when developing the initial search strategy and will be consulted about other search strategies as well. During the main concept analysis study, a search strategy using all the relevant identified keywords and index terms will be used for each information source to be searched. The reference lists of all included studies will also be screened to identify additional relevant studies.

The databases to be searched will include CINAHL, MEDLINE, Scopus, ProQuest, Web of Science, and the national Finnish database Medic. These databases collectively provide a comprehensive coverage of publications relating to health care leadership and digital health services. Searches for unpublished studies and gray literature will be conducted using Google Scholar, EBSCO Open Dissertations, and MedNar. Gray literature types eligible for inclusion include editorials, opinion papers, and dissertations. Papers published in English, Finnish, and Swedish will be considered for inclusion. Only papers published between 2010 and the present (2020) will be considered for inclusion because the rapid digitalization of health services over the past decade [48] makes older studies less relevant to the current situation. Keywords to be used will be related to eHealth, information technology, digitalization, health care, health services, and leadership. Keywords will be truncated, where appropriate. In addition, index terms or headings such as Medical Subject Headings will be used in MEDLINE and CINAHL.
Table 1. Search strategy applied in MEDLINE using Medical Subject Headings terms and search terms with abstract, title, and keyword limitations. The search was undertaken on October 19, 2020.

<table>
<thead>
<tr>
<th>Searches</th>
<th>Results, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>exp Telemedicine/</td>
<td>30,325</td>
</tr>
<tr>
<td>exp Leadership/</td>
<td>41,537</td>
</tr>
<tr>
<td>exp Telemedicine/ and exp Leadership/</td>
<td>85</td>
</tr>
<tr>
<td>(eHealth or e-health).tw</td>
<td>4649</td>
</tr>
<tr>
<td>exp Telemedicine/ or (eHealth or e-health).tw</td>
<td>33,067</td>
</tr>
<tr>
<td>(information technology or digital*).tw</td>
<td>150,808</td>
</tr>
<tr>
<td>(health* or medic* or nursing*).tw</td>
<td>4,352,122</td>
</tr>
<tr>
<td>(information technology or digital*).tw and (health* or medic* or nursing*).tw</td>
<td>36,072</td>
</tr>
<tr>
<td>exp Telemedicine/ or (eHealth or e-health).tw</td>
<td>1217</td>
</tr>
<tr>
<td>“leader*”.tw</td>
<td>66,516</td>
</tr>
<tr>
<td>exp Leadership/ or &quot;leader*”.tw</td>
<td>76,359</td>
</tr>
<tr>
<td>exp Leadership/ or &quot;leader*”.tw</td>
<td>97,028</td>
</tr>
<tr>
<td>Telemedicine/ or (eHealth or e-health).tw</td>
<td>1217</td>
</tr>
<tr>
<td>(information technology or digital*).tw and (health* or medic* or nursing*).tw</td>
<td>883</td>
</tr>
<tr>
<td>exp Leadership/ or “leader*”.tw</td>
<td>2861</td>
</tr>
<tr>
<td>limit Telemedicine/ or (eHealth or e-health).tw</td>
<td>883</td>
</tr>
<tr>
<td>(information technology or digital*).tw and (health* or medic* or nursing*).tw</td>
<td>2010-Current</td>
</tr>
</tbody>
</table>

*Text word terms are searched from the titles, abstracts, and keywords.

**Study Selection**

All citations identified by implementing the search strategy described earlier will be collated and uploaded into the Covidence systematic review systematic software package (v2422), which will also be used to remove duplicates. Titles and abstracts will then be screened by two team members independently using the inclusion or exclusion criteria. For papers without abstracts, the full text will be retrieved. After title and abstract screening, the potentially relevant studies will be retrieved in full. Two independent team members will assess these studies in detail and evaluate their suitability based on the inclusion criteria. Reasons for exclusion will be reported for studies that do not satisfy the inclusion criteria. Any disagreements at any stage of the study selection process will be resolved by discussion or by asking the opinion of a third team member. The results of the search will be reported in the final study and will be presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [49]. All search methods, strategies, and sources will be described or named in the final report and will be replicable.

**Data Extraction and Synthesis**

The extracted data will include definitions of leadership in digital health services; its key domains; the setting and population of the study described in the paper; and data needed for the 8-step concept analysis, such as attributes, antecedents, and consequences [23]. Two researchers will participate in data extraction.

**Ethical Considerations**

As concept analyses use only secondary publicly available data from primary research studies and gray literature, no research ethics approval will be needed.

**Validity and Rigor**

Several activities will be performed to enhance the study’s validity and rigor, including the following:

1. **Method:** The scoping review, which will identify all relevant literature on leadership in digital health services, will be conducted following the JBI guidelines [44].
2. **Search:** An information specialist with expertise in health sciences and management research will be consulted when developing the search strategy to increase credibility. In addition, several databases and gray literature sources will be included to ensure the richness of the data.
3. **Screening, data extraction, and synthesis:** Each of the previously mentioned phases will be conducted independently by 2 team members. Having 2 independent team members to select papers, extract data, and conduct synthesis will enhance reliability.
4. **All members of the research team will repeatedly evaluate the manuscript during meetings that will be held as the process progresses.**

**Results**

The search for the relevant studies was performed on November 31, 2020, resulting in 2861 studies after duplicates were removed. The screening of the studies will be completed by the end of January 2021. We expect to begin other phases of concept
Discussions

Principal Findings

In recent years, leadership in digital health services has been scrutinized in relation to issues including HIT adoption and implementation [7,13,50], informatics competence [51,52], and virtual teams [6,21]. Previous studies suggest that there is no consistent treatment of different elements of digitalization (eg, implementation, informatics competence) within leadership in health services and that current approaches to leadership in digital health services are therefore fragmentary and incomplete.

The literature indicates that all health care leaders, regardless of their management position, are involved in health care digitalization [9,13-15] and that nurse leaders play a particularly important role in the early use of HIT [15]. The roles of frontline nurse or physician leaders seem to be essential in supporting health care professionals in the use of HIT [13]. Nurses and physician leaders working in middle management also play an important role in implementing HIT [14], and senior nurses and physician managers seem to be responsible for making decisions about obtaining new HIT [30,53]. Collaborations between nurse leaders and chief information officers have also been scrutinized [50,54]. Overall, leadership in digital health services seems to require interprofessional and intersectoral collaboration involving working together with other health care leaders, chief information managers, health care professionals, research and educational centers, and HIT vendors [14,50,54,55].

Glaser [56] suggested that HIT implementation failures are often because of the actions and inactions of senior leadership. This may be because health care leaders might have insufficient informatics skills. For example, according to Sharpp et al [57], some nurse leaders are inexperienced users of ICT. Several studies have proposed that health care leaders have not received enough, or any, education on informatics [13,29,58]. HIT, thus, seems to be a black box for some health care leaders, and this issue should be examined more thoroughly [30].

Limitations

The preliminary search of MEDLINE conducted while developing this study protocol retrieved many potentially relevant papers. Therefore, the search strategy (especially for the largest databases) will involve only title and abstract searches to ensure that the review balances feasibility with comprehensiveness. Limiting the searches to titles and abstracts may cause some relevant studies to be excluded from the concept analysis. However, title limitation appears to be quite common in reviews focusing on health care digitalization [13,59]. The concept analysis model by Walker and Avant [23] provides the analyst 8 steps to guide their analysis. However, despite these 8 steps, the more detailed analysis has been left to the analyst to figure out individually [43].

Conclusions

There is a clear need to conceptualize leadership in digital health services because leadership in health services seems to be incoherent, providing no consistent perspective on the phenomenon. In addition, this study shows that the concept analysis model of Walker and Avant [23] is suitable for conceptualizing leadership in digital health services. Such a concept analysis could be beneficial in several ways. First, it could help guide research on and modelling of leadership within health care studies. Second, providing a clear definition of leadership in digital health services could guide health care leaders and managers in their work, facilitate interprofessional and multisectoral collaboration, and advance clinical practice, especially in relation to digitalization. Third, conceptualization could be used to guide the training of health care leaders to help them better meet current and future challenges relating to health care digitalization.

Our evaluation of the need to conceptualize leadership in digital health services made it clear that in addition to providing a basis for further research, defining and clarifying the concept of leadership in digital health services could facilitate the development of higher quality digital health services by actualizing the roles and responsibilities of leaders in digitalized health care. A clear definition may also help educational and health care organizations to provide better education and training for health care leaders in ICT, which would, in turn, support the digitalization of health care.

Acknowledgments

The authors would like to thank the information specialist Sirpa Grekula from the University of Oulu Library who helped them to develop a suitable search strategy for the study. This work was supported by the Strategic Research Council at the Academy of Finland under Grant 327145.

Conflicts of Interest

None declared.

References


http://www.researchprotocols.org/2021/2/e25495/


Abbreviations

HIT: health information technology
ICT: information and communication technology
JBI: Joanna Briggs Institute
PCC: Population, Concept, and Context

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Clinical and Epidemiological Characteristics of Postdischarge Patients With COVID-19 in Tehran, Iran: Protocol for a Prospective Cohort Study (Tele-COVID-19 Study)

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Abstract

Background: COVID-19 was declared a pandemic on March 11, 2020. Given that the severe shortage of hospital beds has led to early discharge and insufficient patient education on home care routines and isolation protocols, the close follow-up of patients and their immediate relatives is an integral part of transitioning from hospital care to home care for patients with COVID-19.

Objective: We designed the Tele-COVID-19 prospective cohort to follow-up with COVID-19 patients in Tehran, Iran, and improve health care delivery and the recording of postdischarge patients’ clinical profiles.

Methods: All adult patients who were admitted to the COVID-19 wards of teaching hospitals in Tehran, Iran were eligible to participate in this cohort study. At baseline, patients were recruited from 4 major hospitals from March 9, 2020 to May 20, 2020. Telephone follow-ups, which were led by volunteer medical students, were conducted on postdischarge days 1-3, 5, 7, 10, and 14. We collected data on a range of sociodemographic, epidemiological, and clinical characteristics by using a standard questionnaire.

Results: Of the 950 patients with confirmed COVID-19 who were approached, 823 (response rate: 86.6%) consented and were enrolled into the cohort. Of the 823 participants, 449 (54.5%) were male. The mean age of participants was 50.1 years (SD 12.6
The COVID-19 disease, which is caused by the SARS-CoV-2 virus, was declared a pandemic on March 11, 2020. Based on the existing evidence, the risk of infection appears to be relatively low for the general population. However, older people, immunocompromised people, and those with underlying health conditions, such as cardiovascular diseases, are at an elevated risk of morbidity and mortality. As of December 11, 2020, 71,088,688 patients with confirmed COVID-19 and 1,595,096 deaths have been reported across the globe. To date, effective treatment options for COVID-19 are unavailable. However, more than 2500 trials and studies are being conducted worldwide to develop and evaluate different therapeutic options for COVID-19. Implementing swift, community-centered preventive measures, providing timely diagnoses, treatments, contact tracing services, and methods for the successful isolation of patients at home, and reducing the household transmission of the virus among infected patients’ close contacts have been at the core of recommended strategies for combating the disease.

Despite the extensive worldwide efforts for controlling the pandemic, the constantly rising patient load and limited personal protective equipment supplies have overwhelmed health care systems across the globe. However, the toll of the COVID-19 pandemic has been heavier for low- and middle-income settings, wherein health care systems are already underfunded, understaffed, and overstretched. Iran is one of the countries that was hit the hardest by the COVID-19 outbreak. The first patient with confirmed COVID-19 in Iran was reported on February 19, 2020 in the city of Qom, which is 200 km away from Tehran, the capital city of Iran. As of December 11, 2020, 1,092,407 patients with confirmed COVID-19 and 51,727 deaths have been reported in the country. Iran’s initial response to the pandemic included physical distancing control policies that aimed to minimize close contact within communities, as well as individual-level restrictions (eg, quarantine and isolation) and community-level restrictions (eg, educational and recreational facility closures, nonessential business closures, and the cancellation of public/mass/crowded gatherings). Nevertheless, economic sanctions, inadequate financial and human resources, inefficient leadership, and limited hospital capacities for the rapidly growing number of patients with COVID-19 who require hospitalization have created real and considerable challenges for controlling the epidemic.

Conclusions: The Tele-COVID-19 cohort will provide patients with sufficient education on home care and isolation, and medical advice on care and the proper use of drugs. In addition, by preventing unnecessary hospital returns and providing information on household SARS-CoV-2 transmission as early as possible, this cohort will help with effective disease management in resource-limited settings.

**International Registered Report Identifier (IRRID):** DERR1-10.2196/23316

**KEYWORDS**
cohort studies; COVID-19; health care delivery; Iran; medical education; telemedicine

**Introduction**

The COVID-19 disease, which is caused by the SARS-CoV-2 virus, was declared a pandemic on March 11, 2020. Based on the existing evidence, the risk of infection appears to be relatively low for the general population. However, older people, immunocompromised people, and those with underlying health conditions, such as cardiovascular diseases, are at an elevated risk of morbidity and mortality. As of December 11, 2020, 71,088,688 patients with confirmed COVID-19 and 1,595,096 deaths have been reported across the globe. To date, effective treatment options for COVID-19 are unavailable. However, more than 2500 trials and studies are being conducted worldwide to develop and evaluate different therapeutic options for COVID-19. Implementing swift, community-centered preventive measures, providing timely diagnoses, treatments, contact tracing services, and methods for the successful isolation of patients at home, and reducing the household transmission of the virus among infected patients’ close contacts have been at the core of recommended strategies for combating the disease.

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because the recruitment of patients depends on the spread of COVID-19 in Tehran, there is no specific end date for recruitment at this point in time.

**Setting**

In total, 4 major teaching hospitals in Tehran (ie, Shohada Tajrish Hospital, Ayatollah Taleghani Hospital, Shahid Modarres Hospital, and Loghman Hakim Hospital) were included at baseline. Collectively, these hospitals have 1652 beds, 136 primary care clinics, more than 100 specialties, and over 3000 employees. Of these 4 hospitals, 3 are located in the northern districts of Tehran and 1 is located in the southern district (Figure 1).

**Figure 1.** Hospitals included in the first phase of recruitment for the Tele-COVID-19 cohort.

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**Eligibility Criteria**

Eligible participants were hospitalized adults (ie, aged >18 years) with COVID-19. Patients who tested positive for SARS-CoV-2 infection in polymerase chain reaction tests, and those who were treated and discharged from COVID-19 wards were recruited into the cohort. Participants were excluded if their contact information was wrong or missing. All patients who did not respond to follow-up phone calls or declined to provide consent were also excluded. Participants were briefed about this study’s aims and objectives via in-person discussions in the hospital and postdischarge phone calls. All participants provided verbal consent, and each patient received a unique national identification code to avoid potential biases that could arise from patients who went to several other health care facilities postdischarge.

**Data Collection**

At baseline, telephone follow-ups, which were led by volunteer medical students, were conducted on postdischarge days 1-3,
5, 7, 10, and 14, in accordance with a predetermined protocol and under the supervision of clinical professors. The calls were made to patients’ cell phones or landline phones from 10 AM to 4 PM. In the case of a nonresponse, calls were repeated 3 times at 2-hour intervals until the end of the calling time. Patients were excluded if they could not be reached by the end of the day. The first round of interviews was conducted by medical clerks. If a patient was assessed to have a concerning or critical condition, a follow-up phone call was made by a senior medical intern after consulting clinical professors for further assessment. Data were recorded on a secure and password-protected web-based platform. Each medical clerk signed a nondisclosure agreement before the enrollment period, to ensure that data remained secure and confidential. Medical clerks could only observe the data that they themselves collected; they could not observe the data that other team members collected. By the end of each patient’s 14-day follow-up period, all data were extracted from the web-based platform and stored on a password-protected external hard drive.

Data were collected by using a pilot-tested, comprehensive COVID-19 risk assessment questionnaire. The development of the questionnaire was informed by the Center for Disease Control and Prevention and the national guidelines of the Ministry of Health and Medical Education, and included the following areas: sociodemographic information (eg, age and sex), a history of potential exposure to SARS-CoV-2 (eg, a travel history to China or the city of Qom and a history of exposure to patients with COVID-19), signs and clinical symptoms (eg, fever, dry cough, dyspnea, nausea, and diarrhea), a medical history of underlying conditions (eg, a history of diabetes, cardiovascular disorders, chronic lung disease, chronic renal disease, and immunodeficiency), habitual history (eg, current smoker, former smoker, and nonsmoker), prescribed drugs at postdischarge (eg, hydroxychloroquine and lopinavir/ritonavir), a history of non-COVID-19–related medications (eg, nonsteroidal anti-inflammatory drugs and statin), and household information on close contacts (eg, high-risk household contacts and household transmissions).

Interview Process

Interviewers were enrolled if they were fourth-year to seventh-year medical students and registered in their respective medical schools at the time of interviews. There were 2 main groups of interviewers, as follows: (1) medical clerks (ie, those in their fourth and fifth years of training) and (2) medical interns (ie, those in their sixth and seventh years of training). Under the supervision of clinical professors, medical interns were mentored by faculty staff. Medical interns also helped with supervising the medical clerks. All interviewers completed a 40-hour crash course. The educational topics in the course were tailored toward COVID-19–related prevention, care, and treatment. The topics included methods for taking a complete history, methods for conducting complete physical examinations, essential practices for COVID-19, guidance on precautionary measures for providing home care and isolating patients and other household members, and the assessment of high-risk conditions (ie, interviewers were given a referral guide for each medical condition). Data collection procedures were pilot-tested with patients through role play to ensure that data were collected consistently. During the phone calls, patients and their household members were educated on home care procedures and isolation guidelines. All clinical signs and symptoms were closely examined and recorded. Treatment regimens and procedures were adjusted accordingly, and patients were instructed to stay at home or return to the emergency room if they or their household members exhibited critical symptoms.

Statistical Analysis

Data entries were double-checked and cleaned by using STATA version 15 (StataCorp LLC). For the purposes of this prospective cohort study, descriptive statistics, including relative frequencies for categorical variables and means and standard deviations for quantitative variables, were reported. However, for the purposes of future studies that derive data from our cohort, associations will be examined by using appropriate regression analyses.

Ethics

The study protocol was reviewed and approved by the ethics committee of the Shahid Beheshti University of Medical Sciences (Ethics approval reference number: IR.SBMU.RETECH.REC.1399.114).

Results

Of the 950 patients with confirmed COVID-19 who were approached at the initial phase of the Tele-COVID-19 study, 823 (86.6%) consented and were successfully enrolled in this study. Of the 823 participants, 261 (31.7%) were from Shohada Tajrish Hospital, 213 (25.9%) were from Loghman Hakim Hospital, 233 (28.3%) were from Ayatollah Taleghani Hospital, and 116 (14.1%) were from Shahid Modarres Hospital. The baseline characteristics of the enrolled patients are presented in Table 1.

Of the 823 participants, 449 (54.5%) were male. The mean age of participants was 50.1 years (SD 12.6 years). Overall, 65 (65/821, 7.9%) participants were health care workers, and 19 (19/821, 2.3%) participants reported that they travelled to known epicenters of COVID-19 within the previous 14 days of the interview. A total of 471 (471/818, 57.6%) reported that they were exposed to a patient with COVID-19 within the past 14 days of the interview. A total of 701 (701/818, 86.2%) patients visited a hospital due to suspicious signs and symptoms, and 59 (59/814, 7.2%) patients sought medical attention due to being exposed to people with probable COVID-19. Overall, 167 (167/811, 20.6%) were current/former smokers. Most patients did not have any underlying diseases (372/676, 55%), and only 25 (25/818, 3.1%) were immunodeficient. The mean length of hospitalization was 5.23 days (SD 4 days).

Detailed data on baseline clinical symptoms was available for 676 patients. Among the baseline clinical symptoms, the 3 most common symptoms were cough (466/676, 68.9%), respiratory distress (394/676, 58.3%), and fever (364/676, 53.8%). Only a small proportion of patients (59/676, 4.3%) had severe conditions (ie, admitted to an intensive care unit or had an oxygen saturation level of <90%). Most patients reported that they would be able to self-isolate at postdischarge (565/676, 83.5%).
Table 1. Baseline characteristics of patients with COVID-19 from the Tele-COVID-19 cohort in Tehran, Iran.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients from each hospital (N=823), n (%)</td>
<td></td>
</tr>
<tr>
<td>Loghman Hakim Hospital</td>
<td>213 (25.9)</td>
</tr>
<tr>
<td>Shohada Tajrish Hospital</td>
<td>261 (31.7)</td>
</tr>
<tr>
<td>Shahid Modarres Hospital</td>
<td>116 (14.1)</td>
</tr>
<tr>
<td>Ayatollah Taleghani Hospital</td>
<td>233 (28.3)</td>
</tr>
<tr>
<td>Sex (N=823), n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>449 (54.6)</td>
</tr>
<tr>
<td>Female</td>
<td>374 (45.4)</td>
</tr>
<tr>
<td>Age (years; N=823), mean (SD)</td>
<td>50.1 (12.6)</td>
</tr>
<tr>
<td>Health care worker (N=821), n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>65 (7.9)</td>
</tr>
<tr>
<td>No</td>
<td>756 (92.1)</td>
</tr>
<tr>
<td>Travel history in the previous 14 days (N=821), n (%)</td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Qom province</td>
<td>10 (1.2)</td>
</tr>
<tr>
<td>Gilan province</td>
<td>8 (0.9)</td>
</tr>
<tr>
<td>No travel history</td>
<td>802 (97.6)</td>
</tr>
<tr>
<td>Exposure to patients with confirmed COVID-19 in the previous 14 days (N=818), n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>176 (21.5)</td>
</tr>
<tr>
<td>No</td>
<td>642 (78.5)</td>
</tr>
<tr>
<td>Reason for hospital visit (N=814), n (%)</td>
<td></td>
</tr>
<tr>
<td>Suspicious clinical signs and symptoms</td>
<td>701 (86.2)</td>
</tr>
<tr>
<td>Exposure to a probable COVID-19 patient</td>
<td>59 (7.2)</td>
</tr>
<tr>
<td>Other</td>
<td>54 (6.6)</td>
</tr>
<tr>
<td>Smoking history (N=811), n (%)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>77 (9.5)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>90 (11.1)</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>644 (79.4)</td>
</tr>
<tr>
<td>Chronic respiratory conditions (N=818), n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>81 (9.9)</td>
</tr>
<tr>
<td>No</td>
<td>737 (90.1)</td>
</tr>
<tr>
<td>Diabetes mellitus (N=820), n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>159 (19.4)</td>
</tr>
<tr>
<td>No</td>
<td>661 (80.6)</td>
</tr>
<tr>
<td>Cardiovascular conditions (N=817), n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>181 (22.2)</td>
</tr>
<tr>
<td>No</td>
<td>636 (77.8)</td>
</tr>
<tr>
<td>Chronic renal conditions (N=821), n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>57 (6.9)</td>
</tr>
<tr>
<td>No</td>
<td>764 (93.1)</td>
</tr>
</tbody>
</table>
## Characteristics

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic liver conditions (N=821), n (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23 (2.8)</td>
</tr>
<tr>
<td>No</td>
<td>798 (97.2)</td>
</tr>
<tr>
<td>Immunodeficiency (N=818), n (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Yes</td>
<td>25 (3.1)</td>
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<tr>
<td>No</td>
<td>793 (96.9)</td>
</tr>
<tr>
<td>Underlying neurological conditions&lt;sup&gt;c&lt;/sup&gt; (N=819), n (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>52 (6.5)</td>
</tr>
<tr>
<td>No</td>
<td>767 (93.5)</td>
</tr>
<tr>
<td>Number of hospitalization days, mean (SD)</td>
<td>5.32 (4)</td>
</tr>
<tr>
<td>Clinical signs and symptoms (N=676), n (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>364 (53.8)</td>
</tr>
<tr>
<td>Chills</td>
<td>327 (48.4)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>225 (33.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>306 (45.3)</td>
</tr>
<tr>
<td>Cough</td>
<td>466 (68.9)</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>394 (58.3)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>270 (39.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>239 (35.4)</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>289 (42.8)</td>
</tr>
<tr>
<td>Loss of weight</td>
<td>69 (10.2)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>144 (21.3)</td>
</tr>
<tr>
<td>Anosmia</td>
<td>127 (18.8)</td>
</tr>
<tr>
<td>Ageusia</td>
<td>134 (19.8)</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>117 (17.9)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>171 (17.3)</td>
</tr>
<tr>
<td>Consciousness alterations</td>
<td>95 (14.1)</td>
</tr>
</tbody>
</table>

### COVID-19 severity<sup>d</sup> (N=676), n (%)<sup>a</sup>

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate</td>
<td>647 (95.7%)</td>
</tr>
<tr>
<td>Severe</td>
<td>29 (4.3%)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Percentages are rounded to 1 decimal point.

<sup>b</sup>Chronic respiratory conditions include asthma, emphysema, and chronic obstructive pulmonary disease.

<sup>c</sup>Underlying medical conditions include chronic neurological diseases and neurodevelopmental/intellectual disability.

<sup>d</sup>Severe cases included people who were admitted to the intensive care unit or had an oxygen saturation level of <90%.

During the initial data collection phase, more than 5000 phone calls were made. Overall, 577 reports were recorded in the daily critical case report sheets. Patients with critical conditions were directly followed by medical interns and clinical professors for more specific medical care. Patients with serious conditions (n=69) were referred to the emergency department, in accordance with hospital staff recommendations. Of these 69 patients, 40 (58%) were rehospitalized. Patients with minor conditions who primarily intended to revisit a hospital were successfully managed over the phone, leading to the prevention of unnecessary hospital visits (296/823, 36%). A total of 60 (60/823, 7.3%) patients who reported that they were experiencing adverse reactions to medications were managed through phone calls.

### Discussion

#### Principal Findings

The Tele-COVID-19 cohort provided a platform for effectively following up with patients with COVID-19 after hospitalization. Our prospective cohort study presents a cost-effective way of
managing postdischarge patients with COVID-19 and supporting them and their family members on their path to full recovery. The Tele-COVID-19 cohort was designed and run by a group of volunteer medical students, who successfully followed up with 823 postdischarge patients with COVID-19 during the baseline wave of this study. Given the burden of COVID-19 on health care systems in resource-limited settings such as Iran, telephone-based follow-up studies that involve medical students may not only enhance patient care, but also enhance medical education for medical students, who are often left out of the COVID-19 response due to concerns about limited personal protective equipment resources and students’ safety [15]. Early, postdischarge telephone follow-up calls have previously been shown to improve patients’ health outcomes and reduce their chances of readmission or critical condition development in the first month after discharge [16-19].

Limitations
We acknowledge that our study has several limitations that are common among studies of a similar nature. First, our nonrandom sample of participants from major hospitals in Tehran may not be generalizable to patients with COVID-19 in other parts of Tehran or Iran. However, it is likely that the characteristics of the participants who were recruited into our cohort are not considerably different from those of patients from other Tehran hospitals that were not included in our study. Second, participants’ self-reported responses with regard to potential risk factors or underlying comorbidities are prone to social desirability and reporting biases. Third, we did not collect any data on the mental health profiles of patients. This could be considered for future waves of data collection. Fourth, most patients in our cohort (647/676, 95.7%) exhibited mild or moderate COVID-19 symptoms. Furthermore, these patients had no adverse underlying conditions. Therefore, these patients do not provide a complete clinical picture of severe COVID-19 in Tehran hospitals.

Conclusions
The Tele-COVID-19 cohort is a unique, student-led cohort that could provide an effective platform for improving our evolving understanding of COVID-19 care and treatment in Iran. Such cohort studies assist the medical community by reducing the number of medical complications among people who are recovering from COVID-19, improving our understanding of the clinical course of the disease, identifying potential drug interactions and the adverse effects of pharmacotherapies, reducing the household transmission and secondary attack rates of SARS-CoV-2, referring discharged patients with critical conditions to the emergency department in a timely manner, reducing patients’ anxiety, and preventing unnecessary hospital visits. Moreover, cohorts like the Tele-COVID-19 cohort provide a cost-effective and rapidly implementable platform for improving our understanding of COVID-19 in resource-limited settings.

Acknowledgments
We are grateful to all participants and their families who spent their valuable time participating in this study, despite the difficult times that they were going through. We are also thankful to the tireless efforts of the academic staff at the Shahid Beheshti University of Medical Sciences and the volunteer medical students who devoted their time to this study. MK, a member of the Pierre Elliot Trudeau Foundations COVID-19 impact committee, is supported by the Pierre Elliott Trudeau Foundation Doctoral Scholarship. MS is supported by a Canadian Institute of Health Research postdoctoral award.

Authors’ Contributions
All authors contributed to the development of the cohort. LJK and MV prepared the first draft of the manuscript under the supervision of MK. All authors reviewed, revised, and approved the final manuscript draft.

Conflicts of Interest
None declared.

References


Protocol

Improving Assessment, Diagnosis, and Management of Urinary Incontinence and Lower Urinary Tract Symptoms on Acute and Rehabilitation Wards That Admit Adult Patients: Protocol for a Before-and-After Implementation Study

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4Centre of Research Excellence in Stroke Rehabilitation and Brain Recovery, Newcastle and Melbourne, Australia
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7John Hunter Hospital, Hunter New England Local Health District, Newcastle, Australia
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9Armidale Hospital, Hunter New England Local Health District, Armidale, Australia
10Tamworth Hospital, Hunter New England Local Health District, Tamworth, Australia
11Calvary Mater Newcastle, Newcatle, Australia
12Port Macquarie Hospital, Mid North Coast Local Health District, Port Macquarie, Australia
13Coffs Harbour Hospital, Mid North Coast Local Health District, Coffs Harbour, Australia
14Sydney Local Health District, Sydney, Australia
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16Continence Service, Hunter New England Local Health District, Newcastle, Australia
17Stroke Foundation, Melbourne, Australia
18Stroke Theme, Florey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne, Australia
19Health Research and Translation, Hunter New England Local Health District, Newcastle, Australia
20Public Health Program, Hunter Medical Research Institute, Newcastle, Australia
21Clinical Research Design & Statistics, Hunter Medical Research Institute, Newcastle, Australia
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24see Acknowledgments

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Abstract

Background: Urinary incontinence (UI) and lower urinary tract symptoms (LUTS) are commonly experienced by adult patients in hospitals (inpatients). Although peak bodies recommend that health services have systems for optimal UI and LUTS care, they are often not delivered. For example, results from the 2017 Australian National Stroke Audit Acute Services indicated that of the one-third of acute stroke inpatients with UI, only 18% received a management plan. In the 2018 Australian National Stroke Audit Rehabilitation Services, half of the 41% of patients with UI received a management plan. There is little reporting of effective inpatient interventions to systematically deliver optimal UI/LUTS care.

Objective: This study aims to determine whether our UI/LUTS practice-change package is feasible and effective for delivering optimal UI/LUTS care in an inpatient setting. The package includes our intervention that has been synthesized from the best-available evidence on UI/LUTS care and a theoretically informed implementation strategy targeting identified barriers and enablers. The package is targeted at clinicians working in the participating wards.

Methods: This is a pragmatic, real-world, before- and after-implementation study conducted at 12 hospitals (15 wards: 7/15, 47% metropolitan, 8/15, 53% regional) in Australia. Data will be collected at 3 time points: before implementation (T0), immediately after the 6-month implementation period (T1), and again after a 6-month maintenance period (T2). We will undertake medical record audits to determine any change in the proportion of inpatients receiving optimal UI/LUTS care, including assessment, diagnosis, and management plans. Potential economic implications (cost and consequences) for hospitals implementing our intervention will be determined.

Results: This study was approved by the Hunter New England Human Research Ethics Committee (HNEHREC Reference No. 18/10/17/4.02). Preimplementation data collection (T0) was completed in March 2020. As of November 2020, 87% (13/15) wards have completed implementation and are undertaking postimplementation data collection (T1).

Conclusions: Our practice-change package is designed to reduce the current inpatient UI/LUTS evidence-based practice gap, such as those identified through national stroke audits. This study has been designed to provide clinicians, managers, and policy makers with the evidence needed to assess the potential benefit of further wide-scale implementation of our practice-change package.

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KEYWORDS
urinary incontinence; lower urinary tract symptoms; inpatient; practice-gap; practice improvement; protocol

Introduction

Background

Urinary incontinence (UI) and lower urinary tract symptoms (LUTS) are commonly experienced by adults admitted to hospitals, also referred to as inpatients, and contribute to the complexity and cost of providing care to these individuals. UI types include functional, neurogenic, stress, overflow, continuous, urgency, and mixed UI [1,2]. LUTS include acute and chronic urinary retention, frequency, urgency, and nocturia [1,2]. Surprisingly, data on the prevalence of UI and LUTS in adult inpatients are limited. However, these conditions have been reported to range from 10% to 45% of patients receiving acute and subacute care in hospitals [3-5]. The often-taboo subject of UI is significantly associated with poorer patient outcomes, including urinary tract or urinary catheter–associated infections [6,7], incontinence-associated pressure injury [8], falls [9], and pain associated with these conditions [6,7]. People with UI are twice as likely to experience depression and are more often socially isolated [6,7]. UI is associated with increased carer stress, and is a main reason for carers feeling unable to continue in the carer role, leading to residential care admissions [11]. Although UI and LUTS are often complex and not always curable, with appropriate clinical care, symptoms can be managed and complications can be avoided.

International and Australian clinical practice guidelines provide recommendations for optimal care for UI and LUTS, based on the current, albeit limited research evidence [1,12-16]. Stroke is an example where UI and LUTS care has been included in condition-specific guideline recommendations [17-19]. Australian stroke guideline recommendations for optimal care are that all people poststroke are screened for continence issues and that those with symptoms receive an assessment, diagnosis, and a tailored inpatient and postdischarge management plan [17]. In the 2017 National Stroke Audit Acute Services, of the one-third of inpatients with UI, only 18% received a management plan [20]. In the 2018 National Stroke Audit Rehabilitation Services, of the 41% of inpatients who had UI, 52% had a documented management plan [21]. These results indicate an evidence-practice gap in current inpatient UI/LUTS care.

Although peak bodies recommend that health services have systems for optimal UI and LUTS care [1,15,17], there is little reporting of effective inpatient interventions to systematically deliver this care, as demonstrated in stroke care. In a recent Cochrane review, it was identified that there was limited evidence for the effectiveness of UI interventions poststroke.
The review included 20 trials (with 1338 participants, reporting 21 comparisons), with the authors reporting that the risk of bias was impossible to judge for many of the included studies because of poor reporting. The authors call for more robust multicenter trials.

As part of our formative quality improvement research [22], in 2009-2010, we translated high-level UI and LUTS guideline recommendations into an intervention that presents clear, concise, and explicit optimal inpatient care in a user-friendly format [23]. We collaborated with health service clinicians and managers from 3 rehabilitation services in the Hunter Region, Australia, to synthesize the best-available evidence into our Structured urinary Continence Assessment and Management Plan (SCAMP) intervention that was specifically designed for inpatients poststroke in metropolitan rehabilitation units [22]. Our SCAMP intervention consists of (1) a 4-page clinical decision support tool guiding comprehensive UI and LUTS assessment, diagnosis, and management; (2) the associated clinical practice guideline; and (3) supporting web-based education modules [22]. Stroke clinicians using the SCAMP intervention identified that it has the potential to be applicable across a range of hospitals in different health districts, for inpatients with a range of diagnoses including stroke, and across the phases of inpatient care.

**Aim**

The aim of this study is to determine if the implementation of our SCAMP intervention is feasible and effective across this range of clinical scenarios.

**Research Questions**

**Primary**

Does the implementation of our SCAMP intervention increase the proportion of inpatients with UI/ LUTS who have an individually tailored UI/ LUTS management plan?

**Secondary**

1. Does the implementation of our SCAMP intervention increase the proportion of:
   - Inpatients with UI/LUTS who have an assessment and diagnosis of types of UI/LUTS?
   - Inpatients with UI/LUTS and their caregivers who are involved in the development of the management plan?
   - Clinicians who rate their knowledge, skills, and confidence in identifying the types of UI/LUTS and assessing, diagnosing, and managing UI/LUTS as good or very good?

2. Does the implementation of our SCAMP intervention reduce in-hospital complication rates associated with UI/LUTS or urinary catheterization?

3. Are any improvements in the above outcomes maintained at 12 months after implementation begins?

4. What are the potential economic implications (cost and consequences) for hospitals implementing our SCAMP intervention?

**Methods**

**Design**

This will be a pragmatic, real-world, before- and after-implementation study conducted at 12 hospitals. Data will be collected at 3 time points: before implementation (T₀), immediately after the 6-month implementation period (T₁), and again after a 6-month maintenance period (T₂; Figure 1). Data will be collected from medical record audits and clinician questionnaires. An economic evaluation from the perspective of hospitals will be conducted. We will report our primary findings according to the Standards for Reporting Implementation Studies (StaRI) [24,25].

**Target Sites**

Eleven hospitals in New South Wales (NSW) and 1 in Queensland, Australia, participated in our study. The hospitals are located in 4 health service districts. The hospitals were a convenience sample. Ten of the hospitals are located in 2 Local Health Districts that form part of the NSW Regional Health Partners, a Centre for Innovation in Regional Health (accredited by the National Health and Medical Research Council). Lead clinicians from the other 2 hospitals heard about our SCAMP intervention at conference presentations and approached the lead author about adopting the intervention.

Fifteen wards where patients after stroke are admitted are participating (Table 1). In Australia, people after stroke are cared for on wards that admit people with a range of conditions.
This care may be provided in a stroke unit embedded in the ward or as part of the general ward population. This study was instigated by stroke clinicians who identified UI/LUTS inpatient care needed to be improved on their ward and that they were willing to commit resources toward improving optimal UI and LUTS care by implementing the SCAMP intervention. The characteristics of each ward are outlined in Table 1. A total of 47% (7/15) of the wards are in 4 hospitals in 2 major cities, and the other 53% (8/15) wards are in 8 hospitals in inner regional locations [26]. The wards included 43% (7/15) rehabilitation wards, 27% (4/15) acute medical wards with an embedded stroke unit, 13% (2/15) wards with both acute and rehabilitation inpatients, 7% (1/15) rehabilitation ward with an embedded stroke unit, and 7% (1/15) medical ward. Before commencing the study, the investigators from each ward nominated the target adult inpatient populations from their ward to be included in the study of acute stroke, acute medicine, and/or rehabilitation for any condition, including stroke (Table 1). Clinician representatives from each site have been project team members from the outset (including authors KB, JAD, JS, FM, AS, JB, SO, AB, and SL).

Table 1. Characteristics of the participating wards.

<table>
<thead>
<tr>
<th>Ward</th>
<th>Ward description</th>
<th>Hospital type and remoteness classification [26]</th>
<th>Previous use of SCAMP(^a) intervention</th>
<th>Patient populations included</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>20-bedded rehab.</td>
<td>Principal referral or major city</td>
<td>Yes</td>
<td>Rehabilitation</td>
</tr>
<tr>
<td>2.</td>
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<td>Principal referral or major city</td>
<td>No</td>
<td>Rehabilitation</td>
</tr>
<tr>
<td>3.</td>
<td>30-bedded rehab.</td>
<td>Principal referral or major city</td>
<td>Yes</td>
<td>Acute medicine, Acute stroke, Rehabilitation</td>
</tr>
<tr>
<td></td>
<td>22 rehab. or hospital overflow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 neurological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>12-bedded ward:</td>
<td>Public acute group A or major city</td>
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<td>Acute medicine, Acute stroke</td>
</tr>
<tr>
<td></td>
<td>8 general medicine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 acute stroke units</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>30-bedded ward:</td>
<td>Public acute group B or major city</td>
<td>Yes</td>
<td>Acute medicine, Stroke: acute and rehabilitation</td>
</tr>
<tr>
<td></td>
<td>26 general medicine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 comprehensive stroke units</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>32-bedded ward:</td>
<td>Public acute group B or inner regional</td>
<td>Yes</td>
<td>Acute stroke, Rehabilitation</td>
</tr>
<tr>
<td></td>
<td>mixed medical and rehabilitation ward</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>32-bedded rehab.</td>
<td>Public acute group B or major city</td>
<td>No</td>
<td>Rehabilitation</td>
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<tr>
<td>8.</td>
<td>28-bedded general med.</td>
<td>Public acute group B or major city</td>
<td>No</td>
<td>Acute medicine, Acute stroke</td>
</tr>
<tr>
<td>9.</td>
<td>22-bedded rehab.</td>
<td>Public acute group A or inner regional</td>
<td>No</td>
<td>Rehabilitation</td>
</tr>
<tr>
<td>10.</td>
<td>28-bedded ward:</td>
<td>Public acute group A or inner regional</td>
<td>Yes</td>
<td>Acute stroke</td>
</tr>
<tr>
<td></td>
<td>24 general medical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 acute stroke unit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>16-bedded rehab.</td>
<td>Rehabilitation or inner regional</td>
<td>No</td>
<td>Rehabilitation</td>
</tr>
<tr>
<td>12.</td>
<td>28-bedded ward:</td>
<td>Public acute group A or inner regional</td>
<td>No</td>
<td>Acute stroke</td>
</tr>
<tr>
<td></td>
<td>4 acute stroke units</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 medical assessment units</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>16 respiratory or cardiac units</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13.</td>
<td>24-bedded ward:</td>
<td>Public acute group A or inner regional</td>
<td>No</td>
<td>Stroke: acute and rehabilitation</td>
</tr>
<tr>
<td></td>
<td>20 general rehabilitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 comprehensive stroke units</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.</td>
<td>18-bedded hospital:</td>
<td>Public acute group C or inner regional</td>
<td>No</td>
<td>Rehabilitation</td>
</tr>
<tr>
<td></td>
<td>8 rehabilitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 general medical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15.</td>
<td>16-bedded rehab.</td>
<td>Public acute group A or inner regional</td>
<td>No</td>
<td>Rehabilitation</td>
</tr>
</tbody>
</table>

\(^a\)SCAMP: Structured urinary Continence Assessment and Management Plan.
Target Population

The population targeted by our practice-change package is clinicians (full time, part time, and casual) employed in each participating ward (including nurses, Nurse Unit managers, physiotherapists, occupational therapists, speech pathologists, social workers, and doctors). Participating clinicians are general medical, rehabilitation, or neuroscience clinicians who are not identified as continence or urology specialists. There are no exclusion criteria, as the study is a service improvement initiative, clinicians will not be consented to receive our practice-change package. The unit of analysis is hospital performance, based on patient-level data.

Practice-Change Package (Study Intervention)

Our practice-change package is designed to support clinicians and health services to deliver guideline-recommended UI and LUTS care. It consists of our SCAMP intervention that we will implement using evidence-based implementation strategies.

Intervention

In 2018, we reviewed all 3 components of our SCAMP intervention with experts from stroke, continence, rehabilitation, and urology to ensure that they met the current best-evidence UI and LUTS care for the majority of adult inpatient populations. Our SCAMP intervention consists of the following:

- The 4-page SCAMP decision support tool, which has been approved by the Hunter New England Local Health District Forms Committee
- The associated Clinical Practice Guideline that includes UI Management Flowcharts modified from the International Continence Society flowcharts
- Eight web-based education modules and a local module on how to use the SCAMP decision support tool (a PowerPoint presentation with a voice-over). The web-based modules cover information on normal bladder function, why continence is an issue after stroke, and 6 of the common inpatient UI and LUTS types and are hosted on the Stroke Foundation website [27]

Implementation Strategies

To enhance the success of our SCAMP intervention, we will use evidence-based theoretical approaches for implementation [28,29]. As there is no one all-encompassing theory that guides implementation of a complex multicomponent intervention, we have chosen to use complementary approaches that align best with the various components of the study, including the project design, assessment of the barriers and enablers, systematic planning and development of implementation and sustainability processes, and the evaluation of the project [29]. The Knowledge to Action framework is a process framework that guides implementation [23]. The Theoretical Domains Framework is the determinant framework that will help us identify the constructs that may influence implementation (barriers and facilitators) [30,31]. The evaluation plan is informed by the RE-AIM (reach, effectiveness, adoption, implementation, maintenance) framework [32,33].

Implementation strategies were selected to overcome barriers identified by project team members with experience in implementation science and known barriers to clinicians implementing guideline recommendations identified in the literature [34,35]. Textbox 1 outlines the planned implementation strategies to support the practice change and how these strategies align with the Expert Recommendations for Implementing Change [36].

To identify ward-specific barriers, local teams will use the Barrier Identification and Mitigation tool [37]. Local teams will observe and ask clinicians about the SCAMP decision support tool and guideline and walk through the process to simulate real ward circumstances. From the data they collect during the identification phase, each team will summarize and prioritize barriers and then develop a local action plan. The practice-change package will be adapted by each site to suit their local context.
Textbox 1. Summary of planned implementation strategies.

- Build a coalition. A coalition has been built that includes 15 wards across 12 hospitals, peak government and nongovernment bodies, and multiple universities.
- Work with educational institutions. Coalition members include institutions that provide tertiary and/or professional development education to the target groups.
- Develop academic partnerships and use data experts. Coalition members include academics from multiple institutions with expertise in implementation science, statistics, health economics, and data management.
- Centralize technical assistance. Sites will be supported by a centralized research team who will provide the evidence-based intervention (Structured urinary Continence Assessment and Management Plan; SCAMP); develop implementation resources in consultation with the team (including education materials and Implementation Training Workshops for site leaders); and evaluation resources (data collection tools, data storage, data analysis, and reporting).
- Access new funding. Sites will be supported to conduct the audits with small grants secured by the research team.
- Identify and prepare champions. Each site will have a local project lead and site champions who will drive the project locally. Leads will be senior clinicians, managers, or educators who have influence over local practice.
- Recruit, designate, and train for leadership. Site leaders will attend 2 training workshops that will include an overview what implementation research is and strategies for implementing evidence-based practice, overcoming barriers, generating sponsorship, communication, and using mixed methods for evaluation.
- Create a learning collaborative. A learning collaborative will be developed where sites learn from and share with each other to improve implementation.
- Develop resource-sharing agreements. Sites will share any implementation resources they develop with other members of the collaborative. This will be facilitated by a shared cloud–based repository.
- Organize clinician implementation team meetings and provide ongoing consultations. Project team members from each site will meet at 2 implementation workshops plus monthly teleconferences for education, consultation, and collaboration.
- Identify barriers and facilitators. Local sites will use the Behaviour Identification and Mitigation tool [37] to develop a local implementation plan.
- Tailor strategies and promote adaptability to meet local needs. Local implementation plans will tailor the implementation strategy and adapt the intervention to suit local needs.
- Distribute educational materials. Local sites will facilitate staff undertaking the education modules that inform the SCAMP decision support tool.
- Conduct educational meetings. Sites will conduct local education meetings to educate staff.
- Change record systems. The SCAMP decision support tool will be implemented at all sites. Paper or electronic versions will be used based on local needs.
- Audit and provide feedback. Before-implementation audit data will be fed back to each site.
- Remind clinicians. A poster display of different continence types and possible management solutions will be made available to all sites.

Outcomes

Our primary outcome is the change ($T_1-T_0$) in the proportion of inpatients who have an individually tailored UI/LUTS management plan. This will be determined via a medical record audit.

Our secondary research outcomes are:

1. The change ($T_1-T_0$) in proportion of:
   a. Inpatients with UI/LUTS who have an assessment and diagnosis of types of UI/LUTS, determined via a medical record audit
   b. Inpatients with UI/LUTS and their carers who are involved in the development of the management plan, determined via a medical record audit
   c. Clinicians who rate their knowledge, skills, and confidence in identifying the types of UI/LUTS and in assessing, diagnosing, and managing UI/LUTS as good or very good, determined via a clinician questionnaire
   2. The change in in-hospital complication rates associated with UI/LUTS or urinary catheterization, determined via medical record audit ($T_1-T_0$)
   3. The change in the aforementioned outcome measures at 12 months after implementation begins ($T_2-T_0$, $T_2-T_1$)
   4. The potential economic implications for hospitals implementing our SCAMP intervention, determined using a cost-consequences analysis method

Data Collection Procedures

Data will be collected at 3 time points (Figure 1): before implementation ($T_0$), after a 6-month implementation period ($T_1$), and after a 6-month maintenance period ($T_2$). Before-implementation data will be used to tailor the intervention to each ward.

Medical Record Audit

Records of adults aged $\geq 18$ years with the ward-nominated conditions who are discharged from each participating ward will be included. To reduce selection bias, we will include
consecutive records of patients discharged from each ward for each month of the 3-month data collection period.

**Screening**

Records will be screened to determine if the patient had UI/LUTS, including an indwelling urinary catheter, during their stay on the participating ward. During screening, we will extract data, including demographic, characteristic information, continence status, and how the UI/LUTS status was determined. Patients will be excluded from the full medical record audit if they are determined to have had no UI/LUTS during admission to the participating ward—deemed palliative/at the end of life and died during their admission or were discharged with this care type. People deemed to be at the end of life will be excluded as their management goals for UI/LUTS are usually different from those receiving acute and rehabilitative treatment. Patients who have an unexpected death, for example, cardiac arrest, during admission will be included.

**Audits**

Medical record audits of patients with UI/LUTS, including those with an indwelling urinary catheter, will be performed for 15 records for each month or until all patients discharged during that month have been screened, whichever occurs first. The medical record audit tool is based on questions in the Australian Stroke Foundation National Audits [20,38,39] and the content of the SCAMP decision support tool. The medical record audit tool was designed by KB and DM, piloted and refined by the project team members, including KB, J Dunne, JS, FM, AS, JB, SO, AB, KP, and SL, who will be performing the audits. The authors then examined the tool for face validity. Medical record audits will be conducted at each hospital by the project team members from that hospital and other local clinicians with legitimate access to the medical records, as per local health service requirements for patient privacy and confidentiality. A web-based medical record audit data dictionary is available. Information regarding assessment, diagnosis, management, complications, level of disability, and the presence of comorbidities relevant to UI/LUTS will be extracted. Study data will be extracted into and managed using the REDCap electronic data capture tool [40], hosted on a secure server at the Hunter Medical Research Institute, NSW.

**Clinician Questionnaire**

Our web-based clinician questionnaire is aligned with 13 of the 14 domains of the Theoretical Domains Framework [31] of behavior change. The optimism domain was not included as we perceived an overlap with the emotions, beliefs about capability, and goals domain questions. Selecting domains to include in a questionnaire is in keeping with other studies that have used the Theoretical Domains Framework [31,41].

The target population for our intervention will be approached via email or in person by their site project team members and invited to complete a deidentified web-based questionnaire. Local site project team members will not have access to individual participant results. Demographic data will include age range, profession, and years of clinical experience. The clinician questionnaire was designed by authors KB, JD, and DM.

**Process Evaluation**

Measures will be collected to assess the process and fidelity of the implementation of the intervention. Spot check audits will be conducted by site members of the research team and site champions to identify any local issues with completing the SCAMP decision support tool. This information will inform local strategies to address the identified issues. We will also record the attendance for ward education sessions and the project team implementation workshops, the monthly project team meetings, the number and availability of identified champions throughout, the number and types of resources generated and reminder activities conducted, the number of audit and feedback sessions conducted, and any local changes made to the SCAMP intervention [42].

**Economic Evaluation**

As there are multiple potential benefits and the cost impacts are unclear from the perspective of the hospitals, we will undertake an exploratory assessment of resource use and costs and present these as a cost-consequences analysis [43]. We will obtain data on the costs of implementing the package (including staff training) and the direct health costs attributable to eligible patients across each study time period for the management of UI/LUTS, and report any potential cost offsets related to the practice-change package. Costs will be valued based on the reference year 2019. Data sources will include screening log and patient-level data from the medical record audits, hospital finance department data, research literature, expert opinion, and project management or administrative data. Costs and outcomes (ie, proportion of inpatients with an individually tailored UI/LUTS management plan and complication rates associated with UI/LUTS or urinary catheterization) will be presented to provide context for the changes in costs relative to the benefits to aid in the future translational potential of this package. All individual health and nonhealth effects of the intervention, including various cost items, will be reported as summary measures, for example, point estimates with a measure of variability (Data Analysis section).

**Sample Size and Power Calculations**

For the primary outcome, 15 consecutive medical record audits per site per month (ie, a pooled sample of 675 audits anticipated per data collection period) will provide >90% power to detect a 10% absolute increase (from before intervention) in the proportion of incontinent patients with a continence management plan (type 1 error rate of 5%). This calculation conservatively assumes that 20% of patients in acute and 50% of rehabilitation sites have a plan before intervention (based on the Australian Stroke Foundation National Audit results for included sites [20,39]).

**Data Analysis**

The before-intervention group, after-intervention group, and maintenance period group results will be presented with descriptive statistics, including site, clinician, and medical record data for characteristics and demographics. No individual will be identifiable. All results will be presented as aggregated...
summary measures, with their variance depending on the distribution of the data (eg, mean and standard deviation, medians, and interquartile range). Groups will be compared with respect to change, from baseline ($T_0$) to immediately postintervention period ($T_1$) and from baseline to maintenance period ($T_2$) using mixed effects logistic regression models, with a random intercept for site, and fixed effect for period. Results are presented as odds ratios with 95% CI and P values.

**Study Discontinuation**

There are no criteria for study discontinuation as it is not anticipated that there are any events that would warrant discontinuation of this study. Any unforeseen adverse events will be reported to the Hunter New England Human Research Ethics Committee (the primary approval committee) and advice sought out regarding the required action. Any deviations from this original protocol will be reported in our study outcomes papers.

**Results**

Preimplementation data collection ($T_0$) was completed in March 2020. As of November 2020, 87% (13/15) wards have completed implementation and are undertaking postimplementation data collection ($T_1$).

**Discussion**

Our practice-change package is designed to reduce the current inpatient UI/LUTS care evidence-practice gap. We will contribute to the implementation research literature by demonstrating the potential impact of using a clinically applicable, evidence-based intervention that has been informed by the knowledge translation theory to optimize uptake in hospitals. We will describe the resources and costs associated with implementing the SCAMP intervention via a cost-consequences economic analysis. Our cost consequence analysis will provide an opportunity to pilot instruments used to collect economic data, such as resource use and clinical outcomes [43]. This analysis will be essential for establishing the benefit of scaling up the practice-change package. This study has been designed to provide clinicians, managers, and policy makers with the evidence needed to assess the potential benefit of further, wide-scale implementation of our practice-change package. We will report our findings according to the StaRI [24,25]. This will ensure that our practice-change package can be replicated in other clinical sites and in future research.

The results from this study will provide evidence to whether our UI/LUTS practice-change package is effective in supporting clinicians and health services deliver optimal care. To ensure that our practice-change package is evidence-based, clinically relevant, and applicable, it has been developed from the outset with our team of inpatient clinicians and managers, clinician researchers, and academics with experience in implementation science. To increase the generalizability and potential scalability of our practice-change package, we are testing it in a range of clinical scenarios and across the phases of inpatient care for people with a range of diagnoses, including stroke, admitted to metropolitan and regional hospitals in 4 health districts in 2 Australian states. It may also be applicable to other health conditions where providing optimal UI and LUTS care is challenging.

**Acknowledgments**

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This study was approved by the Hunter New England Human Research Ethics Committee (HNEHREC reference no. 18/10/17/4.02) and co-registered with the University of Newcastle Human Research Ethics Committee (UON HREC reference no. H-2020-0083). The authors would like to acknowledge the following: the project team members who are not listed as authors: Hunter Stroke Service—Annalise Johnson; Port Macquarie—Emily Saul, Michelle Coad, Jeremy Mulder; Ryde Hospital—Soo Cho, Virginia Mapurazi, Helen Wheat; Coffs Harbour—Helen King; Rockhampton—Sandy Greensill; Wauchope—Catherine Williams; NSW Agency for Clinical Innovation—Kate Jackson (Stroke Network) and Louise Sellars (Rehabilitation Network); Monash University—Joosup Kim and Garveeta Sookram for assistance with the economic evaluation plan; and Hunter Stroke Service—Monique Hourn and Hunter Medical Research Institute—Alix Hall for assistance with Redcap.

Louise-Anne Jordan, who led the initial development of the SCAMP intervention in 2008 and played an integral part in this study protocol, sadly passed away in November 2019. The authors recognize her contributions, leading to her posthumous authorship.

**Authors' Contributions**

DM, KB, DC, and JD led the overall development of the research protocol and DM led the development of the manuscript. L-AJ and M Pollack contributed to the development of the rationale and background for the protocol. JAD, JS, FM, AS, JB, SO, AB, KP, SL, MP, and KH contributed to the development of the protocol, intervention, and implementation support strategies. DM, KB, DC, and JD contributed to the development of data collection methods. DC contributed to the development of data collection...
methods and analysis specific to economic analysis. CO contributed to the study design, sample size calculation, and data analysis plan. JW provided the overall guidance for the proposed conduct. All authors have read and approved the final manuscript.

Conflicts of Interest
This project forms the basis of author KB’s PhD Candidature (University of Newcastle, NSW, Australia).

References


Abbreviations

LUTS: lower urinary tract symptom
NSW: New South Wales
SCAMP: Structured urinary Continence Assessment and Management Plan
StaRI: Standards for Reporting Implementation Studies
T₀: before implementation
T₁: immediately after the 6-month implementation period
T₂: after a 6-month maintenance period
UI: urinary incontinence

©Dianne Lesley Marsden, Kerry Boyle, Louise-Anne Jordan, Judith Anne Dunne, Jodi Shipp, Fiona Minett, Amanda Styles, Jaclyn Birnie, Sally Ormond, Kim Parrey, Amanda Buzio, Sandra Lever, Michelle Paul, Kelvin Hill, Michael R P Pollack, John Wiggers, Christopher Oldmeadow, Dominique Ann-Michele Cadilhac, Jed Duff, The I-SCAMP Project Team. Originally published in JMIR Research Protocols (http://www.researchprotocols.org), 04.02.2021. This is an open-access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work, first published in JMIR Research Protocols, is properly cited. The complete bibliographic information, a link to the original publication on http://www.researchprotocols.org, as well as this copyright and license information must be included.
Prospective Associations Between Fixed-Term Contract Positions and Mental Illness Rates in Denmark’s General Workforce: Protocol for a Cohort Study

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Abstract

Background: In 2018, 14% of employees in the European Union had fixed-term contracts. Fixed-term contract positions are often less secure than permanent contract positions. Perceived job insecurity has been associated with increased rates of mental ill health. However, the association between fixed-term contract positions and mental ill health is uncertain. A recent review concluded that the quality of most existing studies is low and that the results of the few studies with high quality are contradictory.

Objective: This study aims to estimate the incidence rate ratios (RRs) of psychotropic drug use and psychiatric hospital treatment. These ratios will be considered, first, in relation to the contrast fixed-term versus permanent contract and, second, to fixed-term contract versus unemployment.

Methods: Interview data with baseline information on employment status from the Danish Labor Force Surveys in the years 2001-2013 will be linked to data from national registers. Participants will be followed up for up to 5 years after the interview. Poisson regression will be used to estimate incidence RRs for psychiatric hospital treatment for mood, anxiety, or stress-related disorders and redeemed prescriptions for psychotropic drugs, as a function of employment status at baseline. The following contrasts will be considered: full-time temporary employment versus full-time permanent employment and temporary employment (regardless of weekly working hours) versus unemployment. The analyses will be controlled for a series of possible confounders. People who have received sickness benefits, have received social security cash benefits, have redeemed a prescription for psychotropic drugs, or have received psychiatric hospital treatment for a mental disorder sometime during a 1-year period preceding baseline will be excluded from the study. The study will include approximately 134,000 participants (13,000 unemployed, 106,000 with permanent contracts, and 15,000 with fixed-term contracts). We expect to find approximately 16,400 incident cases of redeemed prescriptions of psychotropic drugs and 2150 incident cases of psychiatric hospital treatment for mood, anxiety, or stress-related disorders.

Results: We expect the analyses to be completed by the end of 2021 and the results to be published in mid-2022.

Conclusions: The statistical power of the study will be large enough to test the hypothesis of a prospective association between fixed-term contract positions and mental illness in the general workforce of Denmark.

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KEYWORDS
cohort study; fixed-term employment; fixed term contract; unemployment; psychotropic drugs; psychiatric hospital treatment
Introduction

Background

Mental health problems are the most frequent single cause of disability benefits in the Organization for Economic Co-operation and Development (OECD) [1]. In Denmark, mental health problems account for almost half of all new applications for disability benefits [1].

The prevalence of temporary employment contracts in the European Union (EU) has been quite stable since 2005 [2]. Approximately 14% of employees (27 million persons) in the EU had a fixed-term contract in 2018 [3]. The total cost of mental health illness in the EU-28 nations was estimated to be approximately 600 billion euros in 2015, which corresponds to 4.1% combined gross domestic product of the 28 nations [4]. It has been hypothesized that some cases of mental health illness may be due to insecure employment contracts [5]. The main reason for suspecting a link between fixed-term contracts and mental health problems is that perceived job insecurity has been associated with an increased prevalence of depression, anxiety, emotional exhaustion, life satisfaction, and psychological well-being [6] as well as an increased risk of developing depressive symptoms [7]. In addition, employees in fixed-term contracts often have less influence on workplace decisions than employees with permanent contracts [8,9]. Furthermore, a low decision latitude has been associated with an increased risk of developing clinical depression [10].

However, it is still not clear whether fixed-term contracts pose a risk for poor mental health. A review by Hünefeld and Köper [5] considered 84 estimated associations between fixed-term versus permanent contract and mental health. Statistical significance was reported in 40% of the included studies, but only half of the significant associations were positive. Moreover, a recent systematic review and meta-analysis of studies on fixed-term versus permanent contracts and mental health problems concluded (1) that the quality of most existing studies was low and (2) that the results of the few studies with sufficient quality were contradictory [11].

The association between unemployment and mental health disorders has been robustly researched and published. There is a consensus that people who are unemployed are at increased risk of developing mental health problems and that employees with mental health problems are at increased risk of becoming unemployed [12]. A substantial reason for the association between unemployment and mental illness is attributed to the mental distress of chronic financial insecurity [7]. From this perspective, it has been hypothesized that the anticipation of a job loss can be detrimental to mental health as unemployment itself [7]. Recently, a meta-analysis was carried out to estimate the relative risk of developing depression as a function of unemployment and self-perceived job insecurity [7]. The study included results from 20 cohort studies, of which 14 compared the risk among unemployed with the risk among employees, whereas 6 compared the risk among employees with perceived job insecurity with that among other employees. The odds ratio for the contrast unemployment versus employment was estimated to be 1.19 (95% CI 1.11-1.28), whereas the odds ratio for “secure versus unsecure employment” was estimated to be 1.29 (95% CI 1.06-1.57).

Objectives

This project aims to estimate the incidence rate ratios (RRs) of psychotropic drug usage and psychiatric hospital treatment. These ratios will be considered in relation to the contrast “fixed-term versus permanent contract” and to “fixed-term contract (regardless of weekly working hours) versus unemployment” among the general population of Denmark. The second analysis will be performed to elucidate the hypothesis of Kim and von dem Knesebeck [7], which states that the anticipation of a possible job loss can be as detrimental for the mental health as unemployment itself.

People may work part time due to health issues or because they are not able to find a full-time job. They may also have chosen to work part time, for example, for furthering their education, caring for a parent or child, or engaging in hobbies or sports activities. The reason for excluding part-time workers in the first analysis is that a participant may have chosen to work part time due to ill health. The reason for not excluding part-time workers in the second analysis is that our data do not permit differentiation between part-time and full-time unemployment.

Job insecurity and unemployment have been associated with an increased risk of mental distress from chronic financial insecurity, which in turn has been associated with an increased risk of mental illness [13-15]. It is reasonable to believe that most people are financially more secure in a fixed-term contract position than they are in a state of unemployment. From this viewpoint, we expect the risk of developing mental health illnesses to be higher among unemployed people than among employees with a fixed-term contract. Likewise, we expect the risk to be higher among employees with a fixed-term contract than among employees with a permanent contract.

Methods

Ethics Approval

The study will comply with The Act on Processing of Personal Data, Denmark (Act No. 429 of May 31, 2000), which implements the European Union Directive 95/46/EC on the protection of individuals. The data usage was approved by the Danish Data Protection Agency (file number 2001-54-0180). The ethical and legal aspects of the project were approved by Statistics Denmark, accounting for 704291. In Denmark, register studies, which do not include medical procedures, are not part of the ethical committee system.

Data Sources

All residents of Denmark have access to tax-financed health care. The educational system is generally tax financed. The so-called flexicurity model provides an income safety net for the unemployed, with unemployment insurance benefits for members of unemployment insurance funds. The residents of Denmark are also entitled to maternity and paternity benefits, sickness-absence benefits, disability benefits, and if needed, social security cash benefits. Person-based data on health care services and redeemed prescriptions of medicine and welfare
benefits payments are collected and reported in national registers, with unique personal identification numbers, which are assigned to all residents of Denmark [16].

This study will be based on baseline data on employment status from the Danish Labor Force Survey (DLFS) 2001-2013 and follow-up data on health from a series of registers, which cover the entire population of Denmark. The following registers will be used: the Central Person Register (CPR) [17], the Employment Classification Module (ECM) [18], the Danish Education Registers [19], the Danish Family Income Register [20], the Danish Register for Evaluation of Marginalization (DREAM) [21], the Psychiatric Central Research Register [22], and the National Prescription Register [23]. Linkage will be based on participants’ personal identification numbers. The data sources and information to be included are listed in Table 1.

**Table 1.** The data sources of the project.

<table>
<thead>
<tr>
<th>Data source</th>
<th>Type of data source</th>
<th>Information to be included in the present project</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Danish Labor Force Survey [24]</td>
<td>Survey data obtained from interviews on random samples of the population of Denmark</td>
<td>Date of the interview, employment status, type of employment contract, and nighttime work</td>
</tr>
<tr>
<td>The Central Person Register [17]</td>
<td>National register, which covers all residents of Denmark</td>
<td>Gender, age, date of migration, and date of death</td>
</tr>
<tr>
<td>The Employment Classification Module [18]</td>
<td>National register, which covers all residents of Denmark</td>
<td>Industry sector</td>
</tr>
<tr>
<td>The Danish Education Registers [19]</td>
<td>National register, which covers all residents of Denmark</td>
<td>Educational level</td>
</tr>
<tr>
<td>The Danish Family Income Register [20]</td>
<td>National register, which covers all residents of Denmark</td>
<td>Equalized disposable family income</td>
</tr>
<tr>
<td>The Danish Register for Evaluation of Marginalisation [21]</td>
<td>National register, which covers all residents of Denmark</td>
<td>Date of welfare benefits payment and type of welfare benefits payment</td>
</tr>
<tr>
<td>The Psychiatric Central Research Register [22]</td>
<td>National register, which covers all residents of Denmark</td>
<td>Date of hospital contact and principal diagnosis (ICD-10 code)</td>
</tr>
<tr>
<td>The National Prescription Register [23]</td>
<td>National register, which covers all residents of Denmark</td>
<td>Date of redeemed prescription and type of medicine (ATC\textsuperscript{b}-code)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th Revision.
\textsuperscript{b}ATC: Anatomical Therapeutic Chemical Classification System.

DLFS is based on quarterly random samples of 15- to 74-year-old residents of Denmark, with systematic oversampling of unemployed people. Each participant is invited to be interviewed 4 times over the course of a year and a half. The purpose of the interviews is to collect person-based information on inter alia, labor market attachment, type of contract, and working hours [24]. Among those invited for the DLFS, the response rate decreased over time from 70% in 2002 to 53% in 2013 [25]. The CPR contains, inter alia, information on gender, addresses, and dates of birth, death, and migrations for every person who is or has been a resident of Denmark sometime between 1968 and the present time. The ECM contains annual person-based information on, inter alia, the socio-economic status, occupation, and industry of the residents of Denmark. The Danish Education Registers contain person-based information on, inter alia, a person’s highest educational attainment. The Danish Family Income Register contains information on household income. DREAM contains weekly, person-based information on social transfer payments (welfare benefits payments) such as maternity and paternity benefits, sickness-absence benefits, unemployment benefits, social security cash benefits, and state educational grants. DREAM has existed since 1991 and covers all residents of Denmark. The weekly benefits data are recorded if the person has been on a benefit for 1 or more days of the week. However, as only 1 type of social transfer payment can be registered per week, types of benefits are prioritized in the case of data overlap. The above-mentioned social transfer payments are prioritized in the order listed, that is, maternity and paternity benefits have higher priority than sickness-absence benefits, which in turn have higher priority than unemployment benefits, etc. The Psychiatric Central Research Register contains person-based information on inpatients, outpatients, and emergency ward visits in all psychiatric hospital departments in Denmark. The National Prescription Register contains person-based data on all redeemed prescriptions at pharmacies in Denmark.

This study has access to the data on Anatomical Therapeutic Chemical Classification System (ATC) codes [26] from the National Prescription Register for the time period 2000-2014 and International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes [27] from the Psychiatric Central Research Register for the time period 1995-2017.

**Clinical Endpoints**

RRs will be examined for the following endpoints:

- Redeemed prescriptions for any type of psychotropic medicine, that is, drugs in the ATC-code category N05 (psycholeptica) or N06 (psychoanalectica)
Psychiatric hospital treatment with mood, anxiety, or stress-related disorder (ICD-10: F30–F41 or F43) as the principal diagnosis

The following mental disorders are included in the above case definition:

- F30 Manic episode
- F31 Bipolar affective disorder
- F32 Depressive episode
- F33 Recurrent depressive disorder
- F34 Persistent mood (affective) disorders
- F38 Other mood (affective) disorders
- F39 Unspecified mood (affective) disorder
- F40 Phobic anxiety disorders
- F41 Other anxiety disorders
- F43 Reaction to severe stress and adjustment disorders

**Exposure**

The following exposure categories will be considered: unemployed but actively searching for a job and ready to start working within 14 days, employed on a fixed-term contract position, and employed on a permanent contract. The categories are based on the DLFS-questionnaire [18].

**Covariates**

The literature suggests that estimated risks of mental health depend on gender [28,29], age [30-32], calendar year [33], education level [34], and income [35-38]. Moreover, it has been shown that the birth of a child may result in maternal [39] and paternal [40] postpartum depression.

The following covariates will therefore be regarded in all analyses: gender, age, calendar time of the interview, education level (at the end of the calendar year preceding the interview), equivalent disposable family income (in the calendar year preceding the interview), and maternity or paternity benefits (in the 1-year period preceding the interview).

In addition to the above, the following covariates will be regarded in the analyses of differences between employees with fixed-term and permanent contracts: main industry (in the calendar year preceding the interview), unemployment benefits (in the 1-year period preceding the interview), state educational grants (in the 1-year period preceding the interview), and nighttime work (at the time of the interview). We control for industry, as a previous study has found significant industry-related inequalities in the rate of mood disorders among employees in the general working population of Denmark [41]. We control for unemployment benefits and state educational grants in the 1-year period preceding the interview, as we believe that people’s attitudes toward fixed-term and permanent contracts may depend on their previous labor market attachment. We control for nighttime work because it has been shown that the prevalence of psychotropic drug usage in Denmark is greater among shift workers than among workers without shift work [42].

The variables will be operationalized as follows:

**Gender**

Gender is classified into male or female as registered in the CPR.

**Age**

In this study, we will not have access to the exact dates of birth, but we will have access to information about the birth year of the participants, that is, we will know what their integer age was at the very beginning and at the very end of a calendar year. To form baseline age categories, the participants who were interviewed before July 1 in a given calendar year will be assigned the integer age they had at the beginning of that year, whereas the participants who were interviewed after June 30 will be assigned the integer age they would have at the end of the calendar year. The participants will thereafter be divided into 10-year age groups (20-29,…50-59 years), and the age group will be treated as a categorical variable.

**Calendar Time of the Interview**

The calendar years of the interviews will be treated as a categorical variable and divided into the following categories: 2001-2003, 2004-2006, 2007-2009, and 2010-2013.

**Educational Level (at the End of the Calendar Year Preceding the Interview)**

A person’s highest attained education is registered and classified with a 2-digit code in the Danish Education Registers [19]. In this study, it will be divided as follows (Table 2) into the categories low, medium, high, and unstated.

<table>
<thead>
<tr>
<th>The present project</th>
<th>The Danish Education Registers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>10 Primary and lower secondary education</td>
</tr>
<tr>
<td>Medium</td>
<td>20 Upper secondary education, 30 Basic vocational education, 35 Qualifying vocational education, 40 Short-term tertiary education</td>
</tr>
<tr>
<td>High</td>
<td>50 Medium-term tertiary education, 60 Bachelor’s degree, 70 Master’s degree or equivalent tertiary education level, 80 Doctoral degree or equivalent tertiary education level</td>
</tr>
<tr>
<td>Unstated</td>
<td>Unstated</td>
</tr>
</tbody>
</table>

Table 2. Classification of education levels.
**Equivalized Disposable Family Income (in the Calendar Year Preceding the Interview)**

The equivalent disposable income is the total income of a household, after tax and other deductions, which is available for spending or saving, divided by the number of household members converted into equalized adults; household members are equalized or made equivalent by weighting each according to their age, using the so-called modified OECD equivalence scale (cited from Eurostat [43]).

The equivalent disposable income is calculated in 3 steps (cited from Eurostat [43]):

- All monetary incomes received from any source by each member of a household are added up. These include income from work, investment, and social benefits, as well as any other household income; taxes and social contributions that have been paid are deducted from this sum.
- To reflect differences in household size and composition, the total (net) household income is divided by the number of 'equivalent adults,' using a standard (equivalence) scale: the modified OECD scale. This scale gives a weight to all members of the household (and then adds these up to arrive at the equivalized household size): 1.0 to the first adult, 0.5 to the second and each subsequent person aged 14 and over, and 0.3 to each child aged under 14.
- Finally, the resulting figure is called the equivalent disposable income and is attributed equally to each member of the household.

This study will treat the equivalent disposable family income as a categorical variable, divided into low, medium, and high in accordance with calendar-year specific sample tertiles. The tertiles will be based on all DLFS responders who were 20 to 59 years old and employed at the time of the interview.

**Main Industry (in the Calendar Year Preceding the Interview)**

The industries will be divided into 10 groups, as shown in Table 3. The industrial codes are based on the industrial classification DB93 [44] in 1999-2002, DB03 [45] in 2002-2007, and DB07 [46] in the calendar years 2008-2013.

**Table 3.** Industrial groups coded according to the classifications DB93, DB03, and DB07, respectively.

<table>
<thead>
<tr>
<th>Industrial group</th>
<th>Code according to DB93</th>
<th>Code according to DB03</th>
<th>Code according to DB07</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agriculture, forestry, hunting, and fishing</td>
<td>A+B</td>
<td>A+D</td>
<td>A</td>
</tr>
<tr>
<td>Manufacturing, mining, and quarrying</td>
<td>C+D</td>
<td>C+D</td>
<td>B+C</td>
</tr>
<tr>
<td>Construction</td>
<td>F</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Wholesale and retail trade and repair of motor vehicles and motorcycles</td>
<td>G</td>
<td>G</td>
<td>G</td>
</tr>
<tr>
<td>Transporting and storage</td>
<td>I</td>
<td>I</td>
<td>H</td>
</tr>
<tr>
<td>Accommodation and food service activities</td>
<td>H</td>
<td>H</td>
<td>I</td>
</tr>
<tr>
<td>Human health and social work activities</td>
<td>N</td>
<td>N</td>
<td>Q</td>
</tr>
<tr>
<td>Unstated</td>
<td>X</td>
<td>Missing</td>
<td>Missing</td>
</tr>
</tbody>
</table>

**Unemployment Benefits (in the One-Year Period Preceding the Interview)**

This variable is equal to 1 if the participant, according to DREAM, received unemployment benefits (DREAM codes: 111-115, 121-126, 211-219, 231, 232, and 299) at least once during the 1-year period preceding the DLFS interview. Otherwise, it is equal to 0.

**Maternity or Paternity Benefits (in the One-Year Period Preceding the Interview)**

This variable is equal to 1 if the participant, according to DREAM, received maternity or paternity benefits (DREAM code: 881) at least once during the 1-year period preceding the DLFS interview. Otherwise, it is equal to 0.

**State Educational Grants (in the One-Year Period Preceding the Interview)**

This variable is equal to 1 if the participant, according to DREAM, received state educational grant payments (DREAM codes: 651, 652, and 661) at least once during the 1-year period preceding the DLFS interview. Otherwise, it is equal to 0.

**Nighttime Work**

In the DLFS interview, the participants were asked whether they worked at night during the last 4 weeks. In this study, nighttime work will be treated as a categorical variable in accordance with the 3 response categories Yes, regularly, Yes, occasionally, and No.

**Follow-Up**

The study will be based on data that already exist. The included participants of the DLFS will be followed by national registers. The follow-up in the register data will start on the date when 6 weeks would have passed since the first DLFS interview and end on the date when any of the following events occur: 5 years pass since the date of the start of the follow-up, the participant emigrates, the participant dies, the participant meets the clinical endpoint of the analysis, or the study period ends. The end of the study period was set at the end of the calendar years 2014.
and 2017 for redeemed prescriptions of psychotropic drugs and psychiatric hospital treatments, respectively. Person-years at risk will be calculated for each of the included participants. Participants who die or emigrate during the follow-up will be censored at the time of the event. That is, they will participate with person-years at risk until the time of death or emigration.

**Inclusion Criteria**

The primary analyses will be based on data from the participants’ first interview in the time period 2001-2013. In the comparisons between employees with a full-time fixed-term versus a full-time permanent contract, we will require inclusion criteria 1-6 fulfilled (see below). In the comparisons between employees with a fixed-term contract (regardless of weekly working hours) versus unemployed people, we will require that criteria 1-4 and criteria 7 are fulfilled.

Inclusion criteria:

1. The participants were aged between 20 and 59 years at the time of the interview.
2. They did not receive any social transfer payments other than holiday allowance (DREAM code: 121), unemployment benefits (DREAM codes: 111-115, 122-126, 211-219, 231, 232, 299), maternity or paternity benefits (DREAM code: 881), or state educational grants (DREAM codes: 651, 652, 661) during the one-year period preceding the interview.
3. They did not receive any psychiatric hospital treatment with mental disorders (ICD-10: F01–F99) as the principal diagnosis during a 1-year period preceding the start of follow-up.
4. They did not redeem any prescription for psychotropic drugs (ATC: N05–N06) during a 1-year period preceding the start of follow-up.
5. They were employees, according to the interview.
6. They usually worked ≥32 h a week, according to the interview.
7. They were either unemployed but actively searching for a job and ready to start working within 14 days or employed with a fixed-term contract at the time of the interview.

Moreover, it is necessary that the concerned DLFS–based exposure variables and covariates are nonmissing.

**Primary Statistical Analysis**

Poisson regression will be used to estimate incidence RRs for psychiatric hospital treatment for mood, anxiety, or stress-related disorders and redeemed prescriptions for psychotropic drugs, as a function of employment status at baseline. The following contrasts will be considered: (1) Full-time fixed-term contract versus full-time permanent contract and (2) fixed-term contract (regardless of weekly working hours) versus unemployment. All analyses will be controlled for age, sex, disposable family income, educational level, calendar year of the interview, and reception of maternity or paternity benefits sometime during a 1-year period preceding baseline. The RRs for the contrast fixed-term versus permanent contract will, in addition to the above, be controlled for baseline industry group and nighttime work as well as reception of unemployment benefits and state study grants, sometime during a 1-year period preceding baseline. The logarithm of person-years at risk will be used as an offset. Likelihood ratio tests will be used to test first for main effects and then for effects of interaction with gender, age, and education level. We test for interactions, as it has been suggested that the strength of adverse health effects of fixed-term contracts depends on gender [47], age [48], and education level [49].

The main effects will be tested both for psychiatric hospital treatments and redeemed prescriptions for psychotropic drugs. The interaction effects will only be tested for redeemed prescriptions for psychotropic drugs. A Bonferroni correction will be used to adjust for multiple testing. We want the overall significance level to be less than or equal to 0.05. Hence, each of the 10 tests will be conducted at a significance level of 0.005. RRs for main effects will be estimated and presented with 99.5% CI. Moreover, the RRs for redeemed prescriptions for psychotropic drugs will be stratified (and presented with 99.5% CI) by gender, age, and educational level.

**Power Calculations**

Under the null hypothesis, we expected to find approximately 29 new cases of psychotropic drug usage and 3.4 new cases of psychiatric hospital treatment for mood, anxiety, or stress-related disorders per 1000 person-years at risk [50]. If we assume that approximately 15% of the otherwise eligible participants will be excluded due to exclusion criteria 1-4, the total number of expected cases in the concerned exposure categories will be approximately as shown in Table 4.

<table>
<thead>
<tr>
<th>Exposure category</th>
<th>Expected number of eligible participants</th>
<th>Expected number of psychotropic drug cases</th>
<th>Expected number of psychiatric hospital cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed-term full-time contract</td>
<td>10,600</td>
<td>1300</td>
<td>170</td>
</tr>
<tr>
<td>Permanent full-time contract</td>
<td>106,000</td>
<td>13,000</td>
<td>1700</td>
</tr>
<tr>
<td>Fixed-term contract (regardless of weekly working hours)</td>
<td>15,000</td>
<td>1800</td>
<td>240</td>
</tr>
<tr>
<td>Unemployment</td>
<td>13,000</td>
<td>1600</td>
<td>210</td>
</tr>
</tbody>
</table>

On the basis of the expected number of cases, the Poisson distribution, the Gauss propagation of error formulas, and the central limit theorem, we estimated the statistical power of the planned significance tests. The statistical powers for the main effects are given in Figures 1 and 2, for incident use of psychotropic drugs and psychiatric hospital treatment for mood, anxiety, or stress-related disorders, respectively, as a function of the underlying RR.
**Figure 1.** Power to detect main effects of fixed-term contracts on the rates of new cases of psychotropic drug use, as a function of underlying rate ratios ($\alpha=0.005$).

**Figure 2.** Power to detect main effects of fixed-term contracts on the rates of new cases of psychiatric hospital treatment for mood, anxiety, or stress-related disorders, as a function of underlying rate ratios ($\alpha=0.005$).
The statistical powers to detect interaction effects were estimated in relation to the Cohen w [51], where w=0.1 is defined as a small effect, w=0.3 is defined as a medium effect, and w=0.5 is defined as a large effect. On the basis of the expected number of cases, test specific degrees of freedom, and the noncentral chi-square distribution, we estimated that the power to detect a small effect (w=0.1) is greater than 0.98 in each of the planned interaction tests of this project.

The calculations indicate that the power is sufficiently large to test both the main and interaction effects of fixed-term contracts on the incidence of psychotropic drug usage. The powers to detect effects of fixed-term contracts on the incidence of psychiatric hospital treatment for mood, anxiety, or stress-related disorders (Figure 2) are, however, quite low, and this needs to be taken into account when the results are evaluated.

Sensitivity Analyses

We will conduct 6 sensitivity analyses. The endpoint of the sensitivity analyses will be redeemed prescriptions of psychotropic drugs. Interaction effects will be disregarded. RRs will be estimated and presented with 99.5% CI. The RRs and their associated confidence intervals will not be regarded as statistical significance tests. However, they may strengthen, weaken, or invalidate the statistical conclusions of the primary analyses.

**Sensitivity Analysis 1: Exclusion of All Cases that Occurred Within 5 Years Preceding the Start of Follow-Up**

The primary analysis will exclude all people who received psychiatric hospital treatment or redeemed a prescription for psychotropic drugs sometime during a 1-year period before the start of the follow-up. Hence, no known current cases of psychiatric treatment will be included in the follow-up. It is, however, possible that people who received treatment more than 1 year before the follow-up will influence the analysis. To shed some light on this issue, we will conduct a sensitivity analysis in which we will exclude all people who received psychiatric hospital treatment or redeemed a prescription for psychotropic drugs sometime during a 5-year period before the start of the follow-up. This sensitivity analysis will be based on data from the participants’ first interview in the period 2005-2013. Moreover, it will only include people who lived in Denmark throughout the concerned 5-year period. The statistical models and inclusion criteria will otherwise be the same as in the primary analysis. The interpretation of results will include the fact that approximately 20% of the population experiences mental health problems during their lifespan due to different causes; so the analysis may be overcontrolling.

**Sensitivity Analysis 2: Relapse Rate Ratios**

At this point, it is useful to further elucidate (examine) the possible influence of former cases of psychiatric treatment on the association between fixed-term contract and psychotropic drug usage. To this end, we will estimate relapse RRs among the participants who were excluded from the first sensitivity analysis due to psychiatric hospital treatment or redeemed prescription for psychotropic drugs sometime between 1 and 5 years before the start of follow-up.

Current cases, that is, people who received treatment sometime during a 1-year period before the start of follow-up will still be excluded. The statistical models will otherwise be the same as in sensitivity analysis 1.

**Sensitivity Analysis 3: Long-term Exposure Versus Exposure at a Single Time Point**

In the primary analysis, we regard the contrasts full-time fixed-term contract versus full-time permanent contract and fixed-term contract versus unemployment with the exposure categories defined at a single time point (the first interview). We want to know whether the strength of the concerned associations will increase if we base the exposure categories on more than one interview and only include people who belong to the same exposure category in all of their interview rounds. In other words, we want to know whether the strength of the associations will increase if we base the contrasts on long-term exposure instead of exposure at a single time point. To shed some light on this issue, we will conduct a sensitivity analysis in which we will only include people who (1) participated in more than one interview, (2) were aged between 20 and 59 years during their last interview, and (3) belonged to the same exposure category in all of their interview rounds. The follow-up of the included participants will commence 6 weeks after their last interview. The statistical models and inclusion criteria will otherwise be the same as in the primary analysis.

**Sensitivity Analysis 4: Minimally Adjusted Rate Ratios**

In the primary analyses, we will exclude all people who received sickness benefits or social security cash benefits during a 1-year period before the baseline interview. Moreover, we control for disposable family income as well as a series of other covariates. It is possible that the rigorous inclusion criteria and the many control variables will lead to overly conservative estimates. Therefore, we will conduct a sensitivity analysis in which we will (1) remove the second of the inclusion criteria listed in the method section and (2) remove all control variables except for gender, age, and education. The methods will otherwise be the same as in the primary analyses.

**Sensitivity Analysis 5: Reason for Being on a Fixed-Term Contract**

All EU-Labor Force Survey participants with a fixed-term contract are asked for the reason of having a fixed-term contract. Their answers are categorized as follows:

- It is a contract covering a period of training (apprentices, trainees, research assistants, etc)
- Person could not find a permanent job
- Person did not want a permanent job
- It is a contract for a probationary period

We want to know whether the risk of developing mental health illnesses among employees with a fixed-term contract depends on the reason for being on a fixed-term contract. To answer this question, we will estimate incidence RRs for redeemed prescriptions of psychotropic drugs as a function of the reason for being on a fixed-term contract. Participants who did not want a permanent job (category 3) will serve as the reference group. We will include all employees on...
fixed-term contracts, who fulfilled inclusion criteria 1-5, as listed in the method section. The analyses will initially be conducted only with full-time employees (232 h a week) and then with all employees regardless of weekly working hours. The analyses will be controlled for all variables given in the Covariate section. The statistical model and follow-up periods will be the same as in the primary analysis.

**Sensitivity Analysis 6: Stratification by Industry Sector**
We know that the prevalence of fixed-term contracts in the Nordic countries depends on the industry sector [52], and that the rates of mood disorders in the general working population of Denmark depend on the industry sector [41]. It is possible that the effect of fixed-term contract positions on mental health illnesses also depends on the industry. Therefore, we conduct a sensitivity analysis in which we will stratify the results of the comparison between employees with a fixed-term and a permanent contract by the industry sector. The industries are grouped as shown in Table 3. The inclusion criteria and covariates will be the same as in the primary analysis.

Reasons why the association between fixed-term contracts and mental health illnesses might depend on industry could be, first, that chances for reemployment may depend on the industry sector and, second, that expectations regarding a fixed-term versus permanent contract may depend on the industry.

Another reason for stratifying by the industry sector is that the social partners might be interested in seeing the association between fixed-term contracts and mental health illnesses in their own industry sector.

**Possible Confounding From Smoking, Being Overweight, and Obesity: a Feasibility Study**
Studies have suggested that smoking habits [53,54] and being overweight [55] predict depression. It has been estimated that the risk ratio of new-onset depression is 1.46 (95% CI 1.03-2.07) for smokers versus nonsmokers [53], 1.08 (95% CI 1.02-1.14) for overweight versus normal weight, and 1.57 (95% CI 1.23-2.01) for obesity versus normal weight [55]. The DLFS does not contain any information about smoking habits and body weights of the participants. Therefore, we cannot control for these factors in the analyses. However, we have access to some collateral data, which we have used to estimate to what extent and in what direction the RRs of the present project are likely to be influenced by differences in distributions of body mass index and smoking habits. The collateral data were gathered from a survey on work and health in a random sample of the Danish population in 2005. The response rate of the survey was 62% [56]. In this study protocol, we have used the survey data to estimate the prevalence of smoking, being overweight, and obesity among 20-59-year-old people in Denmark, stratified by the exposure categories of interest to this study. The crude prevalence is given in Table 5, whereas prevalence that is standardized for age, gender, and education is given in Table 6. The total sample of 20- to 59-year-old people was used as the standard population.

**Table 5.** Crude percentages of current smokers, people with moderate overweight (25≤BMI<30), and people with obesity (BMI≥30), by exposure category, in a random sample of 20- to 59-year-old people in Denmark, 2005.

<table>
<thead>
<tr>
<th>Exposure category</th>
<th>Current smoker, n (%)</th>
<th>25≤BMI&lt;30, n (%)</th>
<th>BMI≥30, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed-term full-time contract (n=748)</td>
<td>221 (29.5)</td>
<td>231 (30.9)</td>
<td>72 (9.6)</td>
</tr>
<tr>
<td>Permanent full-time contract (n=8016)</td>
<td>2438 (30.4)</td>
<td>2859 (35.7)</td>
<td>834 (10.4)</td>
</tr>
<tr>
<td>Fixed-term contract (regardless of weekly working hours; n=908)</td>
<td>281 (30.9)</td>
<td>267 (29.4)</td>
<td>77 (8.5)</td>
</tr>
<tr>
<td>Unemployment (n=393)</td>
<td>141 (35.9)</td>
<td>123 (31.3)</td>
<td>54 (13.7)</td>
</tr>
</tbody>
</table>

**Table 6.** Age (10-year classes), gender and education (low, medium, and high) standardized percentages of current smokers, people with moderate overweight (25≤BMI<30), and people with obesity (BMI≥30), by exposure category, in a random sample of 20- to 59-year-old people in Denmark, 2005.

<table>
<thead>
<tr>
<th>Exposure category</th>
<th>Current smoker, % (95% CI)</th>
<th>25≤BMI&lt;30, % (95% CI)</th>
<th>BMI≥30, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed-term full-time contract</td>
<td>31.8 (28.4-35.6)</td>
<td>33.0 (29.6-36.8)</td>
<td>10.6 (8.5-13.3)</td>
</tr>
<tr>
<td>Permanent full-time contract</td>
<td>30.4 (29.4-31.4)</td>
<td>34.3 (33.3-35.3)</td>
<td>10.1 (9.5-10.8)</td>
</tr>
<tr>
<td>Fixed-term contract (regardless of weekly working hours)</td>
<td>33.3 (30.1-36.8)</td>
<td>32.5 (29.4-35.9)</td>
<td>9.5 (7.6-11.9)</td>
</tr>
<tr>
<td>Unemployment</td>
<td>36.5 (32.1-41.4)</td>
<td>31.9 (27.4-37.1)</td>
<td>14.1 (11.0-18.2)</td>
</tr>
</tbody>
</table>

Table 6 suggests that the standardized prevalence among people with fixed-term full-time contracts are very similar to those among people with permanent full-time contracts. We note, however, that the estimated prevalence of smoking and obesity is greater among the unemployed than among the employees on fixed-term contracts. We want a rough estimate of the effect that such differences may have on the RR of mental health illnesses among employees on fixed-term contracts versus unemployed in our target population. Therefore, we have estimated the expected RR between these exposure categories under the assumption that the groups are equal in all respects other than smoking and BMI distribution and that an RR for depression can be used as a proxy for the RR of mental health illnesses. We used the following equation:
where $RR_1=1.08$ is the estimated rate ratio for depression among people in the category $25\leq\text{BMI}<30$ versus $\text{BMI}<25$, $RR_2=1.57$ is the estimated rate ratio for depression among people in the category $\text{BMI} \geq 30$ versus $\text{BMI}<25$, and $RR_3=1.46$ is the estimated rate ratio for depression among smokers versus nonsmokers. The parameters $p_1$, $p_2$, and $p_3$ are the standardized sample prevalences of overweight, obesity, and smoking, respectively, among people with fixed-term contracts (cf. Table 6). The parameters $q_1$, $q_2$, and $q_3$ are the corresponding prevalence among the unemployed people (cf. Table 6).

The calculation yielded an estimated rate ratio of 0.96. This means that a failure to control for overweight, obesity, and smoking in this project is expected to bias the estimated rate ratio for mental health illnesses among fixed-term versus unemployed people downward with a factor of 0.96.

**Results**

We expect the analyses to be completed by the end of 2021 and the results to be published mid-2022.

**Discussion**

This study protocol contains a statistical analysis plan for a research project aimed at estimating prospective associations between fixed-term contracts and mental health illness in the general population of Denmark. As all covariates, outcome variables, inclusion criteria, statistical models, and significance levels are completely defined, published, and peer-reviewed before we link the exposure data of the project to its outcome data, we minimized the risk of hindsight bias.

A major strength of the project is that the data material is large enough to afford sufficient statistical power to detect important associations between fixed-term contracts and incident use of psychotropic medication. Another strength is that the outcome variables as well as the censoring variables (death and emigration) will be ascertained through national registers, which cover the entire population of Denmark. The study is weakened by the low response rate in the DLFS, which makes the representativeness of the participants questionable. Another weakness is the lack of data on lifestyle factors.

Studies have shown that the prevalence of depression tends to be higher among migrants than in the general population [57]. Studies of the general working population in Sweden [58] and Spain [59] have shown that immigrants are more likely to be on a fixed-term work contract. A survey of the general workforce in Canada found that newcomer immigrants (within the first 5 years) were on fixed-term contracts more often than natives [60]. Due to the comparability with Sweden and Canada, we expect the figures to be similar in Denmark. The response rate in questionnaire surveys among ethnic minorities in general is relatively low [61,62]; for example, half among non-Western immigrants compared with Danes [53]. The background to this study is the DLFS; thus, the issue of ethnicity cannot be addressed, as there are relatively few with immigrant background answering the survey.

Finally, it should be noted that the results of the study may not be fully transferable to other countries. Due to the relatively low employment protection in Denmark combined with a comprehensive income safety net for the unemployed, the so-called flexicurity model, it can be hypothesized that this may result in fewer fixed-term contracts in Denmark compared with other European countries [63].

**Acknowledgments**

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**Conflicts of Interest**

None declared.

**References**


Abbreviations

ATC: Anatomical Therapeutic Chemical Classification System
CPR: Central Person Register
DLFS: Danish Labor Force Survey
DREAM: Danish Register for Evaluation of Marginalization
ECM: Employment Classification Module
EU: European Union
ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th Revision
OECD: Organization for Economic Co-operation and Development
RR: rate ratio

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Cardiomyocyte Injury Following Acute Ischemic Stroke: Protocol for a Prospective Observational Cohort Study

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Abstract

Background: Elevated cardiac troponin, which indicates cardiomyocyte injury, is common after acute ischemic stroke and is associated with poor functional outcome. Myocardial injury is part of a broad spectrum of cardiac complications that may occur after acute ischemic stroke. Previous studies have shown that in most patients, the underlying mechanism of stroke-associated myocardial injury may not be a concomitant acute coronary syndrome. Evidence from animal research and clinical and neuroimaging studies suggest that functional and structural alterations in the central autonomic network leading to stress-mediated neurocardiogenic injury may be a key underlying mechanism (ie, stroke-heart syndrome). However, the exact pathophysiological cascade remains unclear, and the diagnostic and therapeutic implications are unknown.

Objective: The aim of this CORONA-IS (Cardiomyocyte injury following Acute Ischemic Stroke) study is to quantify autonomic dysfunction and to decipher downstream cardiac mechanisms leading to myocardial injury after acute ischemic stroke.

Methods: In this prospective, observational, single-center cohort study, 300 patients with acute ischemic stroke, confirmed via cerebral magnetic resonance imaging (MRI) and presenting within 48 hours of symptom onset, will be recruited during in-hospital stay. On the basis of high-sensitivity cardiac troponin levels and corresponding to the fourth universal definition of myocardial infarction, 3 groups are defined (ie, no myocardial injury [no cardiac troponin elevation], chronic myocardial injury [stable elevation], and acute myocardial injury [dynamic rise/fall pattern]). Each group will include approximately 100 patients. Study patients will receive routine diagnostic care. In addition, they will receive 3 Tesla cardiovascular MRI and transthoracic echocardiography within 5 days of symptom onset to provide myocardial tissue characterization and assess cardiac function, 20-min high-resolution electrocardiogram for analysis of cardiac autonomic function, and extensive biobanking. A follow-up for cardiovascular events will be conducted 3 and 12 months after inclusion.

Results: After a 4-month pilot phase, recruitment began in April 2019. We estimate a recruitment period of approximately 3 years to include 300 patients with a complete cardiovascular MRI protocol.
Conclusion: Stroke-associated myocardial injury is a common and relevant complication. Our study has the potential to provide a better mechanistic understanding of heart and brain interactions in the setting of acute stroke. Thus, it is essential to develop algorithms for recognizing patients at risk and to refine diagnostic and therapeutic procedures.

Trial Registration: Clinicaltrials.gov NCT03892226; https://www.clinicaltrials.gov/ct2/show/NCT03892226.

International Registered Report Identifier (IRRID): DERR1-10.2196/24186

(IntJMIR Res Protoc 2021;10(2):e24186) doi:10.2196/24186

KEYWORDS
 ischemic stroke; troponin T; myocardial ischemia; myocardial injury; stroke-heart syndrome; cardiac imaging techniques; magnetic resonance imaging; Takotsubo syndrome; autonomic nervous system

Introduction

Background

Elevated cardiac troponin (cTn), which is a sign of myocardial injury, frequently occurs in the early phase after an acute ischemic stroke (AIS) and is associated with poor functional outcome, especially increased mortality [1,2]. Using high-sensitivity assays, cTn is detectable in more than 90% of stroke patients; 30%-60% have at least one cTn above the assay-specific 99th percentile upper reference limit (URL) [2,3]. Approximately 5%-20% show a rise/fall pattern indicating acute myocardial injury according to the fourth universal definition of myocardial infarction (MI) [4]. In the latter group, acute coronary syndrome has to be suspected [4-6]. Following the American guidelines (American Heart Association/American Stroke Association), it is specifically recommended to measure cTn in stroke patients [7,8]. However, recommendations on how to deal with elevated cTn in the context of AIS remain vague [8]. Furthermore, expert consensus documents on practical considerations on the clinical use of cTn list ischemic stroke as one of the illnesses that leads to clinical uncertainty in the context of interpretation of elevated cTn [9].

The phenomenon of acute brain injuries (including an ischemic stroke and intracranial hemorrhage) leading to cardiac complications, including elevated cardiac enzymes, is known for a long time. In reference to AIS, it has recently been described as stroke-heart syndrome (SHS) [10-13]. However, the exact pathophysiological background of myocardial injury (ie, cTn elevation) after stroke is not entirely understood [13,14]. Several hypotheses have been discussed. Besides concomitant acute MI caused by atherothrombotic coronary artery disease (type 1 MI), situations of oxygen supply/demand mismatch have to be considered as underlying reasons. For example, tachyarrhythmia, hypotension/shock, anemia, or respiratory failure, which are frequently seen in stroke patients, can lead to demand ischemia [4,15]. Furthermore, systemic conditions such as sepsis or chronic kidney disease may cause or facilitate myocardial injury [16].

In the TRELAS (Troponin Elevation in Acute Ischemic Stroke) study, patients with AIS with markedly elevated cTn were significantly less likely to have a corresponding culprit lesion on coronary angiography when compared with age- and sex-matched patients with non-ST elevation acute coronary syndrome (ACS; showing no significant difference in the degree of cTn elevation) [17]. Together with the finding that half of the patients with AIS with markedly elevated cTn had no coronary artery disease at all, this implies that alternative mechanisms beyond ACS may play an important role [17]. This is supported by animal research and clinical and neuroimaging studies, suggesting that stroke-associated myocardial injury may originate from structural and/or functional interference within the central autonomic nervous system (CAN) with an overshooting sympathetic response [18-20]. On a cellular basis, it is assumed that excessive catecholamine and cortisol levels lead to an increased sarcoplasmic calcium influx with a consecutive hypercontraction of the sarcomeres, electrical instability, and metabolic and oxidative stress. Consequently, these pathological mechanisms can induce a contraction band necrosis and interstitial inflammatory reaction [12,21]. In summary, elevated troponin levels are frequent, and the underlying pathologies can be manifold, ranging from concomitant type 1 MI, demand ischemia, and chronic structural cardiac disease to systemic conditions. However, especially in situations with acute cTn elevation after AIS, the CAN seems to play an important role in the development of myocardial injury not only by triggering direct myocardial toxicity but also by facilitating situations of demand ischemia [13,14,22]. Nonetheless, the exact cascade of events remains mostly unclear, and when it comes to diagnostic procedures and treatment of affected patients, therapeutic options lack good scientific evidence [8].

Objective

The aim of the Cardiomyocyte injury following Acute Ischemic Stroke (CORONA-IS) study is to gain mechanistic insights into stroke-associated myocardial injury. We intend to provide a detailed characterization of (1) myocardial tissue; (2) myocardial, ventricular, and atrial function; and (3) associated autonomic dysfunction by using multimodal diagnostic measures.

Methods

Study Design

The CORONA-IS study is an investigator-initiated, prospective, observational, single-center cohort study that aims to include 300 patients with AIS. In November 2018, the Ethics Committee of the Charité-Universitätsmedizin Berlin, Germany (EA4/123/18), approved the study. All study procedures are carried out in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The study was pre-registered under clinicaltrials.gov, NCT03892226. All
patients with AIS admitted to the hospital within 48 hours of symptom onset are listed in a hospital-based registry as part of an assessment of high-sensitivity cTn (hs-cTn) development in patients with AIS. All study patients have to fulfill the study inclusion criteria listed in Textbox 1, and all participants have to provide written informed consent (for exclusion criteria refer to Textbox 2).

Textbox 1. Inclusion criteria.

- ability to provide informed consent
- age ≥18 years
- diagnosis of acute ischemic stroke and hospital admission within 48 hours of symptom onset
- visible diffusion-weighted imaging lesion in cerebral magnetic resonance imaging
- repeated measurement of high-sensitivity cardiac troponin within 24 hours of admission

Textbox 2. Exclusion criteria.

- pregnancy or breastfeeding
- impaired renal function (estimated glomerular filtration rate <30 ml/min/1.73 m²)
- contraindications to undergo magnetic resonance imaging (eg, cardiac pacemaker, implantable cardioverter-defibrillator, and cerebral clips)
- persistent or permanent atrial fibrillation (patients with paroxysmal atrial fibrillation will be included if they are in sinus rhythm at admission or during cardiac monitoring of the stroke unit)
- ST-elevation in electrocardiogram fulfilling criteria of myocardial ischemia
- history of cardiac intervention (eg, coronary artery bypass surgery or percutaneous coronary intervention) within the last 4 weeks

Depending on serial measurements of hs-cTn during the acute hospital stay ( assay characteristics: hs troponin T, Roche Elecsys, Gen 5; 99th percentile upper reference limit=14 ng/l; 10% coefficients of variation (CV) precision=13 ng/l; limit of detection=5 ng/l) and according to the fourth universal definition of MI, 3 groups are defined (Table 1) [4]. We aim to include 100 patients in each group. The cTn values are based on at least two blood exams: the first one at hospital admission and a control measurement within 24 hours after admission.

Table 1. Definition of the 3 groups based on patients' high-sensitivity cardiac troponin values.

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>hs-cTn values (URL(^b)=14 ng/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Normal hs-cTn levels</td>
<td>Both hs-cTn levels ≤URL</td>
</tr>
<tr>
<td>Group 2</td>
<td>Chronic myocardial injury (elevated but stable cTn levels)</td>
<td>At least one hs-cTn level &gt;URL but no rise/fall (&gt;20%) in serial measurements</td>
</tr>
<tr>
<td>Group 3</td>
<td>Acute myocardial injury (dynamic elevation)</td>
<td>At least one hs-cTn level &gt;URL and rise/fall (&gt;20%) in serial measurements^c</td>
</tr>
</tbody>
</table>

\(^{a}\)hs-cTn: high-sensitivity cardiac troponin.

\(^{b}\)URL: upper reference limit (=14 ng/l).

\(^{c}\)Or initial cTn value ≤URL and second value >URL+increase >50% URL (ie, 7 ng/l).

In addition to routine clinical procedures (refer to the Baseline Visit section), study patients receive a baseline assessment, an additional blood draw for biobanking, 3 Tesla (3T) cardiovascular magnetic resonance imaging (CMR), transthoracic echocardiography (TTE), and a 20-min high-resolution electrocardiogram (ECG) for a comprehensive assessment of cardiac autonomic function as well as a questionnaire testing cognitive function and the perception of stress. Furthermore, 3 and 12 months after discharge, patients will be followed up via structured telephone interviews for cardiovascular events and clinical outcomes (Figure 1).
Figure 1. Study procedure of the Cardiomyocyte injury following Acute Ischemic Stroke study. Patients with a confirmed diagnosis of acute ischemic stroke via magnetic resonance imaging within 48 hours of symptom onset are eligible for inclusion. Patients receive a baseline visit, transthoracic echocardiography, 20-min electrocardiogram recording, blood sampling for biobanking, and cognitive testing within the first 2 days after enrolment. 3T cardiovascular magnetic resonance imaging takes place 3-5 days after symptom onset. Telephonic follow-up for cardiovascular events and functional outcomes will be conducted after 3 and 12 months. CMR: cardiovascular magnetic resonance imaging; d: day; ECG: electrocardiogram; MoCA: Montreal-Cognitive-Assessment; PSS: Perceived Stress Scale; TTE: transthoracic echocardiography; y: year.

Participants
Patients with a diagnosis of AIS, defined by a diffusion-weighted imaging lesion on magnetic resonance imaging (MRI), and hospital admission within 48 hours of symptom onset are included in the study. The study is carried out at the Department of Neurology, Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany.

Baseline Visit
The baseline assessment of the study patients includes demographics, medical history, medication, and information about the current stroke (time of symptom onset, time of hospital admission, and treatment including thrombolysis or thrombectomy). Stroke severity is classified using the National Institutes of Health Scale Score. The degree of disability is assessed using the modified Rankin Scale score. The presence of chest pain and dyspnea at admission and before the event is documented. Cognitive function and the individual perception of stress will be assessed via 2 questionnaires: Perceived Stress Scale and Montreal-Cognitive-Assessment [23,24]. In addition, the results of routine diagnostic procedures and stroke unit monitoring (eg, vital signs, 12-lead ECG, laboratory results, cerebral computed tomography imaging/MRI, and ultrasound of the brain-supplying arteries) are recorded.

Cardiovascular MRI Protocol
Patients receive a 3T cardiovascular MRI (CMR). The examination is performed on a 3T MR scanner (Siemens Magnetom Prisma fit 3T, Siemens) using ECG for cardiac gating.

The detailed CMR protocol is depicted in Figure 2. Initially, for localizing, a half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequence is conducted. Second, to evaluate the morphology and function of the left ventricle (LV) and right ventricle (RV), steady-state free-precession cine images (SSFP) are acquired during repeated breath-holds. Data are obtained for 3 long axes (4-chamber [4Ch], 3-chamber [3Ch], and 2-chamber [2Ch] view) and RV (imaging parameters: repetition time [TR] 45.78 ms, echo time [TE] 1.43 ms, flip angle [FA] 80°, and slice thickness 6.0 mm) and short axes stack—after contrast media application—to cover the LV (imaging parameters: TR: 44.80 ms, TE: 1.4 ms, FA: 58°, and slice thickness 7.0 mm, no gap). Furthermore, after cine long axis, 3 cine short axes (base, middle, and apex) are conducted, serving as a base for mapping imaging (imaging parameters: TR: 44.80 ms, TE: 1.4 ms, FA: 58°, and slice thickness 7.0 mm). Motion-corrected T2 mapping is conducted using a fast low-angle shot (FLASH) gradient echo sequence in a 4Ch view and 3 short axis views (SAX) as basal, medial, and apical slices. T2 maps are based on images with T2 preparation times of 0/30/55 ms, slice thickness of 6.0 mm, TR of 251.49 ms, and TE of 1.32 ms.

Postcontrast imaging is performed after intravenous injection of 0.15 mmol/kg body weight Gadobutrol (Gadovist, Bayer Healthcare). Focal fibrosis imaging (late gadolinium enhancement [LGE]) is conducted 10 min after Gadobutrol application. LGE imaging is performed using a phase-sensitive inversion recovery sequence (PSIR) in the same slice position as cine imaging (4Ch, 3Ch, and 2Ch view; imaging parameters: TR: 750.0 ms, TE: 1.55 ms, FA: 20°, and slice thickness: 7.0 mm) as well as full coverage of the LV in a short axis package (imaging parameters: TR: 1002.4 ms, TE: 1.24 ms, FA: 55°, and slice thickness: 8.0 mm). TI was adapted to suppress the myocard.
Finally, for further myocardial tissue characterization, motion-corrected T1 mapping based on the Modified look-locker inversion recovery technique (MOLLI) using a 3-3-5 pattern is performed before and 15 min after contrast media application in 4Ch view and 3 short axes with basal, medial, and apical slices (imaging parameters: TR: 281.64 ms (4Ch) and 332.67 ms (SAX), TE: 1.12 ms, slice thickness: 6.0 mm, and Generalized Autocalibrating Partial Parallel Acquisition (GRAPPA) acceleration factor: 2).

Pseudonymized CMR data are transferred to the core Lab AG Kardiale MRT (Prof Dr J Schulz-Menger) at the Department of Cardiology, Charité Campus Buch (Berlin), for further analysis. Experienced readers (Society for Cardiovascular Magnetic Resonance level III) analyzing the MR data are blinded to the clinical data. The clinical results are provided to the study patient, and in case of pathological findings that require further diagnostics or treatment, the clinical results are provided to the patients’ treating physician.

**TTE Protocol**

Patients undergo TTE on the first day after enrollment. A second TTE for evaluating dynamic changes in cardiac function is attempted on the third to fifth day thereafter. Trained physicians and trained technicians conduct the examination using the ultrasonic device Vivid T8 (GE Healthcare). The focus of the examination is the left and right ventricular systolic as well as diastolic function and morphology. According to the guidelines of the American Society of Echocardiography, images are acquired using standard views [25]. The TTE protocol includes two-dimensional imaging, M-mode measurements, color Doppler imaging and spectral Doppler imaging (continuous-wave [CW], pulsed-wave [PW], and Doppler tissue imaging [DTI]), as well as strain imaging using a 2D-speckle-tracking technique. Systolic LV function will be defined according to the recommendations for cardiac chamber quantification by echocardiography in adults as normal range (left ventricular ejection fraction [LV EF] 52%-72% [male]/54%-74% [female]), mildly abnormal (42%-51% [male]/41%-53% [female]), moderately abnormal (30%-40%), and severely abnormal (<30%) [26]. Values of signs suggesting pathologic RV systolic function are defined as TAPSE (tricuspid annular plane systolic excursion) <17 mm and s’ velocity <9.5 cm/s [27]. In addition, diastolic function will be evaluated according to the criteria of the Heart Failure Association of the European Society of Cardiology [28]. An independent rater blinded to clinical information will evaluate the echocardiographic data.

**Autonomic ECG Markers**

In addition to routine 12-lead ECG at admission and stroke unit monitoring, included patients receive an additional 20-min high-resolution resting ECG during the first day after enrollment using the portable medilog AR4+ device (Schiller AG). The aim is to measure specific autonomic markers periodic repolarization dynamics (PRD) and deceleration capacity (DC), reflecting sympathetic and vagal components of cardiac autonomic function in addition to standard measures of heart rate variability (HRV) in time and frequency domain [29-31]. The 7 electrodes of the high-resolution ECG are applied according to the Frank lead configuration in the 3 orthogonal axes X, Y, and Z. The examination is performed under standardized conditions (supine position, patient is not allowed to talk or change the position during the recording). For analysis, the pseudonymized ECG data are transmitted to the core lab of the academic working group biosignal analysis (Prof Dr A Bauer) at the cardiology department of the Medical University of Innsbruck, Austria. Members of the working group analyzing the data are blinded to all clinical information.

**Biobanking**

The study protocol includes an additional blood examination for biobanking to allow future study of further potential mechanisms. Blood drawing takes place during the first day after enrollment and includes 2 EDTA (for both whole blood and plasma samples), 1 heparin, 1 coagulation sodium citrate, and 1 serum tube. Blood withdrawal, centrifugation, and processing will be conducted by a trained study nurse. Blood samples are transferred to the Central Biomaterial Bank Charité for management and storage. After processing, the stored samples consist of 5.7 mL of EDTA whole blood; 1.5 mL of citrate plasma; and 2 mL of EDTA plasma, heparinized plasma, and serum samples each. These samples will allow measurement of various potential biomarkers of interest. Dependent on further funding, we consider to determine biomarkers of cardiac injury and stress, proinflammatory markers, and markers of endothelial dysfunction (such as N-terminal B-type natriuretic peptide [NT-proBNP], midregional proatrial natriuretic peptide [MRproANP], Copeptin, interleukin-6, interleukin-1ß, Soluble suppression of tumorigenicity 2 [sST2], and monocyte chemoattractant protein-1 [MCP-1]). Furthermore, we consider exploring whether patients with signs of stroke-associated...
myocardial injury present distinct miRNA-pattern. Finally, the design allows future cooperation with other research groups.

**Follow-Up Telephone Interview**

A follow-up regarding major cardiovascular events takes place 3 and 12 months after enrollment via telephone interview and is conducted by a trained participant of the research group. A major cardiovascular event is defined as the occurrence of transient ischemic attack and ischemic stroke, intracranial hemorrhage, MI, coronary artery bypass surgery or percutaneous coronary intervention, new atrial fibrillation, hospitalization for heart failure, and death. The functional outcome is assessed using the modified Rankin Scale. In case of death, the date of death is recorded using information from registration offices. In the case of cardiovascular events, medical records will be requested from the treating physician/institution. Furthermore, Charité records will be screened for readmission or further treatment. In case of unclear loss to follow-up, mortality status will be retrieved from the residents’ registration office.

**Study Outcomes**

Our main hypothesis is that the development of stroke-associated myocardial injury in patients with AIS is based on a stroke-related interference in the CAN resulting in myocardial tissue alterations and dysfunction (ie, stroke-induced "myocardial stunning") [13]. Using a systemic and multimodal diagnostic approach, we aim to provide a detailed characterization of myocardial tissue, cardiac function, and autonomic cardiac regulation (Figure 3). Thus, outcome measures are primarily based on cardiac tissue characterization via CMR, functional assessment using TTE and CMR measurements, and values of specific autonomic ECG markers.Textbox 3 shows the detailed outcome measures. In summary, as we assume that patients with stroke-associated myocardial injury show a Takotsubo syndrome (TTS)/stress cardiomyopathy pattern of lesions in the myocardium, we will focus on the presence of wall motion abnormalities together with myocardial edema (T2 mapping) but without corresponding LGE in CMR [32,33]. Left ventricular dysfunction and wall motion abnormalities will be measured via cine imaging in CMR and TTE. As a correlate of chronic myocardial injury, we further assess myocardial fibrosis/scar via LGE, diffuse fibrosis via T1 mapping, and extracellular volume fraction (ECV%) [34]. To facilitate the differentiation between stroke-induced and coronary-mediated myocardial injury, we evaluate typical CMR signs suggesting a recent MI (ie, presence of co-occurring LGE and acute edema in CMR). Infarcted myocardium will be defined as a region with a mean signal intensity >5SDs relative to the remote uninjured myocardium on LGE images [35].

**Figure 3.** Diagnostic assessment of the Cardiomyocyte injury following Acute Ischemic Stroke study. Illustration of the target points of the multimodal diagnostic workup to provide a thorough phenotyping of patients with stroke-associated myocardial injury. cMRI: cerebral magnetic resonance imaging; ECG: electrocardiogram; MRI: magnetic resonance imaging; TTE: transthoracic echocardiography.
Textbox 3. Study endpoints.

<table>
<thead>
<tr>
<th>Primary outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Frequency of Takotsubo syndrome pattern on cardiovascular magnetic resonance imaging (CMR); consisting of wall motion abnormalities together with myocardial edema (T2 mapping) but without late gadolinium enhancement</td>
</tr>
<tr>
<td>• Frequency and extent of myocardial edema</td>
</tr>
<tr>
<td>• Frequency of recent myocardial infarction on CMR</td>
</tr>
<tr>
<td>• Frequency and extent of ischemic and nonischemic myocardial fibrosis according to late gadolinium enhancement imaging and according to extracellular volume fraction on T1 mapping</td>
</tr>
<tr>
<td>• Frequency of left ventricular dysfunction in CMR (ie, ejection fraction and end diastolic left ventricular volume)</td>
</tr>
<tr>
<td>• Frequency of impaired left ventricular systolic and diastolic function in the transthoracic echocardiography</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Frequency of pathologic values of Periodic Repolarization Dynamics (PRDs) and Deceleration Capacity (DC; PRD ≥ 7.5 deg²; DC ≤ 2.5 ms)</td>
</tr>
<tr>
<td>• Frequency of values corresponding to high perceived stress in the Perceived Stress Scale (values ranging from 27 to 40)</td>
</tr>
<tr>
<td>• Frequency of cardiovascular events after 3 and 12 months</td>
</tr>
<tr>
<td>• Functional outcome after 3 and 12 months assessed using the modified Rankin Scale.</td>
</tr>
</tbody>
</table>

Sample Size Calculation and Statistical Analysis

Regarding the primary hypothesis and based on the published literature, we expect a rate of acute myocardial edema on T2 mapping in CMR in approximately 15% of patients with acute myocardial injury [17,36]. In the comparison groups with no or chronic myocardial injury, we expect a significantly lower rate (approximately 2%) presenting with acute myocardial edema [37].

To show a significant difference between the groups (two-sided α = .05), a sample size of 48 patients per group is required to reach a power of 80% and 89 patients per group for a power of 90%. Taking into consideration that in previous studies, due to impaired compliance or technical problems, the complete protocol of CMR could be realized only in approximately 85% of the study patients, we aim to include approximately 100-105 patients in each group.

Group comparisons (when comparing between the 3 groups) of the primary and secondary outcome measures (frequencies of specific alterations in CMR, TTE, and ECG) will be conducted using the chi-square test for categorical variables and, in case of continuous variables, using one-way analysis of variance or Kruskal-Wallis test, as appropriate. When comparing 2 groups (group 3 vs group 1 or group 3 vs group 2), Student t test will be used to compare continuous data. Logistic regression analyses will be used to calculate odds ratios and 95% CI to examine the association between elevated hs-cTn levels and the presence of specific structural and functional cardiac alterations in CMR and TTE. Multiple regression analyses using backward selection will be used to identify factors associated with certain myocardial alterations or ECG findings.

Results

Screening started in January 2019. After the initial pilot phase, the first patient was enrolled in April 2019. We estimate a recruitment period of approximately 3 years to enroll 300 patients with the complete CMR protocol. At the time of submission, 107 patients had been included. The final results are expected in 2023.

Discussion

Overview

This prospective, observational CORONA-IS study aims to clarify the underlying pathobiology of stroke-associated myocardial injury. The observation that patients with acute, severe neurological events often develop cardiac complications is well known and has been described as SHS or brain-heart syndrome [13]. Although there are strong indicators, suggesting that a stroke-induced dysregulation of the CAN leads to functional and structural cardiac alterations, many aspects of the pathophysiology remain unknown, and so far, no diagnostic or therapeutic algorithms for the treatment of these patients are available. Therefore, the aim of the CORONA-IS study is to explore and clarify the pathway from the brain to the heart, focusing on the crucial role of the autonomic nervous system and the cardiac phenotype.

The first goal is to visualize downstream cardiac mechanisms using CMR and TTE. We expect stroke patients with acute myocardial injury to show a higher rate and a different pattern of myocardial edema than patients with normal cTn. More precisely, we expect a myocardial edema (in T2 mapping in CMR) with wall motion abnormalities but without LGE [36,38]. This combination of edema without LGE is also seen in TTS, a condition that is in turn associated with an increased sympathetic stimulation [39]. TTS typically occurs following an emotionally or physically triggering event, but it can also develop after an acute neurologic illness [40]. In addition, we aim to assess alterations suggesting an acute or recent MI in the different groups. So far, several studies have applied CMR in stroke patients but mostly as part of a diagnostic workup to determine possible cardioembolic etiology in cryptogenic stroke [41-43]. For example, the HEBRAS (HEart and BRain interfaces...
in Acute ischemic Stroke) study will determine whether an enhanced diagnostic MRI workup (including CMR) combined with prolonged Holter monitoring will increase the detection rate of pathologic cardiac findings in patients with AIS [44]. To date, myocardial tissue characterization in patients with stroke-associated myocardial injury has not been investigated via CMR.

Besides structural alterations of the myocardium, we further aim to clarify whether patients with AIS and stroke-associated myocardial injury show—especially transient—functional cardiac alterations. Cardiac dysfunctions, including wall motion abnormalities or reduced EF, are often seen in patients with ischemic stroke and other acute severe neurologic conditions [1,45,46]. Regarding our study population, we expect to see higher rates of changes in left ventricular systolic and diastolic functions in patients with dynamic troponin elevation.

The second aim of the study is to investigate the role of CAN in the development of stroke-associated myocardial injury. There are different ways to display the influence of CAN on the cardiovascular system. Invasive diagnostic methods with direct recording of neural activity are not feasible in clinical settings. Noninvasive methods include for instance measurement of baroreceptor sensitivity or HRV. Reduced HRV and impaired baroreceptor sensitivity are associated with higher stroke severity and worse clinical outcomes [47,48]. However, these diagnostic tools represent only the combined sympathetic and parasympathetic influence on the cardiovascular system. There is evidence that increased sympathetic nervous activity can lead to destabilization of the myocardial repolarization phase [49].

In the CORONA-IS study, we will use the novel ECG markers, PRD, and DC. PRD assesses rhythmic modulations of cardiac repolarization in the low-frequency spectral range (≤0.1 Hz) [31,50]. Experimental and clinical evidence suggests that these low-frequency alterations are caused by phasic efferent sympathetic activity. DC is an integral measure of deceleration-related oscillations of the heart rate and primarily reflects parasympathetic activity [51]. PRD alone and in combination with DC have been shown to be a strong and independent predictor of sudden cardiac death in patients with MI [30,31,52]. To date, these markers have not been investigated in patients with AIS. They could provide important information regarding the assumed dysfunction of the CAN causing stroke-associated myocardial injury. It has to be kept in mind that these noninvasive measures can only serve to display an association between altered autonomic cardiac control and the presence of myocardial injury in stroke patients. To show a direct causation, further studies with nonobservational designs will be necessary. As the clinical differentiation between concomitant MI and stroke-associated myocardial injury is difficult, we aim to investigate whether specific biomarkers can help distinguish between both conditions. Therefore, we conduct thorough biobanking to evaluate the role of various potential biomarkers.

Limitations

Some limitations of the study will need to be considered. First, as the aim of CORONA-IS is to investigate patients with stroke-associated myocardial injury (ie, SHS), it is necessary to avoid including patients with clearly coronary-mediated myocardial ischemia. Hence, patients with signs of a concomitant or recent MI (ie, typical alterations in the ECG, such as ST elevations or a new left bundle branch block, as well as a recent coronary artery bypass surgery or percutaneous coronary intervention) will be excluded. Second, as CMR and the assessment of autonomic ECG markers depend on a rhythmic heartbeat, patients with persistent or permanent atrial fibrillation will not be included, even though they may be prone to develop stroke-associated myocardial injury. Third, specific contraindications to undergo CMR (eg, certain metallic implants, claustrophobia, or physiologic constitution such as severe obesity or an inability to stay in the supine position) may lead to an underrepresentation of these patients in the study. To correct for potential selection bias in the final analysis, the screen log of the study will be analyzed at the end of data collection to assess whether the rate of excluded patients due to CMR contraindications differed among the 3 groups. Finally, considering the necessity of giving informed consent to participate in the CORONA-IS trial, patients with large infarctions and aphasia may also be underrepresented.

Conclusions

In summary, the CORONA-IS study aims to provide a deep phenotyping of patients with stroke-associated myocardial injury by using different diagnostic tools, such as 3T CMR, TTE, specific novel autonomic ECG markers, and different blood biomarkers. The goal of this prospective, observational study is to develop a better understanding of the characteristics and the pathophysiology of stroke-associated acute myocardial injury (SHS) to identify patients at risk and improve diagnostic and therapeutic procedures.

Acknowledgments

The authors would like to thank Kristin Simon and the Trial Team (Centrum für Schlaganfallforschung Berlin [CSB]) for their support in conducting this study. JS would like to thank the Corona foundation (Essen, Germany) for supporting the work of the research group Integrative Kardio-Neurologie.

Authors’ Contributions

The study is conceived by JS. JS, RG, HS, CN, JSM, and ME contributed to the design. RG, HS, SH, and EB are substantially contributing to the data acquisition. EB and JM contribute substantially to the CMR data analysis. AB created the technique and software of the autonomic ECG marker analysis performed in the study. HS wrote the manuscript and conceived the figures. All
authors contributed to the revision of the manuscript before submission for publication. All authors have read and approved the final manuscript.

Conflicts of Interest
ME received funding from Deutsche Forschungsgemeinschaft under Germany’s Excellence Strategy – EXC-2049 – 390688087, BMBF, DZNE, DZHK, EU, Corona Foundation, and Fondation Leducq. ME reports grants from Bayer and fees paid to the Charité from Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, Amgen, GSK, Sanofi, Covidien, Novartis, Pfizer, all outside the submitted work.

References


CAN: central autonomic nervous system
CMR: cardiovascular magnetic resonance imaging
CORONA-IS: Cardiomyocyte injury following Acute Ischemic Stroke
cTn: cardiac troponin
DC: deceleration capacity
ECG: electrocardiogram
EF: ejection fraction
FA: flip angle
HRV: heart rate variability
hs-cTn: high-sensitivity cTn
LGE: late Gadolinium enhancement
LV: left ventricle
MI: myocardial infarction
MRI: magnetic resonance imaging
PRD: periodic repolarization dynamics
RV: right ventricle
SAX: short axis view
SHS: stroke-heart syndrome
TTE: transthoracic echocardiography
TTS: Takotsubo syndrome

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Feasibility of a Web-Based Platform (Trial My App) to Efficiently Conduct Randomized Controlled Trials of mHealth Apps For Patients With Cardiovascular Risk Factors: Protocol For Evaluating an mHealth App for Hypertension

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Abstract

Background: Mobile health (mHealth) interventions can improve health by improving cardiovascular risk factors, but their adoption in care by physicians and patients is untapped. Few mHealth apps have been evaluated in clinical trials, and due to the fast pace of technological development, those previously evaluated are often outdated by the time trial results are available. Given the rapid pace of change in this field, it is not feasible to rigorously evaluate mHealth apps with current methodologies.

Objective: The overall aim of this pilot study was to test the feasibility of using a web research platform called Trial My App to conduct efficient and rigorous web-based randomized controlled trials (RCTs) of mHealth apps relevant to patients with cardiovascular risk factors by evaluating an app that targets hypertension.

Methods: For this study, 200 participants with suboptimally controlled hypertension will be recruited through advertisements in newsletters, media, and the internet, as well as through referrals from their health care providers. Screening, consent, randomization, and collection of patient-important health confidence and self-management ability outcomes will be conducted online through the Trial My App research platform. Participants will be randomized into 2 groups: 100 that will use an mHealth app for tracking hypertension and 100 that will be considered as an educational control. All participants will complete questionnaires at 0, 1, 3 and 6 months after enrolment. A substudy to validate the method of blood pressure readings and the consistency of data entered through Trial My App will be conducted with 40 participants.

Results: The development of the Trial My App web platform has been completed. The creation of survey instruments has been completed in collaboration with our patient partners and advisory board. Recruitment is expected to begin in the first quarter of 2021; data collection and analysis are expected to be completed approximately 1 year after study commencement. Results will
be disseminated through conferences and publications. The primary outcomes of this study include the feasibility of conducting an RCT using the Trial My App platform by reporting recruitment, retention, and completion statistics. We will validate app-entered data with a standard 7-day home blood pressure measurement method. Lastly, the pilot, nonblinded RCT will assess the effectiveness of the mHealth app in improving the control of hypertension compared with the control of hypertension in the educational control group.

**Conclusions:** This study will determine if it is feasible to use the Trial My App web-based platform to evaluate the effectiveness of mHealth apps for patients with cardiovascular risk factors. As more mHealth apps are evaluated in RCTs, patients will be able to select apps that meet their needs and physicians will be able to make evidence-based recommendations to their patients for apps aimed at improving cardiovascular health.

**Trial Registration:** ClinicalTrials.gov NCT04528654; https://clinicaltrials.gov/ct2/show/NCT04528654

**International Registered Report Identifier (IRRID):** PRR1-10.2196/26155


**KEYWORDS**
mHealth; mobile health; hypertension; app; patient-oriented; feasibility; cardiovascular disease; internet-administered; randomized controlled trial

**Introduction**

Smartphones provide continuous connection to the internet and can run sophisticated software apps. Globally, over 3.5 billion individuals own a smartphone [1]. The delivery of health care interventions via mobile phones is known as mobile health (mHealth). In 2017, 86% of the Canadians surveyed owned a smartphone or tablet and 78% downloaded mHealth and other types of apps to these devices [2]. Of the 66% of Canadians who indicated that they self-track at least one aspect of their health, 40% used electronic devices to do so and 32% reported using at least one mHealth app to monitor their health [2,3]. Other authors have reported that up to 58% of the smartphone users have downloaded an mHealth app [4] and 3.6 billion health apps were projected to be downloaded in 2017 [5]. Since smartphones are used to track health and are often continuously carried by users, mHealth apps allow for frequent data collection and feedback for behaviors that affect health, and interventions can be deployed to many users at a relatively low cost [6].

Health behaviors, including smoking, inactivity, and poor diet, are the major contributors to cardiovascular disease [7]. The American Heart Association has endorsed provider and patient self-management of cardiovascular disease risk factors as an effective form of secondary prevention [8]. Though the field of mHealth is in its infancy, early studies have shown that apps can improve health-related behaviors and reduce cardiovascular risk factors, largely through knowledge translation, by improving adherence to or by uptake of medications and behaviors that are known to be effective [9]. Randomized controlled trials (RCTs) report that apps can help patients lose weight [10-14], quit smoking [15], and increase physical activity [16]. An RCT of lifestyle-focused text messages reduced low-density lipoprotein cholesterol levels, systolic blood pressure, and BMI in patients with coronary heart disease [17], and a systematic review of RCTs of home blood pressure telemonitoring showed reduced systolic and diastolic blood pressure [18,19]. Thus, current data suggest that mHealth interventions can improve health by improving such cardiovascular risk factors, but their adoption in health care by physicians and patients is minimal. The 2014 National Physician Survey of licensed Canadian physicians reported that 83% did not recommend mobile apps to their patients, although 72% of the general practitioners and 53% of the specialists referred patients to websites and 50% used mobile apps such as e-textbooks or calculators in their practices [20]. We recently conducted a needs assessment survey of 113 physicians, which showed that over half of the physicians recommended apps to their patients despite their lack of clinical evidence. Many physicians in the survey indicated that they rely on personal opinions and patient recommendations to support their recommendations of apps despite wanting to choose apps that have a higher level of evidence such as RCTs or expert panel reviews. Our needs assessment also indicated that physicians do not recommend apps because they are not aware of them or do not have time to review their clinical efficacy. Without proper testing and evaluation, gaps in app development, including lack of expert involvement, poor user input validation, lack of evidence base, and poor quality of information, may pose clinical risks and safety harms to consumers [21]. With the growing interest in mHealth to monitor patient health, it is imperative that physicians stay informed and minimize their medical-legal risks by recommending apps with proven efficacy.

Despite this desire for better evidence, only a minority of the mHealth apps available in web-based app stores and commonly downloaded by patients have been evaluated in clinical trials, and due to the fast pace of technological development, those that have been evaluated are often outdated by the time trial results are available. Of the top 100 grossing health and fitness apps, researchers found that none had been formally evaluated in clinical studies [22]. Multiple reviews have highlighted the lack of quality research evidence on the efficacy of apps [9,23-25]. mHealth research has several unique challenges contributing to this problem. Chiefly, technology is rapidly progressing and equally rapid techniques for evaluating such technology are needed. Testing must be cost-efficient, given the limited funding for evaluating mHealth interventions compared with pharmacological interventions or medical devices [9]. These constraints limit the evidence base and the incorporation of apps in patient care.
The rapid proliferation of smartphone technology provides untapped potential to improve the efficient conduct of such research. Using internet-enabled devices to perform research can potentially (1) accelerate large-scale enrolment by contacting and screening potential participants who do not frequently interact with the health system through clinics or hospitals and (2) reduce costs and improve participation by allowing frequent and inexpensive data collection directly from participants. With the rapid development of internet-connected and smartphone-connected consumer devices that can collect biometric data, smartphones also have the potential to collect objective, real-time data directly from patients [26].

Methods

Overview

We have developed an innovative research approach using a web-based platform called Trial My App, which is designed to perform efficient trials of apps relevant to patients with cardiovascular risk factors. In our initial phase, we engaged an advisory board of patients to codevelop criteria for app and trial outcome selection, which will be used to support further deployment of Trial My App. The patients used apps for goal setting, decision-making, information sharing, and empowerment in managing their health. From these themes, we derived a series of survey questions to determine if an app was meeting these outcomes, and we included this survey in the pilot trial. Content analysis by the advisory board also indicated that patients considered a number of favorable technical factors when selecting their mobile apps: (1) relevant feedback on progress, (2) security, (3) low cost, (4) customizability, (5) usability, (6) information credibility, (7) multifunctional app integration, and (8) interdevice compatibility. The undesired features were as follows: (1) unreliable technology, (2) distraction, (3) collection of personal information, and (4) learning curve. These criteria were applied to shortlist apps for hypertension, and through discussion with the research team and patient partners, we identified Sphygmo BP as the intervention app for this pilot trial (Multimedia Appendix 1).

Sphygmo BP was created in partnership with the University of Alberta to help patients with hypertension to self-manage their blood pressure. The app tracks and averages blood pressure, glucose levels, weight, temperature, respiratory rate, and oxygen saturation. It also includes educational components to facilitate better patient awareness of management strategies for blood pressure and is designed to facilitate patient-physician communication through telemonitoring.

Objectives

The primary objective of the study is to test the feasibility of conducting an RCT of an mHealth hypertension-tracking app using the Trial My App platform. The secondary objective is to test if the use of the Sphygmo BP app reduces blood pressure in patients with suboptimally controlled hypertension when compared with the use of a website with information on hypertension. It would be valuable for patients and physicians to know whether the use of the app is likely to result in reductions in blood pressure that have been shown to reduce clinical outcomes.

Study Design

This is a pilot, nonblinded parallel-group RCT, comparing the use of a hypertension app versus an education control in participants with suboptimally controlled hypertension. Outcomes include feasibility, clinical, and patient-important endpoints.

Eligibility Criteria

The inclusion criteria are as follows: (1) age over 18 years, (2) diagnosis of hypertension, (3) interested in using an app for hypertension management, (4) access to a smartphone with internet connection, and (5) access to a blood pressure monitoring device (in home or community setting, eg, pharmacy). The exclusion criteria are as follows: (1) participant-reported blood pressure within target (target range for patients with diabetes is systolic blood pressure <130 mm Hg and diastolic blood pressure <80 mm Hg; for those without diabetes, target range is systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg according to Hypertension Canada guidelines [27]) within the 2 weeks prior to enrolment, (2) emergent hypertensive concerns (potential participants with systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥120 mm Hg will be advised to seek medical attention and will be excluded), (3) current use of a mobile app for hypertension management, (4) living outside of Canada, (5) pregnancy, and (6) unwillingness or inability to give informed consent.

Recruitment

The primary study site will be the Health Information Research Unit at McMaster University in Hamilton, Ontario. A combination of passive and active recruitment strategies will be used. A variety of recruitment materials will be distributed by a research assistant throughout the community and outpatient or specialty clinic waiting rooms. These materials include videos, papers, and web-based posters/postcards, emails, as well as posts advertising on social media. Social media recruitment on Facebook, Twitter, and Google Network will consist of general posts and targeted ads using Facebook Ads Manager. Partner newsletters and websites include Hamilton Academy of Medicine, McMaster Institute for Research on Aging, McMaster Okanagan Charter, and RSearch. We will also engage clinicians and their administrative staff within the McMaster Department of Medicine, Hamilton Health Sciences outpatient clinics, Queen Square Family Health, and other community, primary, and specialty clinics in Ontario to identify potential participants and invite them to register with Trial My App to determine if they want to participate in the trial. Snowball sampling through participants and personal networks may also be used. Interested candidates will be provided a link or a quick response code to access the website within the marketing materials. They could also contact our research assistant through a dedicated Trial My App email account if they prefer the initial contact by email or phone.

All trial stages, including screening, consent, randomization, and collection of clinical and patient-important outcomes data, will be performed virtually using the Trial My App platform. This phase includes a substudy to validate the web-based...
collection of patient data. Ethics approval of the substudy will be sought separately. Participants will be asked to register on the Trial My App site with an email and a password. The informed consent form is in Multimedia Appendix 2. Once they have electronically consented to using the web app, they will complete a user profile questionnaire and be screened for participation in the pilot trial in a subsequent survey. Multimedia Appendix 3 contains all user baseline, screening, and follow-up questionnaires. If participants meet inclusion criteria, they will be asked to electronically consent to take part in the pilot trial and provide data at 0, 1, 3, and 6 months. The participant flow is shown in Figure 1. The diagram of the app flow is shown in Figure 2.

**Figure 1.** Participant flow diagram. RCT: Randomized controlled trial; mHealth: mobile health.
Sample Size

In the feasibility study, at least 80% of the participants in each group who successfully complete the final questionnaire within 1 year of trial start will be considered as the primary feasibility outcome. To estimate a completion rate of 80% in each group within a margin of error of 8% and with a confidence interval of 95%, we estimated a sample size of at least 100 participants in each group, and 200 participants in total is required. With a sample size of 200 participants in total (ie, 100 per group), we will have 80% power to detect a reduction in blood pressure of 8 mm Hg, which is considered a minimally clinically important difference. Assuming an 18 mm Hg standard deviation in systolic blood pressure, to detect an 8 mm Hg difference between groups with a power of 80% and a type I error of 5%, we would ideally require 81 participants in each arm [28].

Accounting for a 20% dropout rate, we aim to enroll 100 participants in each arm. We recognize that the selected app may not result in such a large difference in the systolic blood pressure, but the calculation is to guide our recruitment targets. If a difference in the blood pressure is found, we will be able to inform patients and physicians that this app may have a major impact on clinical outcomes such as heart attack, stroke, and congestive heart failure.

Intervention

After screening and baseline questionnaires, participants will be randomized using a web-based blocked randomization list of 4, 6, or 8 block sizes and a 1:1 allocation ratio. The intervention group will be instructed to download the Sphygmo BP app via a link provided within the Trial My App. The control group will receive a link to the Heart and Stroke foundation website, which includes information on hypertension management and measuring blood pressure [29]. All participants are expected to continue to receive usual care by their physician, including any anti-hypertensive medication and lifestyle changes.

Data Collection

At 1, 3, and 6 months after enrollment into the RCT, Trial My App will send email reminders with a link to follow-up questionnaires to all participants to assess self-reported blood pressure and several patient-reported outcomes. Completing follow-up will be defined as answering the questionnaire within 7 days of receipt of the questionnaire notification via email. To encourage participation and reduce attrition, participants will receive a Can $10 (US $1=Can $1.27) electronic gift card for each completed assessment and an additional Can $10 gift card if they complete all 4 follow-up assessments.

Outcomes

Feasibility Outcomes

Our primary goal at this stage is to determine whether the Trial My App platform can be used to conduct RCTs evaluating mHealth apps by the ability to complete an adequately powered RCT of at least 80 participants in each group that successfully complete the study and the 6-month questionnaire within an arbitrarily defined reasonable time frame of 12 months. The remaining feasibility outcomes and associated indicators are shown in Table 1.
Table 1. Feasibility outcomes and indicators.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition</th>
<th>Indicator</th>
<th>Minimum required sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participation completion</td>
<td>Number of participants who successfully complete the final questionnaire</td>
<td>80% out of total randomized participants in each group</td>
<td>100 participants per group is needed to achieve a margin of error of 8% with a 95% confidence level</td>
</tr>
<tr>
<td>Eligibility</td>
<td>Proportion of participants who sign up that meet eligibility criteria</td>
<td>At least 50% of responses to baseline and screening questionnaires are eligible</td>
<td>200 participants in total to achieve a margin of error of 7% with a 95% CI</td>
</tr>
<tr>
<td>Recruitment</td>
<td>Number of eligible participants recruited and consented</td>
<td>At least 50% of target sample size of 200 randomized within 6 months</td>
<td>200 participants in total to achieve a margin of error of 7% with a 95% CI</td>
</tr>
<tr>
<td>Retention</td>
<td>Proportion of withdrawal and dropouts after recruitment</td>
<td>Less than 20% of the participants lost to 6-month follow-up</td>
<td>200 participants in total to achieve a margin of error of 5.5% with a 95% CI</td>
</tr>
<tr>
<td>Outcome acceptability</td>
<td>Follow-up questionnaire completion rates</td>
<td>70% of the questionnaires that are submitted within 7 days of notification reminder</td>
<td>200 participants in total to achieve a margin of error of 6.3% with a 95% CI</td>
</tr>
<tr>
<td>Intervention acceptability</td>
<td>Frequency of app usage in the intervention group</td>
<td>Answers to frequency of use and features used questions in follow-up questionnaires</td>
<td>N/A*</td>
</tr>
<tr>
<td>Appropriateness of data collection processes</td>
<td>Completeness of data</td>
<td>50% of the questionnaires completed and less than 20% of the missing response rates in each questionnaire</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*a: not applicable.

Pilot Efficacy Outcomes

The secondary objective of the RCT is to conduct a trial comparing the intervention hypertension app with a control group. The main outcome is clinical changes in blood pressure based on self-reported answers in the questionnaires. The remaining patient-reported outcomes and their associated indicators from baseline to 6 months are shown in Table 2.

Table 2. Efficacy outcomes and indicators.

<table>
<thead>
<tr>
<th>Outcome, definitions</th>
<th>Indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical assessment</td>
<td>Statistically significant difference in mean change in systolic blood pressure measurements (defined as P&lt;.05 using a Pearson test)</td>
</tr>
<tr>
<td>Difference in mean change in blood pressure from baseline to 6 months between groups</td>
<td>Blood pressure measurements compared to standard ranges</td>
</tr>
<tr>
<td>Proportion of patients at their recommended blood pressure</td>
<td></td>
</tr>
<tr>
<td>Self-management ability</td>
<td>H-SCALE* score and statistically significant correlations with blood pressure at 95% CI</td>
</tr>
<tr>
<td>Difference in mean change of self-managing behaviors</td>
<td></td>
</tr>
<tr>
<td>Difference in mean change in feelings of self-efficacy</td>
<td>Frequency distribution and mean of Health Confidence Score at 95% CI</td>
</tr>
<tr>
<td>Patient-reported outcomes</td>
<td>Agreeability with goal setting, decision making, sharing data, and empowerment statements in questionnaires developed from the advisory board themes (at 95% CI)</td>
</tr>
<tr>
<td>Descriptive analysis of patient-oriented experiences between groups at baseline and 6 months</td>
<td></td>
</tr>
</tbody>
</table>

*a: H-SCALE: Hypertension Self-Care Activity Level Effects.

Statistical Analysis

Descriptive statistical analysis will be performed on the data set using appropriate statistical methods to measure feasibility. Efficacy outcomes will be compared between the intervention and control groups by using logistic regression.

Ethics Approval

This study has received approval from the Hamilton Integrated Research Ethics Board, #8039. This is a minimal risk study and the subject matter is not likely to be distressing to participants. Participation in this study may be inconvenient, taking about 10-20 minutes to complete at each timepoint (baseline, 1, 3, and 6 months). In the event of possible emotional distress,
participants will be able to discontinue the use of the web app. Participant identifiers will be replaced with a code number; therefore, the data that researchers will access are not identifiable. As the intervention app is designed to track blood pressure to facilitate management and communication and participants will continue to receive usual care, no other harms are foreseen. Participants will be asked to complete an electronic consent form. The research team will have access to the final trial data set and ensure that all privacy policies are strictly maintained. Data will be securely stored on a MedStack server built into the Trial My App platform. MedStack is a health data privacy compliance automation platform that builds, measures, and actively manages compliance and provides secure, flexible, and single-tenant cloud infrastructure tailored to Trial My App. Medstack complies with Ontario’s Personal Health Information Privacy Act legislation. The information collected will be anonymized and encrypted before transferring to a secure server and firewall-protected network on a password-protected computer located at the Health Information Research Unit at McMaster University.

Results

Trial Progress

The development of the Trial My App web platform has been completed with a software developer and has undergone functionality and remote usability testing to uncover technical bugs and improve the design. The creation of survey instruments has been completed in collaboration with our patient partners and advisory board. Recruitment is expected to begin in the first quarter of 2021; data collection and analysis are expected to be completed approximately 1 year after study commencement. Dissemination of results will occur through conferences and publications.

Patient Engagement Strategy

Two patients with lived experience of cardiovascular diseases are collaborating as partners on the research team and additional patients serve on an advisory board overseeing the development of Trial My App. They have identified criteria for selecting apps to evaluate in future RCTs and aided in developing outcomes that are relevant to patients managing their cardiovascular risk factors with apps. Key contributions of our patient partners include joining bimonthly meetings with the research team to discuss project planning, developing questions for and taking part in the advisory group, testing the usability of Trial My App, reviewing and contributing to publications and other knowledge translation outputs, and contributing to production and circulation of recruitment materials. Any required training on these skills is provided by the research team.

Discussion

To our knowledge, this study is the first of its kind to create a web-based platform to conduct RCTs of mHealth apps for cardiovascular risk. A limitation of this methodology is the collection of self-report data as it is subject to several response biases, including social desirability, recall, or measurement error biases. The research team will include an additional substudy to measure the concordance of self-reported blood pressure measurements submitted via the Trial My App web app and the reference standard of 7-day average home blood pressure measurements [33]. A subgroup of participants will measure their blood pressure by using identical automatic home blood pressure monitoring devices 4 times daily for 1 week. The research team anticipates that participants will use the apps to varying degrees to help them manage their health, as they would normally; assessing these elements are beyond the scope of the study. The investigators expect that the pilot findings will demonstrate the feasibility of gathering valid patient-reported outcomes via web-based questionnaires that can be applied more broadly to other clinical studies. The findings of this trial may inform the evaluation of other mHealth apps for other conditions at a relatively low cost and more quickly than using traditional RCT methods. These results will also provide useful information for app developers who are interested in testing their apps for clinical effectiveness as well as patients and clinicians who are interested in incorporating effective mHealth apps into their care.

Acknowledgments

The project is funded by a grant from the Canadian Institutes of Health Research. The funding agency does not have any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Any opinions expressed are only those of the authors and do not necessarily represent the views of any of their affiliated institutions. The authors acknowledge the comments of the peer reviewers from the funding agency in improving the quality of this protocol.

Authors’ Contributions

CL, VB, and IG conceived the original study idea. CL is the principal investigator and drafted the manuscript. CL is the grant holder. VB, IG, JV, JDS, MG, and EV provided clinical and feasibility testing expertise. JM provided statistical expertise. MB and our advisory board provided help with the development of questionnaires and patient-relevant outcomes. ZM (ZLTechnovation) provided expertise in the development of the web platform. All authors contributed to the review of the study protocol and approved the final manuscript.
Conflicts of Interest

VB reports honoraria and an educational grant from Pfizer, honoraria from Bayer, and loan of devices from Apple for research purposes.

Multimedia Appendix 1
Description of the blood pressure management app used for the study.
[DOCX File, 508 KB - resprot_v10i2e26155_app1.docx]

Multimedia Appendix 2
Information and consent form.
[DOCX File, 64 KB - resprot_v10i2e26155_app2.docx]

Multimedia Appendix 3
Study instruments.
[PDF File (Adobe PDF File), 170 KB - resprot_v10i2e26155_app3.pdf]

Multimedia Appendix 4
Peer review report.
[PDF File (Adobe PDF File), 446 KB - resprot_v10i2e26155_app4.pdf]

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22. Meng Y, Wong SS. Trend and features of top 100 grossing health and fitness iPhone apps. FASEB J 2014;28.1_supplement.1028.5


Abbreviations

mHealth: mobile health
RCT: randomized controlled trial

https://www.researchprotocols.org/2021/2/e26155

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Corrigenda and Addenda

Correction: The Effect of Question Order on Outcomes in the Core Outcome Set for Brief Alcohol Interventions Among Online Help-Seekers: Protocol for a Factorial Randomized Trial

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Related Article:
Correction of: https://www.researchprotocols.org/2020/11/e24175
doi:10.2196/26578

In “The Effect of Question Order on Outcomes in the Core Outcome Set for Brief Alcohol Interventions Among Online Help-Seekers: Protocol for a Factorial Randomized Trial” (JMIR Res Protoc 2020;9(11):e24175) the authors noted one error. The protocol included an appendix which contains questionnaires which have been proposed to measure a core outcome set for brief alcohol interventions. However, rather than including their own appendix, the authors acknowledge that they should have referenced the Open Science Framework project which contains materials for the core outcome set.

The file labelled as Multimedia Appendix 1 in the originally published article has been removed from the corrected version. In-text references to this appendix have been replaced by a citation to Reference 18, which contains a link to the Open Science Framework project. Accordingly, the file labelled as Multimedia Appendix 2 in the originally published article has renamed Multimedia Appendix 1 in the corrected version. In-text references to Multimedia Appendix 2 have been changed to Multimedia Appendix 1. These changes affect the text in the following places:

In the Methods section, under “Trial Design and Interventions”, the sentence:

The 10 COS outcomes will be divided into 4 clusters (for details, please see Multimedia Appendix 1)

has been replaced by:

The 10 COS outcomes will be divided into 4 clusters [18]

Under “Setting and Participants”, the sentence:

An example of an advert is shown in Figure 1, and study information presented to individuals who click on the advert can be found in Multimedia Appendix 2.

has been changed to:

An example of an advert is shown in Figure 1, and study information presented to individuals who click on the advert can be found in Multimedia Appendix 1.

Likewise, the sentence:

Individuals will be asked to read the study information presented when the advert is clicked on and confirm that they are at least 18 years old and consent to take part in the trial (see Multimedia Appendix 2).

has been changed to:

Individuals will be asked to read the study information presented when the advert is clicked on and confirm that they are at least 18 years old and consent to take part in the trial (see Multimedia Appendix 1).

Under “Outcomes”, the sentence:
The primary outcomes are the 10 outcomes of the COS measured using the recommended questionnaires (Multimedia Appendix 1) has been changed to:

The primary outcomes are the 10 outcomes of the COS measured using the recommended questionnaires [18]
Correction: mHealth-Supported Delivery of an Evidence-Based Family Home-Visiting Intervention in Sierra Leone: Protocol for a Pilot Randomized Controlled Trial

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Related Article:
Correction of: https://www.researchprotocols.org/2021/2/e25443

In “mHealth-Supported Delivery of an Evidence-Based Family Home-Visiting Intervention in Sierra Leone: Protocol for a Pilot Randomized Controlled Trial” (JMIR Res Protoc 2021;10(2):e25443) the authors noted one error.

The name of the last author in the originally published paper was listed as “Theresa Betancourt”. This has been corrected to “Theresa S Betancourt”.

The correction will appear in the online version of the paper on the JMIR Publications website on February 4, 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.

Submitted 03.02.21; this is a non–peer-reviewed article; accepted 03.02.21; published 04.02.21.

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Abstract

Background: Data stewardship is an essential driver of research and clinical practice. Data collection, storage, access, sharing, and analytics are dependent on the proper and consistent use of data management principles among the investigators. Since 2016, the FAIR (findable, accessible, interoperable, and reusable) guiding principles for research data management have been resonating in scientific communities. Enabling data to be findable, accessible, interoperable, and reusable is currently believed to strengthen data sharing, reduce duplicated efforts, and move toward harmonization of data from heterogeneous unconnected data silos. FAIR initiatives and implementation trends are rising in different facets of scientific domains. It is important to understand the concepts and implementation practices of the FAIR data principles as applied to human health data by studying the flourishing initiatives and implementation lessons relevant to improved health research, particularly for data sharing during the coronavirus pandemic.

Objective: This paper aims to conduct a scoping review to identify concepts, approaches, implementation experiences, and lessons learned in FAIR initiatives in the health data domain.

Methods: The Arksey and O’Malley stage-based methodological framework for scoping reviews will be used for this review. PubMed, Web of Science, and Google Scholar will be searched to access relevant primary and grey publications. Articles written in English and published from 2014 onwards with FAIR principle concepts or practices in the health domain will be included. Duplication among the 3 data sources will be removed using a reference management software. The articles will then be exported to a systematic review management software. At least two independent authors will review the eligibility of each article based on defined inclusion and exclusion criteria. A pretested charting tool will be used to extract relevant information from the full-text papers. Qualitative thematic synthesis analysis methods will be employed by coding and developing themes. Themes will be derived from the research questions and contents in the included papers.

Results: The results will be reported using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews) reporting guidelines. We anticipate finalizing the manuscript for this work in 2021.

Conclusions: We believe comprehensive information about the FAIR data principles, initiatives, implementation practices, and lessons learned in the FAIRification process in the health domain is paramount to supporting both evidence-based clinical practice and research transparency in the era of big data and open research publishing.

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Introduction

Advancement in information communication technology is impacting the health ecosystem’s technological and analytical capabilities to store, curate, share, and analyze data from standard and nonstandard sources [1]. In the human health domain, big data may be obtained multidimensionally from records in health care facilities, biomedical research institutions, population surveys, surveillance, and patients [2]. Together, professional data management and big data analytics offer high-potential knowledge to transform health care delivery and life sciences research. The availability of data from numerous sources and advanced analytics promise to improve the prevention, diagnosis, and treatment of diseases and the well-being of individuals and societies [3]. However, health data are often stored in independent noncommunicating silos, where open data sharing remains a challenge [4].

Digitalization brings opportunities and concerns in health care data processing. Despite many potential benefits, it also poses potential threats, such as breaches of privacy, disinformation and misinformation, and cyberattacks [5]. There is a need to balance an individual’s rights to the protection of personal data from potential threats with the institutions’ needs to process these data. The EU General Data Protection Regulation (GDPR) informs this context. The recent reform in the GDPR focuses on the rights and freedoms of people and the establishment of rules for the processing of personal data [6]. The concerns about privacy and personal data protection resulted in reforms of the existing legislation in the European Union. The GDPR aims to reform the existing measures on the topic of personal data protection of EU citizens with a strong input on the rights and freedoms of people and the establishment of rules for the processing of personal data [7]. OpenEHR is a standard that embodies many principles of interoperable and secure software for electronic health records [8].

The European GDPR is the most recent data regulatory framework as of September 2020 and has implications on the ethical sharing of research data [9]. As the EU population continues to be more conscious about the data protection regulations for citizens’ sensitive personal data (eg, EU GDPR), patients and the general public are becoming more aware of the use of their personal data [10]. The principle of data minimization implies that personal data shall be adequate, relevant, and limited to only what is necessary in relation to the purposes for which they are processed [7].

Boeckhout et al [11] highlighted that the GDPR also ensures that the terms of data use, data subjects, and rights in further processing are clearly defined. It has been suggested that FAIR (findable, accessible, interoperable, and reusable) data and metadata standards could help facilitate compliance with the principle of data minimization by allowing for an assessment of which data to reuse based on an analysis of metadata [11].

Beyan et al [12] have shown that an enormous amount of usable health data is currently imprisoned inside the organizational territories of hospitals, clinics, and within patients’ devices due to ethical concerns and data protection rules. However, data reuse, even if secondary to data collection and first analysis, may drive more extensive and valuable new research directions than intended for the primary purpose [13]. In Germany, for example, the Medical Informatics Initiative aims to use clinical data to improve health research and facilitate the digitalization of medicine on a national scale [14]. France has also launched the Health Data Hub with similar aims [15]. Currently, researchers and stakeholders are working on infrastructure to support distributed and federated solutions to make the data, software, or digital objects smart in their original silos [12]. Europe would benefit from an integrated infrastructure in which data and computing services for big data can be easily shared and reused, and plans are underway to establish the Europe Research Area for this purpose [16]. Finally, funding agencies and open science advocates are insisting on adherence to open science policies and strategies to manage publicly funded research processes and outcomes [17]. The Health Research Board (HRB) of Ireland, for example, has put in place the HRB Policy on Management and Sharing of Research Data, which requires research to be open. This policy is applicable to data gathered and generated in whole or in part from HRB-funded research, starting from January 1, 2020.

The need for good data stewardship among different stakeholders in scientific research is the basis on which the FAIR data principles (findability, accessibility, interoperability, and reusability) were coined in 2014 by the FORCE11 (The Future of Research Communication and e-Scholarship) community [18,19]. These principles were formed to serve as guidance to achieve better research data stewardship practices in the life sciences [20]. They also serve as a set of widely applicable “permissive guidelines,” offering a basis for developing flexible community standards for the health data community [21]. Since research papers and data products are now being recognized as key outcomes of the scientific enterprise, various stakeholders in scientific and governmental institutions are increasing their efforts toward establishing more comprehensive plans for data management and stewardship [16,22]. Adherence to the FAIR principles has been shown to lead to a more transparent approach to data stewardship, which in turn contributes to the maximal use and reuse of data in the scientific community [23]. Consequently, adherence to the FAIR data principles is more frequently expected by researchers, publishers, funding agencies, and policy makers [24]. Achieving data FAIRness also enhances the discovery of, access to, integration of, and analysis of scholarly and scientific data [25].

In 2020, Vesteghem et al [26] outlined data sharing challenges that make data aggregation costlier and more labor intensive in precision oncology. Obstacles include legal issues that hinder data sharing between research groups, privacy issues, ethical issues, data storage issues, and system incompatibility issues [26]. Various initiatives have been launched to tackle these challenges by standardizing and facilitating the implementation of data pipelines [27,28]. Although the application of the FAIR...
data principles in data stewardship is a fairly new approach in health research, it has been shown to be instrumental in addressing these challenges in the field of precision oncology [14]. It has also been suggested that FAIR data may be useful in addressing the need to generate and share high-quality data to facilitate the World Health Organization elimination goals for neglected tropical diseases [29]. Much work has been conducted to implement the FAIR principles in other domains, such as computational workflows [30], food and nutrition [31], materials science [32], and oceanography [33].

The aims for conducting this work are to (1) provide an overview of applications of the FAIR data principles that are focused on health data research and (2) map out the existing evidence accordingly.

**Methods**

**Study Framework**

This scoping review will adopt the framework outlined by Arksey and O’Malley [34]. The authors will employ this method to quickly map key concepts underpinning the research area of interest and the main sources and types of evidence available. Our work is focused on an area that we have not seen being reviewed comprehensively. The framework includes the following steps: (1) identifying the research question; (2) identifying relevant studies; (3) selecting the studies; (4) charting the collected data; and (5) collating, summarizing, and reporting the results.

**Stage 1: Identifying the Research Questions**

We have already conducted a pilot overview of the existing literature as an informal desk review and literature exploration. This overview included published works in PubMed, Google Scholar, and Web of Science. The medical and public health research librarian used the FAIR data principles’ keywords to match medical subject headings (MeSH) used to tag PubMed peer-reviewed literature, along with combinations of terms used in clinical research, public health, health care, pharmacology, and patient data. Multimedia Appendix 1 enumerates the results of these advanced searches.

As part of the ongoing evidence synthesis from medical and human health research journal articles that used FAIR data markup, the bibliographies of key papers were scrutinized for other complementary publications, and those articles were added to the PubMed collections shared with the authors. Further, as the key FAIR data and health articles inspired new citations, often authored by similar consortia of writers or networks of researchers, the newer citing articles were added to the stage 1 collection to demonstrate possible progress in the field of shared or open medical data. Recurrent alerts were set up to capture newly published literature on PubMed, Google Scholar, and Web of Science (Multimedia Appendix 1). White papers, conference publications, guidelines, and other grey literature from the Google and Web of Science alerts were scrutinized and added to a Dropbox of publications for the principal researchers to review. Close examination of key references in bibliographies and citing articles to gauge the impact of FAIR shared data on ensuing research and health practice will be followed as part of the secondary analysis. Publications from 2020 focusing on open sharing of COVID-19 data will be of particular importance in gauging the impact of the FAIR principles on human health data in pandemics.

Our informal desk review has shown that many approaches used in the implementation of the FAIR data principles are applied to the life sciences domain [18]. We have also seen in the literature that there is indeed a growing interest in following the phases of the research life cycle when conducting research [35,36]. These findings resonate with the authors’ motivation to better understand the approaches used in the implementation of the FAIR data principles and the impact that these implementations may have on the way research in health will be conducted. These findings are also the basis on which the research questions were formulated. As we formulated the research questions, we decided that the review should only include works that show either an actual approach to implementing the FAIR data principles in the health domain or the recorded results of the implementation of the FAIR data principles. The review will exclude works that introduce or give an overview of the FAIR principles. Works that show the implementation of the principles in a domain other than health will also be excluded.

As we intend to conduct this exploratory review in an iterative manner, further refinement of the research questions may become necessary. Close examination of key references in bibliographies and citing articles to gauge the impact of shared data on ensuing research and health practice will be followed as part of the secondary analysis. All proposed refinements of the research questions and search methods will be scrutinized by the authors prior to approval. We will also provide comprehensive provenance information on changes in the protocol to be fully transparent.

**Objectives and Research Questions**

The general objective of this protocol is to conduct a scoping review to identify concepts, approaches, implementation experience, and lessons learned from the FAIR data principle initiatives in the health domain. The following research questions (RQs) have been formulated to meet the objective of the scoping review:

- RQ 1: What approaches are being used or piloted in the implementation of the FAIR data principles in the health data domain since the conception of these principles in 2014?
- RQ 2: What are the challenges and risks regarding the approaches used in the practical implementation of the FAIR data principles in the health data domain?
- RQ 3: What are the suggested concepts and approaches to mitigating the concerns of the implementation of the FAIR data principles in the health data domain?
- RQ 4: Which are the active public and private research and service networks involved in the implementation of the FAIR data principles in the health data domain?
- RQ 5: What are the reported outcomes for data sharing, data reuse, and research publication after the implementation of the FAIR data principles in the health data domain?
Stage 2: Identifying Relevant Studies

With the aid of an experienced research librarian, at least two researchers will identify relevant studies from 3 primary electronic databases: PubMed, Web of Science, and Google Scholar. In addition to those, relevant grey literature from existing networks, relevant organizations, and conferences as well as the reference lists from potential papers will be searched. The keywords for the scoping review search strategies have been categorized tentatively to terms related to the FAIR data principles, data sharing, and health. Although refinement of the selected MeSH terms are possible, open terms have been proposed for the construction of the search strategy of this protocol. The Boolean operators “AND” and “OR” will be used to guide the search strategy. The following descriptors and keywords and their combinations were used to construct the strategies: “open science,” “data collection,” “data provenance,” “open access publishing,” “data*,” “repositor*,” “registr*,” “pharma*,” “health*,” “research,” “biomedical research,” “data management,” “FAIR data principles,” “FAIR principles,” “FAIR guiding principles,” “Data steward*,” “Data management systems,” “findable,” “findability,” “access,” “accessibility,” “interoperable,” “interoperability,” “reusable,” “reusability” (Multimedia Appendix 1).

The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews) reporting guidelines will be used for reporting the findings [37]. The operational definition of “health” for this scoping review is based on the European Union’s 2018 General Data Protection Regulation and the health ecosystems components framed by the World Health Organization [2,6]. Accordingly, health data in this protocol are defined in the context of data from service and research practice in health services (clinical records, electronic health records and electronic medical records, prescribing, diagnostics, laboratory, insurance, disease surveillance, immunization records, public health reporting, vital statistics, registries, clinical trials, clinical research, and public health research).

As an inclusion criterion, we will consider literature published between January 1, 2014, and December 31, 2020. The start date in 2014 is chosen due to the fact that FAIR concept initiatives and official publications became first available in that year. Moreover, to be included as a potential paper, the literature needs to be published in English and include the scope of FAIR principle applications in the health domain (defined by the operational definition). Literature published before 2014, in a language other than English, and in domain areas other than health or the operational definition of health will be excluded. All search results from online databases and grey literature sources will be exported to a reference management software to eliminate duplications. Unique search results will be exported to a screening tool to facilitate an independent screening process for the potential papers.

Stage 3: Study Selection

Rayyan software (Qatar Computing Research Institute) has been chosen as the primary screening and data extraction tool to expedite the initial screening of abstracts and titles using a semiautomated process while incorporating a high level of usability. This software supports research teams in the easier exploration of literature searches within a shorter time as well as in sharing and comparing individual researchers’ decisions to include or exclude studies [38]. According to the inclusion and exclusion criteria, nonrelevant studies will be excluded from the study at this point. If the relevancy of the publication is unclear from the title or abstract, the reviewer will read the full publication to determine the eligibility of the publication. Any further changes to the search criteria to improve the search findings will be made at this stage as necessary. In the next step, the eligible publications screened in the first stage will be independently read in full by 2 researchers to further determine the relevance of the publication content to the research questions. When agreement cannot be reached during the initial screening and full-text screening stages, an independent researcher will be consulted. A PRISMA flow diagram will be generated to provide visual data for the selection process [37].

Stage 4: Data Charting

A data-charting form will be used by the reviewers to determine which variables to extract. The form is flexible for continuous updating in an iterative manner during the data-charting process, but any changes will be tracked. The descriptive analytical approach, as described by Arksey and O’Malley [34], will be employed in the data collection process. In this process, the researchers will critically examine the identified articles and documents that meet all of the eligibility criteria and extract the relevant data from each publication using the pretested charting form. The data will be organized into a chart with 2 main sections to describe the overview or summarized basic information of the publication (metadata) and the research questions based on our objectives (Table 1). Initially, 2 authors will independently extract data from the first 5 included studies using the data-charting form and meet to determine whether their approach to data extraction is consistent with the research question and purpose.
Table 1. Data-charting form.

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Section 1: Overview</strong></td>
<td></td>
</tr>
<tr>
<td>Publication type</td>
<td>Summary of the basic information of the publication</td>
</tr>
<tr>
<td>Country</td>
<td>Peer reviewed or grey literature</td>
</tr>
<tr>
<td>Objective</td>
<td>Name of the country or countries where the study took place or focused on</td>
</tr>
<tr>
<td>Methodology</td>
<td>Aim or objective of the publication</td>
</tr>
<tr>
<td>Study design and data management</td>
<td>The specific procedures or techniques used to identify, select, process, and analyze information</td>
</tr>
<tr>
<td>Setting of the study</td>
<td>Includes whether the researchers used quantitative, qualitative, or mixed-method approaches</td>
</tr>
<tr>
<td>Summarized results</td>
<td>The site in which the researcher conducted the study</td>
</tr>
<tr>
<td><strong>Section 2: Research questions</strong></td>
<td>A short summary of the findings</td>
</tr>
<tr>
<td>Suggested health care domain–specific FAIRificationa concepts and approaches</td>
<td>Includes the research questions and the date that the literature was published</td>
</tr>
<tr>
<td>FAIR implementation challenges, risks, and lessons learned</td>
<td>A description of FAIRification concepts and approaches in the health care domains</td>
</tr>
<tr>
<td>Active networks involved in the implementation of the FAIR data principles in the health domain</td>
<td>Encountered challenges or anticipated changes and lessons learned at different stages of FAIR data principle concept introduction, infrastructure implementation, and FAIRness evaluation</td>
</tr>
<tr>
<td>FAIRification reported outcomes</td>
<td>Dedicated networks of scientific communities, research institutions, repositories or data archives, consortia, funding agencies, and citizens who are actively engaged in advocating FAIR principle data stewardship in the health care domain</td>
</tr>
</tbody>
</table>

*aFAIR: findable, accessible, interoperable, reusable.*

**Stage 5: Collating, Summarizing, and Reporting the Results**

This scoping review focuses on the range of data curated and the health data research content identified. Quantitative assessment is limited to a count of the number of sources reporting a particular FAIR thematic issue or recommendation. After charting the relevant data from the studies in spreadsheets, the results will be collated and described using summary statistics, charts, figures, and common tools for analytical reinterpretation of the literature [34]. Mapping the themes derived from the research questions (FAIR implementation approaches, available FAIR networks, FAIR infrastructural and security challenges, etc) and other emerging themes during charting and analysis will be done. Moreover, the impact of the findings in relation to the overall study purpose, implications for future research, practice, and policy will be discussed accordingly [34]. The results will be reported using the PRISMA scoping review reporting guidelines [37].

**Results**

**Overview**

Our PubMed preliminary search has yielded 360 results (Multimedia Appendix 1). The search strategy we used to identify these results will be iteratively revised as we search for the results that best fit the inclusion criteria. We are also working on translating this MeSH search strategy into terms for alerts on the Google Scholar and Web of Science databases. The identification of relevant studies began in April 2020. Data extraction will be carried out in the last quarter of 2020. After completion of steps 1 to 3, we will use the title and abstract and a full-text review to determine the number of studies that meet the inclusion criteria. Full-text data extraction will also be used to confirm the number of studies included. Step 5 will involve summarizing and synthesizing the results. We anticipate finalizing the manuscript for this work by March 2021.

**Anticipated Outcomes**

This scoping review will provide insight on the initiatives, concepts, and implementation practices of FAIR data principles in health data stewardship. More specifically, it will allow for the exploration of (1) approaches being used or piloted for the implementation of the FAIR data principles in the health domain since the conception of these principles in 2014; (2) challenges, risks, lessons learned, and the suggested concepts and approaches to mitigate the concerns of implementation of the FAIR data principles in the health domain; (3) active research and service networks involved in the implementation of the FAIR data principles in the health domain; and (4) the reported
outcomes for data sharing, data reuse, and research publication after the implementation of the FAIR data principles in the health domain. We anticipate increases in data repositories demanding FAIR data markup suitable for artificial intelligence extraction of statistics. We also anticipate a greater demand for the implementation of the FAIR principles in light of the ongoing COVID-19 pandemic as well as more open research activities by public and private research and service networks involved in the implementation of the FAIR data principles in the health domain. An example of such an initiative is the Research Data Alliance [39].

The results will be used to generate recommendations on how to integrate the FAIR principles in health research, and we will generate different knowledge dissemination materials to share project results with various stakeholders, partners, associations, and networks who may benefit from this work.

**Discussion**

**Future Work**

The findings of this proposed work may be used to help identify the types of available evidence that support the incorporation of FAIR data principles in health. The results will also help to clarify key concepts in the scientific literature and serve as an introduction to how research on FAIR practices is conducted. This methodological framework will help us identify the overall state of research activities that explore initiatives, concepts, and implementation practices of FAIR data principles in health data stewardship. The outcome of this review can be used to further determine areas of research based on current gaps in the literature. Conducting this scoping review will also help determine the practicality and relevance of a full systematic review on the same issues by assessing the availability of literature. Similarly, gaps that still exist in the uptake and implementation of the FAIR principles in health research will also be identified as areas of further research. This work will be of interest to various stakeholders, including health and academic institutions, publishers, researchers, and funding agencies. In the wake of the COVID-19 pandemic, it is extremely critical that health data stewardship is practiced in a FAIR manner to facilitate the globally coordinated response [40]. As this work intends to include works that have been published up until December 31, 2020, we expect that we will gather a lot of information about what has been done worldwide regarding the FAIR data principles in health during this critical time. For purposes of the dissemination of the results of this work, the authors will consider submitting abstracts for presentation to various scientific forums and submit a manuscript for publication in a peer-reviewed journal.

**Ethics**

Once complete, this work will be published in a peer-reviewed journal, and the results will also be presented at appropriate forums or conferences. Ethical approval is not required, as only secondary data from published sources will be included in the scoping review and the public is not invited to participate in this work.

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**Conflicts of Interest**

None declared.

**Multimedia Appendix 1**

Supplementary Material.

[DOCX File, 20 KB - resprot_v10i2e22505_app1.docx ]

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Abbreviations

FAIR: findable, accessible, interoperable, and reusable
FORCE11: The Future of Research Communication and e-Scholarship
GPDR: General Data Protection Regulation
HRB: Health Research Board
MeSH: medical subject heading
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews
RQ: research question

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