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Adapting DIALOG+ in a School Setting—A Tool to Support Well-being and Resilience in Adolescents Living in Postconflict Areas During the COVID-19 Pandemic: Protocol for a Cluster Randomized Exploratory Study

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Abstract

Background: Colombia has a long history of an armed conflict that has severely affected communities with forced internal displacement and violence. Victims of violence and armed conflicts have higher rates of mental health disorders, and children and adolescents are particularly affected. However, the mental health needs of this population are often overlooked, especially in low- and middle-Income countries, where scarcity of resources exacerbates the problem that has been further compounded by the global COVID-19 pandemic. Thus, special attention should be paid to the development of interventions that target this population.

Objective: Our research aims to adapt an existing patient-centered digital intervention called DIALOG+ from a clinical setting to an educational setting using stakeholders' (teachers' and students') perspectives. We aim to evaluate the feasibility, acceptability, and estimated effect of implementing this intervention as a tool for the identification and mobilization of personal and social resources to mitigate the impact of social difficulties and to promote mental well-being.

Methods: We will conduct an exploratory mixed methods study in public schools of postconflict areas in Tolima, Colombia. The study consists of 3 phases: adaptation, exploration, and consolidation of the DIALOG+ tool. The adaptation phase will identify possible changes that the intervention requires on the basis of data from focus groups with teachers and students. The exploration phase will be an exploratory cluster randomized trial with teachers and school counselors to assess the acceptability, feasibility, and estimated effect of DIALOG+ for adolescents in school settings. Adolescents' data about mental health symptoms and wellness will be collected before and after DIALOG+ implementation. During this phase, teachers or counselors who were part of the intervention group will share their opinions through the think-aloud method. Lastly, the consolidation phase will consist of 2 focus groups with teachers and students to discuss their experiences and to understand acceptability.

Results: Study recruitment was completed in March 2022, and follow-up is anticipated to last through November 2022.

Conclusions: This exploratory study will evaluate the acceptability, feasibility, and estimated effect of DIALOG+ for adolescents in postconflict school settings in Colombia. The use of this technology-supported tool aims to support interactions between teachers or counselors and students and to provide an effective student-centered communication guide. This is an innovative approach in both the school and the postconflict contexts that could help improve the mental health and wellness of adolescents

in vulnerable zones in Colombia. Subsequent studies will be needed to evaluate the effectiveness of DIALOG+ in an educational context as a viable option to reduce the gap and inequities of mental health care access.

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KEYWORDS

mental health; mental disorder; eHealth; digital health; digital intervention; psychosocial intervention; resilience; psychological support; psychosocial well-being; mental well-being; resource-oriented approach; computer-mediated intervention; armed conflict; post-conflict; adolescent health; adolescent; adolescence; child; youth; school; teacher; student; acceptability; feasibility; vulnerable

Introduction

Colombia has traditionally been considered a violent country as a consequence of a long internal armed conflict, which has caused high rates of internal displacement and violence [1]. The number of individuals affected by this conflict has been estimated to approach 9.2 million [2], and despite the peace agreements signed in 2016, the problem persists in many regions of the country [3]. Worryingly, it is estimated that approximately 700,000 people have been affected by internal displacement ever since these agreements were reached [4].

One of the most affected regions in Colombia is the department of Tolima. Its central-western location in the country has made it a strategic corridor for trafficking of narcotics and the armed conflict [5]. Within Tolima, certain rural municipalities including Chaparral, Rioblanco, and Planadas have been particularly affected because of the connection they provide between the Pacific region of Colombia and the center of the country [6]. To prioritize these municipalities, which have been constantly subjected to armed conflict, in 2017, the Colombian government designated territories including Chaparral and Rioblanco as part of a Development Program with a Territorial Approach (PDET). This program aims to accelerate transformation and access to services for the people living in these regions [6,7].

The impact of armed conflict on the people inhabiting these regions is considerable, and international crises and wars have unveiled the consequences that these conditions have on mental health. Several studies demonstrate that individuals displaced by violence are at an increased risk of mental health disorders [3,8,9]. These include posttraumatic stress disorder (PTSD), depression, anxiety, and mood and sleep disorders, among others [10,11]. Even more concerning is the impact that these conflicts have on children and adolescents—a population that tends to have higher susceptibility to mental health conditions [12]. This may be due to the key psychological, biological, and social changes that characterize this period of life [13].

In Colombia, the National Mental Health Survey conducted in 2015, using screening scales, calculated a lifetime prevalence of any mental health disorder of 4.7% in children aged between 7 and 11 years and of 7.2% in adolescents aged 12 to 17 years [14]. Additionally, and in accordance with the worldwide trend, mental health conditions seem to be more prevalent in children and adolescents who have been subjected to internal displacement: the prevalence of an anxiety disorder and PTSD was higher (6.5% and 13.2%, respectively) in children (aged 7 to 11 years) who had experienced displacement due to violence, compared to an estimated prevalence of 1.8% for any anxiety disorder and 6.6% for PTSD in those who had not gone through the same experience [15]. Similarly, the 12- to 17-year-old group who had been displaced had a higher prevalence of any anxiety and depression disorders. Worryingly, the same significant difference in prevalence was reported for suicidal thoughts (19.8%) and suicide attempts (9.1%), which were higher in those who were displaced than in those who were unaffected (5.8% and 2.1%, respectively) [16].

Despite this clear problem and multiple issues, both governmental and individual barriers persist and impede an adequate response to the mental health needs of this vulnerable population [17]. It is estimated that in low- and middle-income countries, there is a significant shortage of mental health professionals such as child psychiatrists, accounting for only 0.1 per 100.000 population [18]. In Colombia, there are 1584 psychiatrists, which implies that there are 3 psychiatrists for every 100,000 inhabitants. However, psychiatrists are concentrated in the capital cities, which prevents access to people in rural areas owing to travel, time, and costs. This is an especially significant barrier to children and adolescents' access to mental health services [19]. Furthermore, the treatment gap (the gap between those requiring and receiving adequate treatment) for mental health disorders in children and adolescents of Central and South America has been estimated to be between 64% and 86%, which is an alarmingly high estimate [17]. According to the Pan American Health Organization, the treatment gap for any mental health disorder in Colombia is 86.1% and was the highest of all the countries in the Americas, followed by Guatemala (84.9%) and México (81.4%) and including the United States (58.9%) [20]. Moreover, the recent COVID-19 pandemic and its restrictions have exacerbated mental distress. Many studies have identified particular stressors that the COVID-19 isolation measures had on children and adolescents: lack of social contact, lack of personal space at home, separation from parents or caregivers, and concerns about academic and social impacts [21,22], all of which can lead to the development of anxiety or depressive disorders [23-25]. As in most countries, lockdown measures have been eased as of this writing, and it is important to keep investigating the impact that these restrictive measures had on children and to consider that the results obtained have to be viewed in a postquarantine context.

The aforementioned barriers, as well as the scarcity of funds allocated to mental health and the lack of education about and community knowledge of mental health issues, can perpetuate the stigma and false beliefs that surround mental health disorders. The lack of education and community knowledge highlights the essential role that teachers and school counselors can play in promoting mental health, well-being, and resilience in children and adolescents [26]. One of the biggest challenges in Colombia relates to the lack of personnel trained in mental health in schools in rural areas where there is usually only 1 counselor per school, who is not always a psychological professional. Interventions that aim to increase and inculcate skills concerning mental health in educators (such as courses or capacity development initiatives that focus on mental health) are fundamental [26,27].

Likewise, the school environment allows a constant interaction among teachers, counselors, and their students, which encourages the creation of a bond based on trust and provides the educators a chance to identify potential mental health disorders [28]. Therefore, an approach to mental health issues in the school setting can aid in overcoming some of the previously mentioned barriers [29].

To promote this approach in schools, we propose implementing an existing patient-centered digital intervention called DIALOG+, which was developed to facilitate the interaction between the clinician and patients with mental health issues [30-33]. This has primarily been implemented in mental health care settings. However, its adaptation outside of the clinical context and into the school context is innovative and has not been attempted before. Through this study, we aim to evaluate the feasibility of implementing DIALOG+ in the educational setting through teachers and counselors as a tool for the identification and mobilization of personal and social resources to mitigate the impact of social difficulties and to enhance quality of life.

Methods

DIALOG+

This tool is a resource-oriented, evidence-based intervention developed to facilitate the interaction between the clinician and patients with a mental health condition, allowing patients to actively participate in clinical meetings [34]. By structuring the interaction that takes place during routine clinical meetings, it encourages self-reflection and expression and empowers patients to improve their mental and social situation themselves. The intervention is supported by an app that can be installed on multiple electronic devices (eg, a tablet or cellphone).

During consultation, and with a patient-centered assessment, DIALOG+ invites the individual to evaluate their satisfaction with 8 life domains (mental health, physical health, work, accommodation, leisure activities, friends, relationship with family or partners, and personal safety) and 3 treatment domains (medication, practical help, and professional appointments). Each item is rated on a scale of 1=“totally dissatisfied” to 7=“totally satisfied,” and patients are asked if they would like additional help with that domain.

Scores are summarized and displayed on the app at subsequent meetings, allowing comparisons with previous scores from previous meetings. Physicians provide positive feedback on any domain showing improvement. This is followed by a 4-step, solution-focused approach to identify psychosocial resources to intervene in up to 3 domains, which the patient has identified as needing assistance to improve their quality of life. DIALOG+ is an evidence-based and effective intervention [32] that has shown to save up to £1345 (US $1510.80) per patient for the UK health system, mainly owing to fewer days of hospitalization among individuals receiving the intervention [30,35].

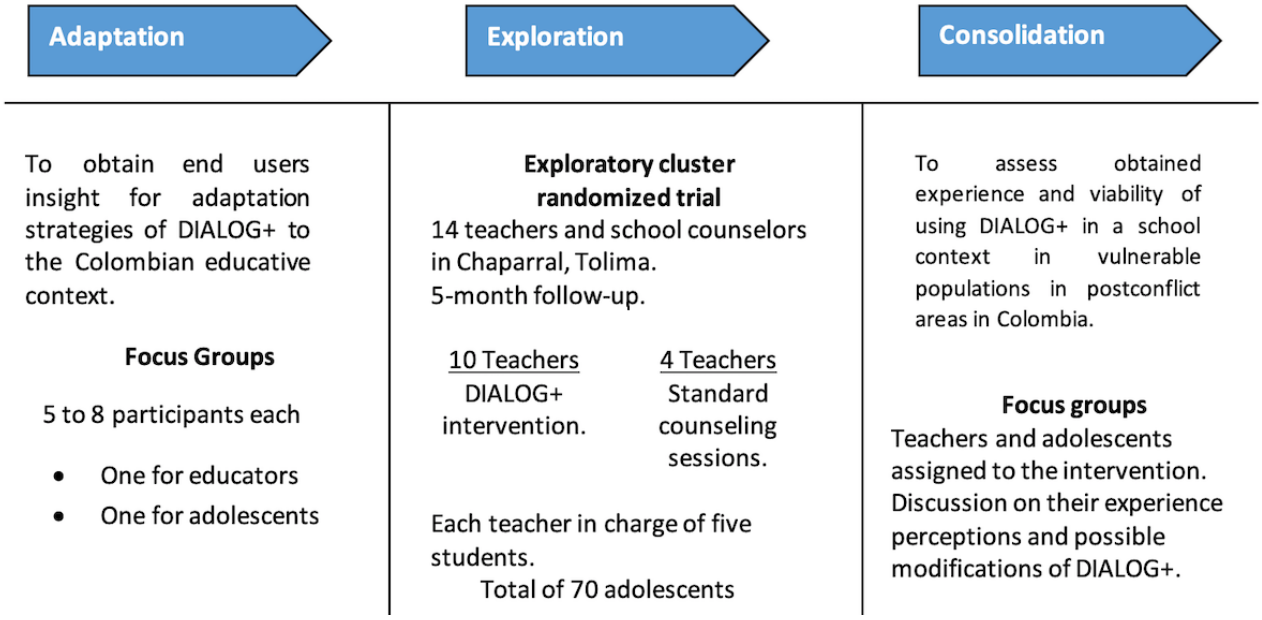
Intervention and Study Design

Overview

This study will adapt the DIALOG+ intervention through a mixed methods study. The quantitative component comprises an exploratory cluster randomized controlled trial. Initially, we will measure variables concerning mental health, resilience, quality of life, and social, and familiar functionality. These will be measured once more after the intervention stage. The qualitative component consists of conducting focus groups with teachers and students, and the think-aloud method [36] to obtain insights into the DIALOG+ adaptation in the school setting.

The study design has 3 phases: adaptation, exploration, and consolidation (Figure 1).

Figure 1. Adaptation, exploration, and consolidation phases.



Adaptation

We will present the existing DIALOG+ tool to teachers and adolescents between 12 and 18 years of age during focus groups to obtain end users' insights into adaptation strategies of DIALOG+ for the Colombian educative context. We will conduct one focus group with adolescents and another one with teachers and educators recruited through convenience sampling. Each focus group will include between 5 and 8 participants who will first sign an informed consent or assent form, and they will then be audio recorded for transcription and analysis. The information obtained in this phase will be key for adapting the intervention and for developing the following phase of the study.

Exploration

This phase consists of an exploratory cluster randomized trial with 14 teachers and school counselors in Chaparral, Tolima. This specific phase will assess the acceptability, feasibility, and estimated effect of applying the DIALOG+ intervention in school settings. Teachers and their students (who together form a cluster) will be randomly allocated to either the experimental (DIALOG+) group or an active control group (counseling as usual). Teachers will act as the unit of randomization with clustering by teacher to prevent contamination effects within the study. Accordingly, we will have 14 clusters comprising 1 teacher and 5 students each. The unit for randomization will be teachers in a ratio of 10:4 to the intervention and the control groups to maximize our data on feasibility and acceptability of the intervention, while providing some comparison data in the control group to estimate effect. Teachers will be recruited first, and they will then identify eligible students. Each teacher will invite 5 adolescents who they consider to be in need of counseling or additional support for presenting a personal, family, or social situation that is affecting their performance at school or their well-being. Students who accept the invitation will be asked to sign the assent and informed consent of their parents. Participants will be excluded from the study if they intend to change towns or school in the near future, or if they cannot participate for the full duration of the study. The teachers will determine the students with whom they will participate in the study. Teachers and their students (who together form a cluster), will be randomly allocated to either the experimental (DIALOG+) group or to an active control group (counseling as usual) by the study coordinator who is blinded to their identities. Each teacher or counselor will be in charge of 5 students during the intervention for a total of 70 students (Figure 2).

Prior to randomization, the selected adolescents will complete a self-administered baseline questionnaire to collect their sociodemographic data and measure symptoms of different mental health disorders.

The following 8 instruments will be used: the Family adaptability, partnership, growth, affection, and resolve; the Self-Reporting Questionnaire to assess mental health problems; the 8-item Patient Health Questionnaire depression scale, to assess depression symptoms; the Generalized Anxiety Disorder 7-item scale to assess anxiety symptoms; the PTSD Checklist to measure symptoms; the 25-item Connor Davidson Resilience Scale to measure resilience; the Rosenberg scale to measure self-esteem; and the Manchester Short Assessment of Quality of Life to measure quality of life.

These will be administered by research assistants who are blinded to the arm allocation and will be repeated at the end of the follow-up.

The experimental intervention will be carried out using DIALOG+, for which each teacher will be provided a tablet with the application and will undertake a 90-minute standardized training session on its use. DIALOG+ consists of 2 main parts: (1) a person-centered assessment, whereby the teachers invite the students to rate their satisfaction with different life domains, followed by (2) a 4-step approach based on the principles of solution-focused therapy [34]. Following review of the scores across the DIALOG scale, which includes comparing the current ratings with the ratings obtained from any previous session, up to 3 of the areas that are listed on the DIALOG scale are chosen

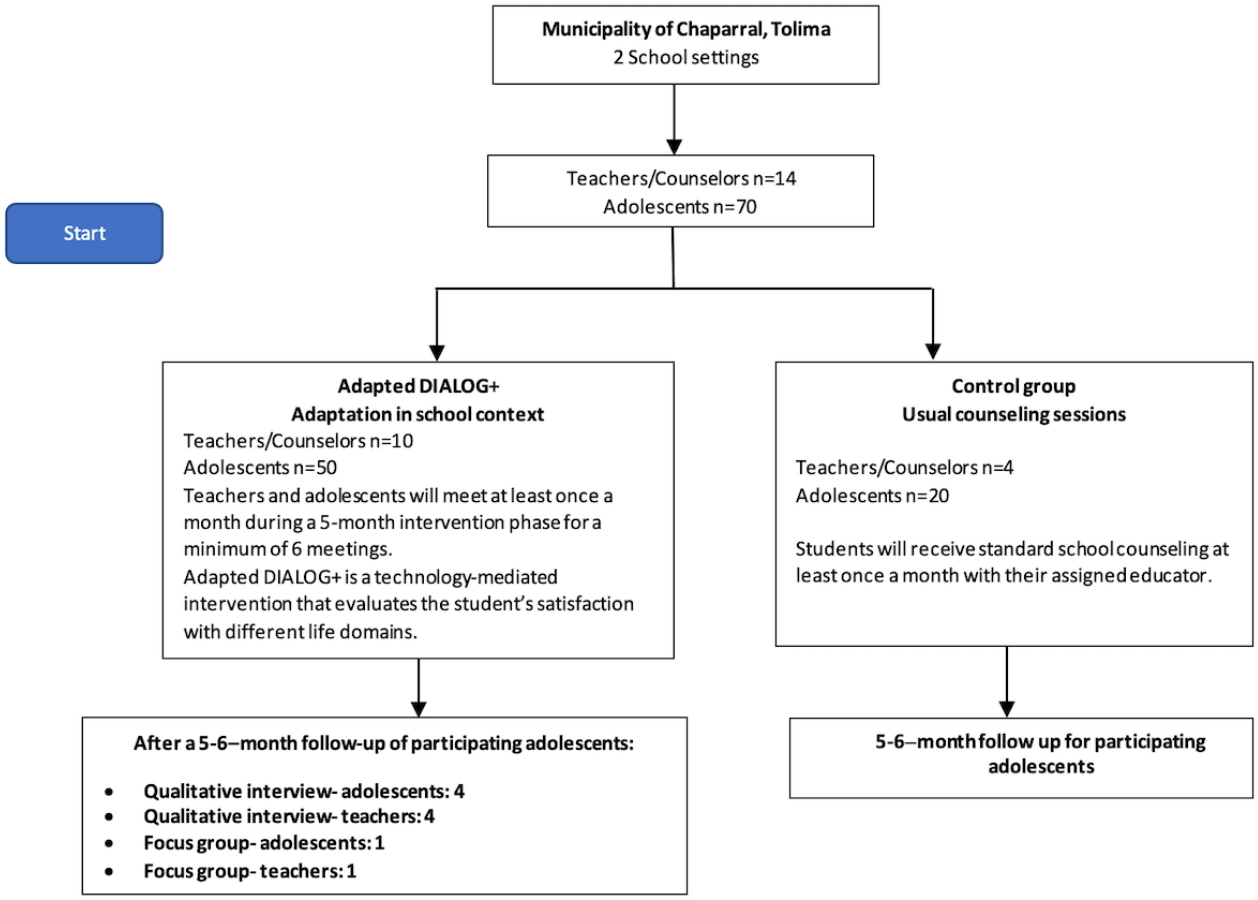
to be discussed in more detail. The 4-step solution-focused approach is used to structure the discussion to identify patients' resources and develop solutions to deal with the adolescents' concerns. At all times, the ratings on the scale are referred to in order to underpin and contextualize the discussion. Step 1, *Understanding*, elicits contextual information about the area under discussion and establishes what is working in that area. Step 2, *Looking Forward*, asks the adolescent to adopt a future perspective and think about the "best-case scenario" within that domain as well as the smallest improvement that can be made to incrementally move up the rating scale. Step 3, *Considering Options*, invites the adolescent to reflect on what he/she and others can do to improve their quality of life. Finally, step 4, *Agreeing on Actions*, summarizes the discussion, and a list of actions is generated and input into the application. Ultimately, the teacher and student together will develop an action plan comprising individual action items for each of the discussed areas to be completed before the next session.

The control arm's meetings will be conducted in the usual manner as teachers conduct counseling. Considering that most teachers have no training in the use of psychological techniques, it is not expected that they will be used.

During this phase, teachers who were assigned to the intervention group will record voice notes expressing their thoughts and opinions about the implementation process using the think-aloud method.

We will assess process measures to better understand the feasibility of the intervention for application in schools in Colombia. We will assess teacher and student recruitment and retention when reporting reasons for refusal and reasons for loss to follow-up, as well as the number and frequency of sessions conducted in both arms. Feasibility criteria will include recruitment of at least 85% of anticipated participants and a retention rate of at least 75%. We will also have at least two-thirds of sessions completed as planned (on average at least 4 sessions) as an additional feasibility criterion.

Figure 2. Exploratory cluster randomized trial.



Consolidation

Finally, we will conduct 2 focus groups with teachers and students. Both groups will be asked to discuss their experience, perceptions, and possible changes or modifications required to adapt DIALOG+ to the school setting. Adolescents will be asked if they perceived changes in their mental well-being. The data obtained will help assess the viability of using DIALOG+ in a school context in vulnerable populations in postconflict areas in Colombia.

Participants

This study will take place in one PDET the Chaparral municipality of Tolima. The recruitment of school teachers or counselors and adolescents will take place in 2 public schools through invitation. Each teacher will invite 5 adolescents whom they consider to be in need of counseling or additional support. Participants will be excluded from the study if they intend to change towns or schools in the near future or if they cannot participate for the full duration of the study.

All adolescents and their parents or guardians and teachers will be asked to provide assent and informed consent by signing an assent and informed consent form before any data collection begins. During the consent process, researchers will ensure that participants and parents or guardians are aware of their right to decline participation at any stage of the study and that withdrawing participation will not affect their rights or access to support.

Participants who withdraw from the study will be able to ask for their data to be removed from analysis. If a participant wishes to withdraw from the study, researchers will record the date of withdrawal and reasons for withdrawal (if provided).

Sample Size

Consistent with the exploratory study design, convenience sampling will be performed. We will conduct the study with 14 teachers and 70 students. The population of adolescents attending the 2 participating schools is 1494. However, the number of participating teachers is limited both by the number of teachers in each school and by the capacity of the teachers to conduct counseling. In each school, there is only one school counselor who is a psychology professional. The teachers who conduct counseling do so because they are interested in the well-being of their students. This is an exploratory study to determine whether it is feasible and acceptable to adapt DIALOG+ in the school setting, with quantitative outcomes to provide estimates of effects that could be used to design a larger study if our findings are supportive of this. Since this is an exploratory trial, the power to detect meaningful differences with statistical significance will be limited. With an intraclass correlation coefficient of 0.05, which we estimated from other studies we have conducted, the planned sample size will allow us to detect an effect size of 0.80 with 78% power and a smaller effect size of 0.5 with 40% power. In the case of the Manchester Short Assessment of Quality of Life, usually the primary outcome in DIALOG+ studies, an effect size of 0.80, would be equivalent to a change of approximately 6 points in total (eg, 1 point on a 7-point scale each on 6 out of 12 items, or 3 points each on 2 areas of life), which reflects a meaningful change.

Ethical Considerations

This protocol has been approved by the Pontificia Universidad Javeriana Faculty of Medicine Institutional Research and Ethics Committee (CIEI-0239-21) and the Queen Mary University of London Research Ethics Committee (ref QMERC20.226). The study was prospectively registered on the ISRCTN registry (ISRCTN14396374). Written assent from the adolescents with consent from the parents or guardians and written consent from the teachers will be obtained prior to any study procedures being conducted.

Measures

Data will be collected using a standardized paper-based case report form. At baseline and after the intervention phase of follow-up, we will collect sociodemographic data from both teachers and students and the previously mentioned mental health measures.

Data Management and Analysis

This study will use a mixed methods design. Quantitative and qualitative aspects will be triangulated in the overall evaluation of the intervention. Both qualitative and quantitative results will be presented for a global analysis of the intervention. For variables measured at 2 time points (baseline and 6-month follow-up), we will report measures of central tendency and dispersion in accordance with the data distribution, and significance tests will be performed. The analysis will use intention-to-treat analysis by including all students in the arm to which they were randomized, whether or not they received the intervention, and including all students in the analysis by using multiple imputation where outcomes are missing. To generate parameter estimates for any changes in outcomes for students using DIALOG+, mean differences (with standard deviations) and effect sizes over 2 time points (baseline and after the intervention period) will be calculated.

Qualitative data will be analyzed using thematic content analysis techniques [37]. Qualitative data will be analyzed using a framework of theoretical domains of behavioral change to understand the experience and issues concerning behavioral change that could be related to the acceptability and use of DIALOG+, as well as possibilities for improving implementation. This will serve to develop concrete plans for the implementation and evaluation of the strategy, such as clinical trials that evaluate the effectiveness of the tool with a larger number of participants. All interviews will be transcribed and analyzed using NVivo software [38], which creates graphical displays and facilitates thematic content analysis.

Dissemination

We will disseminate the knowledge generated to academic audiences through peer-reviewed publications in high-impact scientific journals in Spanish and English and international conference presentations. We will circulate the publications and presentations via the extensive networks of the investigators. Dissemination events will be conducted to ensure that the results are fed back to the Secretary of Education and to the principals of participating schools.

Results

Study recruitment was completed in March 2022, and follow-up is anticipated to last through November 2022. Each phase is expected to produce data that will facilitate the use of the DIALOG+ intervention for Colombian adolescents. The adaptation phase is expected to provide insight into the modifications that the digital intervention requires in terms of domains discussed and the interface. The exploration phase (the longest phase) is expected to provide the most information regarding the feasibility and acceptability of implementation. Baseline and follow-up questionnaires will provide evidence regarding acceptability and parameter estimates for the impact of the intervention. Lastly, the consolidation phase will report on the experiences and perceptions of the experience for both educators and adolescents.

Discussion

The increasing prevalence of mental health disorders in adolescents has highlighted the importance of addressing their mental health needs, particularly in contexts where they have experienced violence and armed conflict and especially after the COVID-19 pandemic. To meet these needs, an innovative approach is required where discussion regarding mental health cannot be limited only to a clinical and health care setting. Increasing the role that school settings have in mental health promotion may improve early identification and intervention with adolescents who are struggling [39]. This approach can also provide support to health security systems that face a challenge in bridging the gap and inequities in health care access such as the one in Colombia.

With this study, through different phases, we aim to assess the feasibility of implementing DIALOG+ in the school setting of adolescents in vulnerable areas in Colombia.

Studies on school-based interventions developed to increase adolescent well-being suggest that interventions may be successfully delivered by teachers and can improve outcomes by reducing symptomatology and encouraging early referral [39-41]. Studies on such interventions in adolescents exposed to conflict are scarce. Experiences with Palestinian adolescents of the Gaza strip revealed that school counseling sessions had a positive impact on PTSD symptomatology; however, no other mental health disorders were evaluated [42]. To the best of our knowledge, the adaptation and assessment of DIALOG+ as a resource-oriented and cost-effective intervention for school adolescents in postconflict Colombia provides an innovative approach in both the school and a postconflict context, and this tool is the first of its kind.

Studies on implementing DIALOG+ have been conducted in adults but no efforts have been undertaken to support the mental health skill development of teaching and counseling staff within the education system. The school setting is an area in which contact with children and adolescents with mental health problems is frequent and ongoing. Therefore, this is a critical and new area of research, as support from school staff is likely to be the only help that those children and adolescents will receive in this setting. Building capacities in teachers and school counselors through mental health courses would be complemented extraordinarily with a study that shows the effectiveness of DIALOG+ as a tool to be used by teachers and counselors in the school environment. This study proposes to evaluate feasibility and acceptability as a first step toward wider testing and possible implementation. It is important to highlight that the content and design of this study were developed through workshops, consultations, and discussions among the researchers, and considerations from local stakeholders with regard to the local context, health care priorities, and logistics of conducting this intervention were acknowledged.

The study design (an exploratory randomized controlled trial) may provide limited conclusions on the effectiveness of DIALOG+ owing to its small sample sizes, which provides limited statistical power and generalizability, but will still provide parameter estimates that will be essential for larger trials should these be indicated. However, we believe it will provide valuable insight into the feasibility and acceptability of DIALOG+ in the school environment, which is the primary aim of the study.

In conclusion, the results obtained in this study will provide valuable information regarding the feasibility of using a digital intervention such as DIALOG+ in the school setting to improve the well-being of vulnerable adolescents in Colombia. Experience obtained will deliver evidence that can be useful in other conflict-affected areas of the world and can provide insight into the usefulness of school-based interventions in general.

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Disclaimer

The opinions, results, and conclusions reported in this article are those of the authors and are independent from the Science, Technology and Innovation Projects (in Spanish, Ciencia, Tecnología e Innovación, CTeI) of National Affairs (Minciencias) and UK Economic and Social Research Council, UK Research and Innovation (ESRC, UKRI).

Authors' Contributions

CG-R and FvL are joint senior authors and led on the conceptualization of the study. The initial manuscript was prepared by MJS-S and MA-S. All authors edited and reviewed the manuscript and approved it for publication.

Conflicts of Interest

None declared.

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Abbreviations

PDET: Development Program with a Territorial Approach
PTSD: posttraumatic stress disorder

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Protocol

Using Normalization Process Theory to Evaluate an End-of-Life Pediatric Palliative Care Web-Based Training Program for Nurses: Protocol for a Randomized Controlled Trial

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Abstract

Background: Palliative care (PC) is a new concept in Iraq, and there is no training for health care specialists or the public. The lack of education and training programs is the most important barrier for PC. Intermediate training is needed for nurses who regularly manage patients with life-threatening diseases. The End-of-Life Nursing Education Consortium for pediatric palliative care (PPC) program is intended for nurses who are interested in providing care to children with life-limiting diseases or providing support in the event of an accident or unexpected death.

Objective: Our trial aims to evaluate the effect of a web-based training course, using the Normalization Process Theory. It focuses on how complex interventions become routinely embedded in practice and on training of a sample of academic nurses in the application of PPC in routine daily practice. It hypothesizes that nurses will be able to provide PC for the pediatric population after completing the training.

Methods: This is a multicenter, parallel, pragmatic trial in 5 health care settings spread across a single city in Babylon Province, Iraq. Participants will be recruited and stratified into 2 categories (critical care units and noncritical care units). In the experimental condition, 86 nurses will be trained in the application of PPC for 2 weeks through a web-based training course powered by the Relais Platform. The nurses will be invited to participate via email or instant messaging (WhatsApp, Telegram, or Viber). They will provide end-of-life care in addition to usual care to children and adolescents with life-limiting conditions. In the control condition, 86 nurses will continue usual care. The program's effectiveness will be assessed at the level of nurses only. We will compare baseline findings (before the intervention) with postintervention findings (after completing the training course). A further assessment will be performed 3 months after the course. As numerous unidentified factors can influence the effect of the training, we will perform a progressive evaluation to assess sample selection, application, and intervention value, as well as implementation difficulties. The nursing staff will not be blinded to the intervention, but will be blinded to the results.

Results: The study trial recruitment opened in July 2020. The first outcomes became available in December 2020.

Conclusions: The trial attempts to clarify the delivery of PC at the end of life through the implementation of a web-based training course among Iraqi nurses in the pediatric field. The study strengths include the usual practice setting, staff training, readiness of staff to participate in the study, and random allocation to the intervention. However, participants may drop out after being transferred to another department during the study period.

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KEYWORDS

End-of-Life Nursing Education Consortium for pediatric palliative care; implementation; Iraq; life-limiting illness; pediatric palliative care; pragmatic trial; web-based training

Introduction

Background

Pediatric palliative care (PPC) involves comprehensive active care for children and young adults, and is a globally recognized priority in caring for those with life-limiting conditions. This recognition was justified by high rates of mortality from cancer specifically. Therefore, skilled and supportive care, pain management, and symptom control at the end of life have been approved in palliative care (PC) [1,2].

Annually, 7 million families could benefit from PPC, but those in low- and middle-income countries seldom have such access, and there are approximately 1.2 million children globally, with more males than females. These children desperately need this type of care, and they eventually die from multiple and varied problems, such as birth defects, malnutrition-related diseases, meningitis, AIDS, and cardiovascular diseases [3].

Overall, in 2011, more than 29 million individuals from diverse age groups died from diseases demanding PC, with the largest proportion being adults rather than children less than 15 years old. Globally, each year, only 63 children out of 100,000 children less than 15 years old require PC at the end of life [3].

The World Health Organization presents PC as an integrated approach involving rules, opioid availability, facility obtainability, and educational platforms, as well as PC-certified activities, and it is available in 15 Eastern Mediterranean countries. Saudi Arabia has the maximum number of PC agendas, in addition to Iran and Lebanon, who award official licensing for their physicians, followed by Egypt and Jordan. Moreover, Oman, Jordan, Egypt, and Qatar have established other advanced programs for training (eg, master's degree or diploma). However, Iraq and occupied Palestinian areas have not started such care [4].

Some physicians and nurses have attended essential and advanced workshops on PC since 2011, but it is still considered a new concept in Iraq, with no formal policies or guidelines relating to this field, and the main contributors for introducing PC are nongovernmental organizations and the Middle East Cancer Consortium [4,5]. The number of qualified doctors is very low in Iraq, as trained physicians are fleeing the country owing to political instability. There are no degree programs in palliative medicine in Iraq, and a quarter of nurses are college graduates, with most lacking primary education [5]. No actual policy changes have been made in the previous 10 years. In the last 6 years, new opioids have been introduced, but they are not permissible for outpatients and not easily available. Only medics in government hospitals can recommend these opioids, and they are for oncology and not PC. Individual funders have started appealing to provide support for oral morphine if permitted by the Ministry of Health. There is no instant morphine or continued-release morphine. Injectable morphine, codeine, and transdermal fentanyl patches became available in 2013, which are obtained for free, and upgrading these drugs has been deliberated [4].

Obstacles to PC can be divided into the following 3 parts: (1) deficit of health policies in the sustenance of PC improvement; (2) nonexistence of significantly trained health care workers; and (3) reduced accessibility to essential PC drugs [6,7]. All these obstacles can be overcome by addressing the important barriers that are delaying PC development in Iraq, namely, lack of public responsiveness, lack of education, lack of training programs, inadequate opioid accessibility, and no identification of PC as a field [3,4].

The political state and uncertainty in the nation have played main roles in postponing the awareness of the public. Furthermore, the greatest pediatric care providers consider that PC is a good means to disclose that more cannot be done [4].

Regarding the present PC condition in many countries in the Middle East, there is a need for emphasis on the teaching of professional staff members and the presence of a consistent renewed expert committee that would be accountable for the development of the modern PC team [8-10].

PC education needs to be provided in English and is desired at the following 3 levels: (1) basic PC preparation for all health professionals; (2) intermediate training for those consistently working with patients having life-threatening illnesses; and (3) professional PC training for managing patients with more than routine symptom management needs [3].

Without appropriate end-of-life education, it is incredibly difficult for nurses to provide adequate care for related issues. Moreover, it is vital to balance education with attention to personal understanding and attitudes toward death and dying to provide students with opportunities to become knowledgeable about death and grief in order to deal with their feelings and to develop further [11]. From 1997 to 2000, there was a lack of overall nursing content related to end-of-life care and limited end-of-life content knowledge among nursing faculty [12,13]. Efforts are needed, including the development and dissemination of new educational recommendations, training materials, and educational requirements, at both the medical school and residency levels, as well as for nursing students and other health professionals, which should address the need for PC education [14].

To detect and address the limited knowledge of end-of-life care, researchers at the City of Hope National Medical Center in the United States conducted a 3-year project titled "Strengthening Nursing Education to Improve End-of-Life Care," which was supported by The Robert Wood Johnson Foundation. The project brought together professional nursing organizations, expert clinicians, and educators in palliative/hospice care to improve the curriculum in order to enhance nursing care at the end of

life. The project revealed chief insufficiencies in nursing education and its role in end-of-life care, and identified a lack of content in nursing text, insignificant content in the nursing curriculum, insufficient nursing faculty knowledge, and many other educational barriers that inhibit good nursing practice in this area [15-17].

"The End-of-Life Nursing Education Consortium-PPC (ELNEC-PPC)" project based on original training was intended to study the concern of nurses in providing care for life-threatening illnesses to children or for accidents or sudden death [18]. Perinatal and neonatal PC is one module [19]. The ELNEC-PPC train-the-trainer program is for 2.5 days, and those who complete the program will be able to actively share information and knowledge to other health care workers in clinical practice or nursing students in colleges. The first training module was started in 2003, and 8 nationwide train-the-trainer programs have been conducted with more than 700 nurses attending from varied pediatric locations across the United States and Canada.

Many children dying from life-threatening illnesses, such as congenital malformations, chromosomal abnormalities, accidents, low birth weight, and sudden infant death syndrome (50 out of every 100,000 children), could be provided PC services, but little consideration is given to reducing the suffering faced by children and their families [7,18].

Pediatric nurses are considered more occupied than any other health care professionals, and they have a distinctive opportunity to assess and address the needs of children who feel pain and die suddenly or shortly after birth, or die in utero (perinatal death), as well as the needs of their families. However, these nurses may have little knowledge about the principles of caring for terminally ill children with different conditions at different ages [20,21].

On the other hand, a problem might occur with the introduction of a new approach to supply and consolidate health care in practice, which is extensively adopted in health services, community health practice, and areas of social policy that have important health consequences, such as education, transport, and housing. The UK Medical Research Council's framework for designing and evaluating complex interventions recommends conducting a process evaluation in order to illuminate inconsistencies between predictable and detected outcomes to understand how context impacts outcomes, and to provide insights to assist implementation [22,23].

Previous reports [24-26] mentioned that a certain problematic translational gap continues to exist between demonstrating the positive impact of a complex health care intervention in a study environment and utilizing this intervention in routine daily practice. The Normalization Process Theory (NPT) [27] and its predecessor, the Normalization Process Model [28,29], provide a framework that conceptually helps in understanding and explaining the dynamic processes that can be encountered through the utilization of complex interventions and technological or organizational innovations.

Previous studies [30,31] specified 4 key analytical domains as nonlinear and mentioned that they cooperate energetically to afford broad enlightenment of implementation processes, which anticipate if participants do not understand, sustain, or consider an intervention valuable or compatible with their current work. The NPT was designed to be applied flexibly, can be used at one or more points in a qualitative study, and has been successfully used. Following the NPT [29,31], the process of implementing a complex intervention can be described and explained by employing the following 4 central theoretical constructs:

1. Coherence: The process and work of sense-making and comprehending that individuals and organizations perform, which promote or inhibit the embedding of a routine practice.
2. Cognitive participation: The process and work that individuals and organizations perform to enroll people to build relationships in a new practice.
3. Collective action: The work that individuals and organizations perform to enact a new practice. Collective action is primarily labeled as a normalization process model and contains 4 subcomponents ("contextual integration," "relational integration," "interactional workability," and "skill set workability").
4. Reflexive monitoring: The work inherent to the formal and informal appraisal of a new practice to measure the benefits and drawbacks, which can develop users' knowledge of the effects of a practice.

The NPT has become a widely used theory for analyzing the implementation of complex interventions and has previously been applied to a wide range of health topics and empirical settings, including chronic health care, maternity care, e-learning, and telemedicine. There have been 8 studies in the eHealth and telehealth care fields and 21 studies in several other health care fields, which entirely concluded that the NPT is a complete and valuable model to drive the process of implementation in the setting of a health facility [31].

A quantitative design in a PC health context has not yet confirmed the validity of the NPT model. The NPT tool Normalization Measure Development (NoMAD) [32] has newly been established for use in quantitative research. Similar to the Conceptual Model of Implementation Research [33], the elements are formulated to feature at application with hindsight. Besides, the customization of the NoMAD tool across several contexts is unclear, and this restricts its practical usage in selected settings. For example, a single element of the NoMAD tool tests whether "sufficient resources are obtainable to maintain the intervention" [32]. Nevertheless, to our knowledge, no NPT studies have concentrated on evaluating a web-based training program in PPC at the end of life for nursing interventions in hospital settings.

Training has been recognized as a key implementation approach for enlightening provider knowledge and skills, with an interest in the use of web-based training methods [34,35]. The indication is accumulating that web-based training can be a working educational instrument aimed at bringing and appraising curricular content through numerous organizations and training levels. With high-speed internet access and the universal presence of computers in homes and clinics, health care

professionals can effortlessly access web-based resources regardless of their settings and can access resources at periods that do not overlap with their clinical tasks or responsibilities [36].

The original policy for providing consistent behavioral interventions in a series of situations involves web-based interventions, which provide the ability to access behavioral maintenance at any time, and result in greater confidence and lower cost compared with clinician-delivered interventions and old-fashioned face-to-face training methods [35,37].

Survey and qualitative studies mentioned that end-of-life care research is feasible and ethical, but funding of end-of-life care research is poor [38,39]. Thus, randomized trials of end-of-life care treatments and services are uncommon, and are often limited by poor enrollment, high attrition, unfairness, confusion, and small samples [40,41].

Specifically, pragmatic multicenter randomized controlled trials (RCTs) are recommended for the evaluation of complex health care interventions to enrich enrollment and broadcasting, and increase the external validity of trial results [42]. Nevertheless, pragmatic RCTs are intended to evaluate treatments in real-world (as opposed to idealistic) conditions, directly enlightening decision-making by patients, providers, and health care policymakers [43].

Comparators

Comparators are often used to decide the work level of an intervention related to a clinically relevant substitute. The choice of the comparator (control group) is always a serious decision in a clinical trial, which has the following major purpose: to allow the differentiation of patient outcomes (for example, changes in symptoms, signs, or other morbidities) triggered by the test treatment from outcomes caused by other factors, such as the natural advancement of the disease, observer or patient potentials, or other treatments. The comparator experience helps identify outcomes when patients do not use the test treatment or when they use a different treatment [44].

The present knowledge regarding the absolute value of anticipated experimental and control interventions is considered as one of the factors that regulate the appropriate choice of a comparator for a trial [45]. The research question type is the main ideal comparator determining factor. Significant comparators are those that involve existing clinical or public health services or facilities (eg, usual care or standard care), other implementations (eg, a firm evidence-based practice intervention by way of a comparator aimed at an intervention that is up to date), and clinically pertinent variations in trial implementation (for instance, similar interventions employing an alternate approach, eg, a face-to-face intervention in studies assessing a telehealth intervention) [46].

The pragmatic model intended for the selection of comparators allows investigators to choose clinically important comparators instead of nonnatural comparators that are unlikely to continually be used in clinical practice. The pragmatic model provides a way to resolve the numerous incongruities and influences related to comparators that are used in intervention trials [46].

For this trial, typical care is the comparator of choice, which is considered as a treatment or service that is consistently used, and it is provided after experimental members have joined. It often differs across individuals and settings, and in some trials, it may be increased or decreased for trial participants [46]. According to a previous report [47], customary care is the favorite comparator among researchers. It has been substituted as a comparator or has been a constituent of the comparator in 99 (49.5%) studies, and often appears under numerous synonymous terms (eg, standard treatment, care, as usual, standard care, treatment as usual, and standard of care). However, a previous report [48] stated that it may vary considerably between centers and countries confounding comparator choice. Using clinical guidelines to define usual care can help standardize comparator treatments; conversely, this may decrease the applicability of the results to actual settings.

Hereafter, the selection of typical care for this trial follows Clinical Practice Guideline recommendations, as well as the organized appraisal of significant literature that appears to be related to PC services, which are not accessible to pediatric patients in Iraq owing to deficiency of knowledge and training among health care professionals or limited care supply [4,10,45]. The trial aims to explain the provision of PC at the end of life through the implementation of the ELNEC course as a web-based training program, using the NPT. Its emphasis is on the complexity of interventions, which are routinely embedded in practice. In addition, the trial aims to identify the changes implemented by participant nurses in their clinical practice after participating in the web-based training program to provide PC alongside usual care (intervention group) versus usual care only (control group) for children with life-limiting conditions or in the case of accidents or sudden death at the end of life. Finally, we want to provide findings that will assist in the interpretation of the trial results.

Objectives

Primary Objective

The primary objectives are as follows: (1) to hold a short ELNEC-PPC web-based training program at selected Hillah city hospitals in Iraq by July 2020, and (2) to evaluate the impact and effectiveness of this project through the NPT at the beginning of the web-based training course, and 2 weeks and 3 months after the end of the web-based training course, define PC advocacy activities, and implement the principles found in the ELNEC-PPC web-based training program at selected Hillah city hospitals in Iraq by August 2020.

Secondary Objective

The secondary objective is to monitor participants for 3 months after the web-based training program in an attempt to raise their PPC knowledge to improve their self-efficacy levels and attitudes toward PPC at selected Hillah city hospitals in Iraq by August 2020.

Methods

Trial Design

This study is designed as a multicenter, investigator-blinded, parallel, 3-month, pragmatic, 2-arm, superiority (provision of PPC with usual care is superior to usual care only) RCT, in which different units from multiple hospitals are stratified and randomized. Randomization will be performed as block randomization with 1:1 allocation, and it will be conducted according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The CONSORT statement is a guideline designed to improve the transparency and quality of the reporting of randomized trials [49,50].

Study Setting

The trial will take place in selected Hillah city hospitals, which are local government organizations that have various pediatric and adult sections. In Iraq, there are 273 public hospitals spread all over the country [51]. Hillah city in Babylon province has 4 hospitals and 1 Babylon Oncology Center. The recruitment of participants will be conducted at the following 5 locations: Imam Sadiq Teaching Hospital (general hospital) with 492 beds, Babylon Maternity and Children Teaching Hospital (obstetric and pediatrics hospital) with 323 beds, Morgan Teaching Hospital (specialized center for tertiary health care), Al-Noor Hospital for Children (pediatrics hospital), and Babylon Oncology Center [52].

Participants will be recruited and stratified into the following groups: (1) critical care units (1 artificial kidney unit, 1 resuscitation emergency unit, 1 catheterization unit, 2 children's emergency units, 1 emergency department, 1 maternity emergency unit, 1 morning resuscitation unit, 1 operation room, and 1 pediatric surgery unit); and (2) noncritical care units (1 blood disease unit, 1 chemo injection unit, 1 health insulation unit, 1 private suite, and 5 pediatric lobby units). Staff in the selected hospitals are not employed in 2 areas at the same time, and pediatric patients with several diagnostic classifications are managed and provided usual care. Recruitment for this study started in July 2020. There is a 2-year outline plan for the research, with likely changes along with primary analysis outcomes.

Inclusion and Exclusion Criteria

The study will include nurses who (1) have been employed by Imam Sadiq Teaching Hospital, Babylon Maternity and Children Teaching Hospital, Al-Noor Hospital for Children, Morgan Teaching Hospital, and Babylon Oncology Center; (2) have completed their bachelor's degree and have a master's or doctorate degree in nursing sciences; (3) have been working for at least 3 months and are not expected to be moved to another internal unit during the research period (including morning and evening shifts); (4) provide nursing care for both male and female hospitalized patients aged ≤18 years; (5) use a computer (desktop or laptop) with access to the internet at home or work (phone line or internet access), or use a smartphone (Android 6.0+ or iOS 11.0+) with internet access (Wi-Fi or mobile data) to join the online training course; and (6) have a working email address or a working mobile number, and have access to a computer or smartphone with internet access to complete questionnaires in a web browser.

The study will exclude nurses who (1) are not interested; (2) are not employed for at least 3 months; (3) work in units other than the selected units; and (4) are enrolled in another experimental trial.

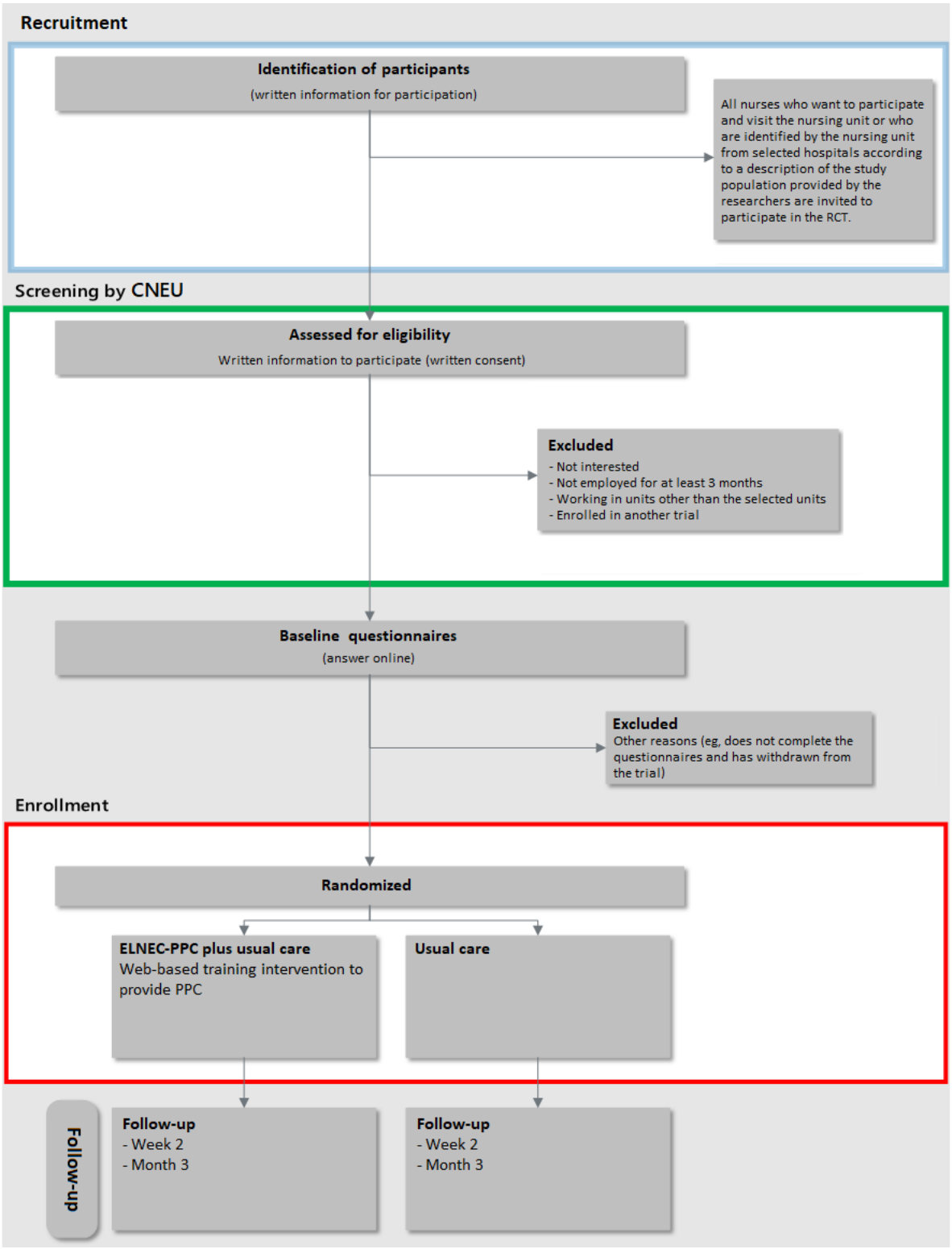
The evaluation of whether the exclusion criteria are met is performed by the investigator during the recruitment phase or according to the participant's responses during the interview.

Screening for Eligibility and Enrollment

The recruitment period is planned to start in July 2020. A total of 172 participants will be recruited in the RCT. Of these, 46.5% (n=80) will be recruited from Imam Sadiq Teaching Hospital, 26.2% (n=45) will be recruited from Babylon Maternity and Children Teaching Hospital, 7.6% (n=13) will be recruited from Morgan Teaching Hospital, 16.3% (n=28) will be recruited from Al-Noor Hospital for Children, and 3.5% (n=6) will be recruited from Babylon Oncology Center. Collaborations will be established with the selected hospitals to facilitate recruitment. The number of participants needed to ensure a sufficient recruitment rate has been determined (see the sample size section).

The recruitment process is outlined in Figure 1. The main investigator will submit the official approval form for conducting the research at the selected hospitals (Multimedia Appendix 1), and the approval form for the training course (Multimedia Appendix 2 and Multimedia Appendix 3), which will be hosted by the Continuing Nursing Education Unit (CNEU) at the Faculty of Nursing.

Figure 1. Participant flow through the trial. CNEU: Continuing Nursing Education Unit; ELNEC: End-of-Life Nursing Education Consortium; PPC: pediatric palliative care; RCT: randomized controlled trial.



Eligible nurses will be invited to participate in the trial by the CNEU team in the selected settings. The unit will refer potentially eligible participants depending on a quick eligibility explanation that the main investigator submits to the unit. The documents are as follows:

1. Nomination form for the training course (Multimedia Appendix 4) for recruitment: Each participant will fill out this form, and the data will be used for contact with each participant. The data fields include name, email address, telephone number (Telegram, Viber, or WhatsApp service), current duty, type of practice unit inside the selected hospital, date, job description, academic qualification, a text box for random numbers in the upper left side of the form, and participant's signature. The number of forms printed is according to the size of the estimated sample for the research (see the sample size section).

2. Table of the estimated sample: This table presents the details of the estimated sample and the types of practice units inside the selected hospitals (Multimedia Appendix 5). Using this table, the person in charge of the CNEU in each selected hospital will select eligible participants.
3. Informed consent form (Multimedia Appendix 6)

Referral to the trial will take place after the CNEU in each selected hospital has selected participants according to the table of estimated sample size that will be provided to the CNEU and the current practice unit (usual procedure). Participants will be recruited through the unit team in the selected hospitals. Participants are provided with an invitation letter that includes written information about the project and numbered, opaque, sealed, and stapled envelopes that contain the nomination form for the training course. The written information provides 2 ways to contact the researcher, if the participant is interested in the project: (1) by email and (2) by telephone (call or instant message by Telegram, Viber, or WhatsApp message). The nomination forms for the training course filled out by candidates are placed in large (A4) sealed envelopes and sent to the CNEU at the Faculty of Nursing that will host the web-based training course.

The start of the study will involve preparation of formal and essential approvals through the academic professor (HJ) responsible for the CNEU at the Faculty of Nursing and coordination with the Babylon Health Department, to obtain official agreements for sample collection according to the study criteria. The candidate envelopes will be opened and the candidates will be entered in an Excel spreadsheet. The information entered in each form will be added in sequence, and the Excel spreadsheet will be backed up, printed, and kept in a safe and secure location. A copy of the spreadsheet will be sent via email to the main investigator to contact the participants via their provided email addresses or phone numbers (Telegram, Viber, or WhatsApp). The enrollment process is outlined in Figure 1. If candidates are eligible and willing to participate, the informed consent form will be signed and the main investigator will contact each participant and send a link to the web-based baseline questionnaire via email or social communication apps (Telegram, Viber, or WhatsApp). Then, randomization will be performed via a web-based randomization system (see the randomization section).

Participants can return the signed informed consent form in a prestamped envelope provided by the unit or can take a picture of the signed consent form and send it via a text message to the main investigator. Subsequently, the main investigator will contact the participants, inform them about the results of the random distribution, and provide instructions according to the group that was randomly chosen (control or intervention group). All instructions will be completed on the phone or via text message, and participants will receive a link to a website from the main investigator (Multimedia Appendix 7), which provides all instructions and details of participation in the training course (also presented in Arabic).

In the CNEU, randomization will be performed. If randomized to the ELNEC-PPC web-based training course in addition to usual care (intervention group), participants will be sent a link to the website that has all instructions for enrolling and registering in the training course and assistance on how to maintain access via instant messaging or email. Moreover, participants will be given information about their follow-up assessments and how to contact the main investigator if needed. If a participant declines to participate, the main investigator will ensure that the information from the baseline questionnaire is deleted. If randomized to usual care, participants will be instructed on the principles of usual care and will be given the same information as provided to the intervention group about their follow-up assessments and how to contact the main investigator if needed. The flow of participants through the trial is described in Figure 1.

Randomization

Participants will be randomized to either (1) ELNEC-PPC web-based training as well as usual care or (2) only usual care. The randomization involves block randomization plus permuted blocks of random size known to the researcher and stratified by the type of unit (ie, critical care unit and noncritical care unit). The allocation ratio between the intervention and control groups is 1:1. Randomization will be performed using the Sealed Envelope website [53].

Randomization involves generating random numbers using a computer. The numbers are distributed and written on the nomination forms for the training course in the text boxes on the top of the forms. According to the sample size, the first random number represents the intervention group and will be written on the form with the code “T,” and the random number for the control group will be written with the code “C.” The forms are placed in sealed envelopes, and these are mixed and placed in a large sealed envelope (A3) (Multimedia Appendix 8). These steps represent the randomization process performed by a nurse. A video is made of the process of preparing the sealed envelopes, with the participant details visible. A second researcher will later view the video to ensure the accuracy of the process. Corresponding envelopes will be opened only by the participants who select them, and they will be allocated accordingly. The enrolled participants will complete all baseline assessments.

Blinding

This is a single-blinded study, and the participants are not blinded to group allocation. Examination and interpretation of the study results will be achieved by investigators blinded to group allocation. Once the study is completed, a copy of the data will be extracted in a pseudonymized form for statistical analyses. The information concerning the group allocation will be added to the data set with the intervention and control groups categorized as T and C, respectively. This work is done under a camera for documentation later (by supervisors), and the complete data entry is performed with blinding of the main researchers. The randomization key (ie, document with group details) will be kept with supervisors. They will provide the randomization key to the researchers once blinded interpretation of the results is finalized.

Interventions

Labeling will be performed according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) recommendations [54] and CONSORT EHEALTH extension [55].

Usual Care

Participant nurses deliver usual care according to their roles appropriate for neonates, infants, toddlers, preschoolers, school-age children, and adolescents in the selected units of perinatal, neonatal, and pediatric settings. It comprises all treatment management procedures, diagnostic procedures, and referral processes, which are considered relevant in terms of case history, clinical results, and practical everyday practice. After trial completion, participants in this group will be allowed to access a web-based training course similar to that provided in the intervention group.

PPC With Usual Care

The online ELNEC-PPC course is being developed in collaboration with Relias Learning Systems [56]. The ELNEC-PPC course involves complete nationwide work to advance palliative end-of-life care delivered through health care experts in perinatal, newborn, and pediatric contexts. The mission depends on the unique ELNEC care course training, which involves cooperation between "The City of Hope" and the American Association of Colleges of Nursing. This design may include a combination of investigation and knowledge in PC and is meant to help with applying evidence-based practice. The American Association of Schools of Nursing Peaceful Death: Recommended Competencies and Curricular Guidelines for End-of-Life PC and the 1997 Drug Report have been considered. The electronic training course is going to be included in modules that are for 2.5 days, and those who complete the ELNEC-PPC course will be able to take the knowledge to clinical practice [18]. The curriculum involves the following 9 modules that are specific to the care of children who have life-limiting illnesses, and their families [57]: module 1, nursing PPC introduction; module 2, perinatal and neonatal PC; module 3, PPC communication; module 4, PPC ethical/legal issues; module 5, PPC cultural and spiritual considerations; module 6, PPC pain management; module 7, management of symptoms; module 8, PPC loss, grief, and bereavement; and module 9, PPC at the time of death.

Each module will cover about 20 minutes of PowerPoint slides and data text, and 40 minutes of activity sessions for clinical application. The clinical course will comprise case management studies, film vignettes including critical thinking questions, and "stop and think" queries that require the user to answer in order to continue through the module. On the completion of each training module, the participant will be requested to reply to 10 National Council Licensure Examination–format questions to complete mastery. This interactive online course is important for all participants in the selected Hillah city hospitals.

The following 8 main themes are present within each of the modules: (1) Family as a unit of care; (2) Important role of the nurse as an advocate; (3) Cultural importance as an influence in PC; (4) Critical demand for notice to special populations like ethnic subgroups, deprived individuals, and uninsured individuals; (5) PC influence on care systems according to context; (6) Critical monetary matters impact PC; (7) PC is not limited to cancer or AIDS, and is vital in serious diseases and cases that can result in sudden death; and (8) Interdisciplinary care is vital for end-of-life care [18].

It has been hypothesized that the NPT would be a useful conceptual tool because it provides a strong analytic framework for understanding the organization and operationalization of tasks (their implementation), creating them as routine elements of lifestyle (their embedding), and sustaining embedded practices in social contexts (their integration) [28].

Process of Implementation

Institutional review board approval will be obtained from Babylon University/Nursing Faculty and from the selected hospitals in Babil Province Health Department, where the study will take place. Informed consent will be submitted to the selected hospitals, and the nurses will be given 1 week to decide if they wish to participate. The Arabic NoMAD pretest electronic questionnaire will be provided to those nurses who decide to participate.

The intervention group will receive the ELNEC-PPC training course through the Relais Academy website. The main investigator will send a link of the e-questionnaire to all participants via their email addresses or via social media (Telegram, Viber, or WhatsApp). It includes questions that describe the experience and role of each participant in providing PPC, and within 2 weeks, each participant will return to their appropriate routine practice. The time periods from pretest (the ELNEC-PPC training intervention) to posttest will be 2 weeks and 3 months.

The main investigator will send a link of the website that provides details of participation in the training course and enrolling at Relias Academy (see link in Textbox 1). The website also provides support in Arabic to all participants in the intervention group. For enrolling at Relias Academy, the participants need to follow the process presented in Textbox 1.

Textbox 1. Process for enrolling at Relias Academy.

1. Go to www.reliasacademy.com
2. Select “Sign In” from the top right corner of the screen
3. Type in your email address and password
4. Email: Provide the email
5. Password: Provide the password
6. Confirm that the End-of-Life Nursing Education Consortium-Pediatric Palliative Care course you are looking for is present
7. Once logged in, click on “Manage Account” and select “Courses”

Participants will login to the site from the link sent to them, and will read the steps necessary to complete the course (our website will provide the information). The site was designed for research purposes by the researchers to deliver the content of the course that was on the Relais Academy platform and provide the required survey to the participants to facilitate the process of implementation. It was created using Google Site, a service provided by Google to build websites, and the way it works is similar to the way a wiki works.

Each participant in the intervention group will complete all 9 modules of the ELNEC-PPC training course. Meanwhile, the main investigator will follow-up with the participants entering the website link and ask them via an instant message or email about the completion of steps and upload of a screenshot for each module to a Google Form URL provide to them.

After 2 weeks, the main investigator will make sure that all participants in the intervention group have completed the tasks assigned to them during the course, by asking the participants via an instant message or email, and will also send certificates for each module. Then, the electronic questionnaire (Arabic NoMAD) will be sent again to be filled out for the second time by the intervention group, and the main investigator will make sure that all the forms have been completed within 2 weeks after the training course. After that, the participants will be monitored at their workplaces for 3 months in order to measure the impact of the training course on their work and the changes that affect their roles, as well as evaluate their experiences using the NPT toolkit. Interviews will be conducted at their workplaces in the selected hospitals.

After 3 months, the main investigator will measure the variables of the interview using the NPT toolkit to create a viewpoint for PPC delivery via nurses at the end of life, and assess the modality of working in the hospital units. Simultaneously, a NoMAD link will be sent to all participants from the 2 arms for the last time to evaluate the long-term impact of the training course on providing PC.

Outcomes

All outcomes of the study will be assessed at the starting point, and after 2 weeks and 3 months. Participant characteristics and demographic variables will be collected at baseline. Participant characteristics include age, gender, and relevant comorbidities, while demographic variables include job category, work experience, academic qualification, job title, and the number of local training courses. The outcomes are based on the recommendations of the NPT and its 4 related constructs [58].

Primary Outcome

The primary outcome involves the evaluation of the ELNEC-PPC course aimed at providing PC in a range of health care contexts through the Arabic NoMAD questionnaire and observation of routine clinical care.

Secondary Outcome

The secondary outcomes involve an interview, operating context examination, and assessment via the NPT toolkit.

Interview Procedure

Semistructured face-to-face interviews will be conducted with all nurses on successfully completing the ELNEC-PPC web-based training course. All participants have direct contact with patients, and 3 rounds of interviews will be conducted after 3 months. After consenting, participants will be interviewed by the main investigator (MA). All interviews will be audio recorded and transcribed. If participants do not want to be recorded, the main investigator will make notes and then transcribe an in-depth discussion account. Some participants will be interviewed in pairs or small groups. They will be asked about the changes they experienced in terms of care after the training. Throughout the interview rounds, participants will be questioned about the most important developments since the start of the program. They will be asked to disclose their opinions around PPC and to clarify the degree to which they would be implementing the method. Themes are based on the NPT [59] and will be reviewed to include problems from the initial meetings. This will assist researchers in exploring participant views on the simplest models of care.

Consequently, the interactive NPT toolkit will be used. It contains 16 questions for thinking through an implementation problem. The embedding will be improved, and statements and explanations will be edited for a web-enabled tool.

Sample Size

The study has been designed as a superiority trial with 2 parallel groups (ELNEC-PPC web-based training plus usual care and usual care only). For calculation of the appropriate sample size, the main researcher uses the assumption that the 5 selected settings have 254 nursing staff members on average eligible for inclusion based on a survey of all included settings before the study to determine the total number of nurses who work in the selected settings and are appropriate for inclusion. Based on this assumption, as well as a 2-sided P value <.05, a 0.90 power, a traditional predictable correlation between 2 measurements

of 0.5, and an intraclass correlation coefficient with $P<.05$, 86 participants were required in the intervention group and 86 were required in the control group for *t* tests. To support equal sample sizes, including for the units of the selected settings, and to account for intrastratified correlations of units, a multilevel analysis will be used. Nursing staff members who are transferred to a dissimilar organization unit will be exchanged from the sample of nursing staff, and changes will take place in the course of the study. To catch up with nursing staff members who are not changed in time, the researchers will insert an additional organization unit from the critical care units for the intervention and control groups, which will result in a total of 172 nursing staff members. All power analyses will be performed using the G*Power software (version 3.1).

Data Collection

NoMAD Instrument

Participants will complete 2 data collection forms at the beginning, and forms will also be completed after the ELNEC-PPC training. The main data collection instrument is NoMAD [33]. The original form of this instrument has been translated into Arabic and adapted to Arabic conditions to evaluate the normalization potentiality of PPC training, which will be provided by a web-based training intervention.

The NoMAD instrument has been translated into the Fusha dialect in translation steps outlined previously [60]. The authors translated the NoMAD instrument from English to Arabic, and then, back translated it to English. The content validity and translated NoMAD acceptability have been measured in a reiterative procedure involving several recognized steps, including translation forward and translation backward, tests of the target language instrument content validity, meetings with specialists, and further revision, as well as a final content validity test of the studied tool. The finalized tool has been created as an electronic form. The Arabic NoMAD prime version, following step 2 of the clarification and adaptation process, has been applied in a pilot study. The Arabic NoMAD instrument is split into the following 3 sections: Section A, which includes 12 items on the respondents; Section B, which includes 3 general items on the intervention; and Section C, which includes 20 identifiable items on the intervention. Regarding the 4 NPT concepts, “Coherence” has 4 questions, “Cognitive Participation” has 4 questions, “Collective Action” has 7 questions, and “Reflexive Monitoring” has 5 questions.

The Arabic NoMAD scale consists of 31 Likert-type items. The items in section B are rated on a 10-point Likert-type scale from “not at all” to “completely.” The items in section C are rated on a 5-point Likert-type scale from “disagree strongly” to “agree strongly.” “Neutral” and “not applicable” are also assumed as choices to explain respondents’ experiences of using the intervention within the workplace (Multimedia Appendix 9). A total of 30 participants have completed the Arabic NoMAD survey, with a 100% reply rate. Content validity computed for the Arabic NoMAD scale (content validity index [CVI]) was 0.91, which is significantly higher than the suggested level of 0.80, and the item-CVI was 0.71-1.00. Scale reliability was also strong, with a Cronbach α coefficient of .77-.86 in the postcourse analysis. In a recent study, the NoMAD instrument demonstrated an indoor consistency score (α coefficient) of .76-.83 [61], and therefore, it may be considered as reliable.

The NoMAD questionnaire has been translated into 7 languages [62]. The Arabic NoMAD instrument provides a versatile “bank of items” [63], with a focus on wide item versions, for instance, to supply more anticipatory assessments. The NoMAD designers propose that the tool must be examined as a “pragmatic measure” of an intervention [64,65], and it motivates adaptation for multipurpose functions in particular application studies and meets clinical practice requirements.

The Arabic NoMAD instrument has 4 building item groups, according to reliability and validity data. In addition, there is no proposal for definite scoring instructions or construct procedures, which should be used in each study.

The time to complete the baseline questionnaire is approximately 20-25 minutes. The follow-up questionnaires are shorter, and the time to complete these is approximately 20 minutes.

At the starting point and 2-week and 3-month follow-ups, participants will be sent an email with a link that directs them to complete the Arabic NoMAD questionnaire. To ensure as high a response rate as possible in the follow-up questionnaires, several reminder emails will be sent (every 3 days). If no response is received, the investigator will attempt to communicate with the participant via text message or phone call and inquire if the participant is ready to reply to the survey over the telephone.

Interviews

Semistructured face-to-face interviews will be conducted with all nurse participants to detect the level of successfully passing the ELNEC-PPC web-based training course from the selected settings. All participants have direct contact with patients, and 3 rounds of interviews will be conducted after 3 months. After consenting, participants will be interviewed by the main researcher (MA). All interviews will be audio recorded and transcribed. If participants do not want to be recorded, the researcher will take notes and subsequently write a detailed account of the discussion. Some participants will be interviewed in pairs or small groups. They will be asked about the changes they experienced with regard to training.

The interactive NPT toolkit will be used for assessment. It contains 16 questions for thinking through an implementation problem. The embedding will be improved, and statements and explanations will be edited for a web-enabled tool.

Access to Data

All personally identifiable data collected in the trial will be kept for 5 years. These data are kept to be able to track any adverse events reported after completion of the trial. After these 5 years, the data set will be fully anonymized. The anonymized full data set will be kept for up to 30 years for research purposes and will be used to create a data model that can inform the further development of potential research of ELNEC-PPC web-based training. Data will be stored at the Postgraduate Department of Nursing College/Babylon University.

Statistical Analysis

Results will be stated according to the CONSORT declaration concerning health [49,50]. The analysis of primary data will follow the intention-to-treat principle and relate the alterations in the overhead outcome measures between the intervention and control groups. SPSS Version 26.0 software (IBM Corp) will be used for the data analysis. Descriptive statistics will be presented by percentage distributions and indicators describing the location (arithmetic mean=M) and deviation (range; standard deviation=SD). The analysis of primary data will predict the mean difference with 95% CI in the NoMAD score at the 3-month follow-up between the intervention and control groups.

The model includes accessible data of nurse participants at all time points (ie, starting point, and after 2 weeks and 3 months). Within the regression model, distinct participants will be considered using a random effect approach, accounting for inside topic covariance construction. The group and time effects will be considered with asset effects using a combined intervention and time variable. Starting point levels will be obtained over 2 research collections supposing that starting point alterations are coincidental [66]. This is aimed at minimal starting point changes in the outcome variable.

Both groups will primarily be labeled according to their starting point features. The initial data will be analyzed to evaluate the effectiveness of ELNEC-PPC web-based training in the intervention group when compared with the findings in the control group, according to the NPT.

The analysis will inspect intervention effects continuously over time, and will assess the interaction between period and group allocation. The difference between the groups will be assessed for the period of the basic model and will be further evaluated according to the stratification by unit category (critical care unit and noncritical care unit) [67].

Repeated measures ANOVA will be performed to assess the multivariate main intervention effects (associated with controls) considering pre, post, and follow-up time points, as well as their interface effects. A 2-sided P value <.05 will be considered significant. The standardized effect size (Cohen d) will also be calculated. Mediator analysis will be controlled to determine which subgroups would benefit further from the intervention, with outcome variables regressing on independent variables, including age group, sex, education, and starting Arabic NoMAD score.

Secondary outcomes will be analyzed using an approach similar to the approach described for the primary outcome with linear mixed models for repeated measures. The data from the 2-week and 3-month follow-ups will also be analyzed using the approach described above for the primary outcome.

Pilot Testing

A pilot study was conducted between March 2020 and July 2020, by using the initial Arabic NoMAD version, following clarification and adaptation. This pilot study was the initial implementation of the PPC web-based training intervention.

The web-based training intervention was used for the provision of PPC in hospitals by staff nurses, and for the application and development of further adaptable and improved operating approaches in health care facilities.

The pilot study was performed to test the instruments, make revisions where necessary, and again test the instruments. Other aspects of the research, such as how to gain access to respondents, were also piloted. Moreover, we tested a process to implement the ELNEC-PPC web-based training intervention, and to gain information about practical procedures regarding recruitment and screening as described in this protocol. Accordingly, the pilot study identified challenges in the recruitment process that could be addressed before the RCT.

The pilot study was conducted with the methods described for the RCT in this protocol. Recruitment ran until testing from all described channels. All participants in the pilot study contributed to the ELNEC-PPC web-based training and usual care (intervention). Outcome data were collected at baseline and after 2 weeks. The outcome data collected will not be included in the RCT analysis.

Ethics Approval

Approvals for the pilot study, RCT, and process evaluation have been obtained from the relevant ethics committees in Nursing College/Babylon University. Approval was sought from the Committee on Scientific Research Ethics (number 291; January 29, 2020) and Babel Health Director (number 124; January 30, 2020). Correspondingly, approval from institutional review boards for the protection of data activities has been obtained within Nursing College. The trial has been registered at ClinicalTrials.gov (NCT04461561).

For this trial, serious adverse events are not expected, and thus, no interim analysis or a priori stopping rules are defined or implemented for this trial. All inquiries from participants reporting technical or medical problems will be registered. The website for providing the training course contains a link to a webpage with frequently asked questions that can guide participants with technical issues. All inquiries will be documented and conferred in an internal review, and the research outcomes will be described.

Results

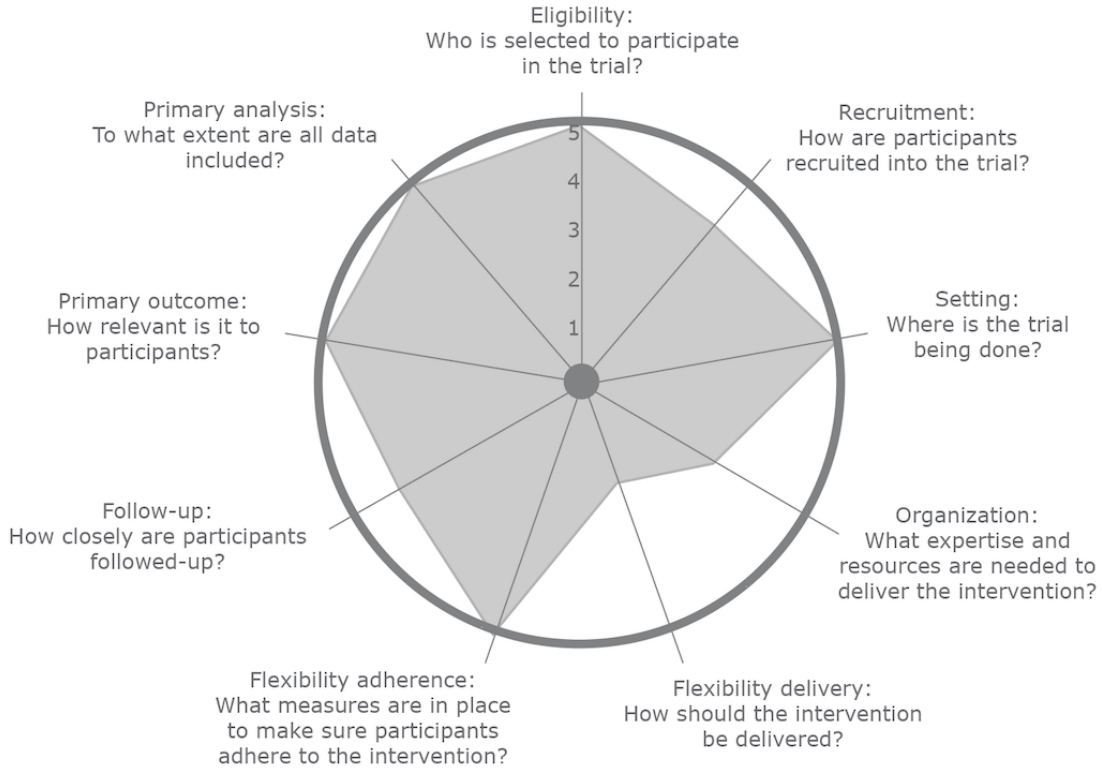
The RCT results will be presented in compliance with the CONSORT 2010 writing recommendations, in addition to the 2013 modification (CONSORT-EHEALTH) focused on writing mobile-based and web-based RCTs [50,55]. Data collection is expected to be completed by March 2021, and the distribution of trial results is planned after analysis.

Discussion

To the best of our knowledge, this RCT will be the first trial to clarify the delivery of PC at the end of life through the implementation of ELNEC-PPC as a web-based training course among Iraqi nurses in the pediatric field. In addition, it will be one of the limited trials to evaluate enhancement in PC as a result of the ELNEC-PPC web-based training program. It will also evaluate the impact and effectiveness of this program by using the NPT, which focuses on how complex interventions

become routinely embedded in practice. The study design has several strengths, including random allocation to dissemination conditions, the inclusion of data on reach, implementation under different conditions, the willingness of staff to participate, and the highly pragmatic nature of the protocol, with planning via the Pragmatic Explanatory Continuum Indicator Summary (PRECIS)-2 guidelines [68] (Figure 2) that show the characteristics of the ELNEC-PPC web-based intervention. The mean score among the 9 domains of the PRECIS is 4.22, which indicates a pragmatic protocol, with training of staff members who work in pediatric units and mixed units under the experimental condition. An important strength of the intervention is its modification according to the requirements and wishes of the health care staff to overcome hindrances, which will benefit health care administration. To increase nursing staff motivation, the web-based course will be provided to participants in the control group on completion of the study.

Figure 2. Illustration of the End-of-Life Nursing Education Consortium-pediatric palliative care web-based training intervention trial according to the Pragmatic Explanatory Continuum Indicator Summary-2 wheel.



The trial has some limitations that must be mentioned. First, the participants will be aware of the intervention being received, which might cause bias. Second, as self-reported data will primarily be used, there might be recall bias. Third, a high dropout rate is likely, even with self-choice and additional strategies to reduce it (for instance, email notices in addition to further incentives). Fourth, the outcomes will be assessed up to only 3 months. Finally, the self-administered web-based intervention might be less efficient.

Up to now, the readiness of nursing staff to join the ELNEC-PPC web-based training course has been outstanding. The first training was provided in March 2020 for the pilot study, and the last training was provided in August 2020. The results became accessible in December 2020. The study will involve numerous departments. All units have a bottom-up approach for offering PC to children with life-limiting illnesses. The selected design is appropriate for the study purposes. The design permits evaluating the training program's influences on normalization and adaptation for providing PPC during daily routine practice promptly. In addition, a brief assessment will be performed at 3 months.

We hope that the findings of this study show that the web-based training intervention not only supports nursing staff in providing PPC in addition to usual care, but also has a positive impact on high-quality nursing care in pediatric governmental health care organizations and provides knowledge about recovery in children with life-limiting illnesses. Health care workers will be able to provide original information intended for modifying the intervention according to their patients' needs. The results will help health care policy makers decide whether to expand the ELNEC-PPC program to all nursing staff in the country.

Acknowledgments

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Authors' Contributions

Study concept and design: AY, NA, and MAAS. Critical revision of the manuscript for important intellectual content: AY, NA, and MAAS. Statistical analysis: MAAS and HM. Administrative, technical, or material support: MAAS and HM. Study supervision: AY and NA. AY and NA have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Official approval form for conducting research.
[PNG File , 4192 KB - resprot_v11i11e23783_app1.png]

Multimedia Appendix 2
Approval form for the training course.
[PNG File , 1227 KB - resprot_v11i11e23783_app2.png]

Multimedia Appendix 3
Additional approval form for the training course.
[PNG File , 2234 KB - resprot_v11i11e23783_app3.png]

Multimedia Appendix 4
Nomination form for the training course.
[PNG File , 23 KB - resprot_v11i11e23783_app4.png]

Multimedia Appendix 5
Details of the estimated sample needed.
[XLSX File (Microsoft Excel File), 28 KB - resprot_v11i11e23783_app5.xlsx]

Multimedia Appendix 6
Informed consent form.
[PDF File (Adobe PDF File), 210 KB - resprot_v11i11e23783_app6.pdf]

Multimedia Appendix 7
Full website screen (in English).
[PNG File , 1015 KB - resprot_v11i11e23783_app7.png]

Multimedia Appendix 8
Randomization process by a nurse.
[PNG File , 162 KB - resprot_v11i11e23783_app8.png]

Multimedia Appendix 9
Normalization Measure Development questionnaire.
[PDF File (Adobe PDF File), 296 KB - resprot_v11i11e23783_app9.pdf]

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Abbreviations

CNEU: Continuing Nursing Education Unit
CONSORT: Consolidated Standards of Reporting Trials
CVI: content validity index
ELNEC: End-of-Life Nursing Education Consortium
NoMAD: Normalization Measure Development

NPT: Normalization Process Theory
PC: palliative care
PPC: pediatric palliative care
PRECIS: Pragmatic Explanatory Continuum Indicator Summary
RCT: randomized controlled trial

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Protocol

The Effects of Tinnitus in Probabilistic Learning Tasks: Protocol for an Ecological Momentary Assessment Study

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Abstract

Background: Chronic tinnitus is an increasing worldwide health concern, causing a significant burden to the health care system each year. The COVID-19 pandemic has seen a further increase in reported cases. For people with tinnitus, symptoms are exacerbated because of social isolation and the elevated levels of anxiety and depression caused by quarantines and lockdowns. Although it has been reported that patients with tinnitus can experience changes in cognitive capabilities, changes in adaptive learning via decision-making tasks for people with tinnitus have not yet been investigated.

Objective: In this study, we aim to assess state- and trait-related impairments in adaptive learning ability on probabilistic learning tasks among people with tinnitus. Given that performance in such tasks can be quantified through computational modeling methods using a small set of neural-informed model parameters, such approaches are promising in terms of the assessment of tinnitus severity. We will first examine baseline differences in the characterization of decision-making under uncertainty between healthy individuals and people with tinnitus in terms of differences in the parameters of computational models in a cross-sectional experiment. We will also investigate whether these computational markers, which capture characteristics of decision-making, can be used to understand the cognitive impact of tinnitus symptom fluctuations through a longitudinal experimental design.

Methods: We have developed a mobile app, AthenaCX, to deliver e-consent and baseline tinnitus and psychological assessments as well as regular ecological momentary assessments (EMAs) of perceived tinnitus loudness and a web-based aversive version of a probabilistic decision-making task, which can be triggered based on the participants' responses to the EMA surveys. Computational models will be developed to fit participants' choice data in the task, and cognitive parameters will be estimated to characterize participants' current ability to adapt learning to the change of the simulated environment at each session when the task is triggered. Linear regression analysis will be conducted to evaluate the impacts of baseline tinnitus severity on adapting decision-making performance. Repeated measures linear regression analysis will be used to examine model-derived parameters of decision-making in measuring real-time perceived tinnitus loudness fluctuations.

Results: Ethics approval was received in December 2020 from Dublin City University (DCUREC/2021/070). The implementation of the experiments, including both the surveys and the web-based decision-making task, has been prepared. Recruitment flyers have been shared with audiologists, and a video instruction has been created to illustrate to the participants how to participate in the experiment. We expect to finish data collection over 12 months and complete data analysis 6 months after this. The results are expected to be published in December 2023.

Conclusions: We believe that EMA with context-aware triggering can facilitate a deeper understanding of the effects of tinnitus symptom severity upon decision-making processes as measured outside of the laboratory.

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KEYWORDS

chronic tinnitus; computational modeling; decision-making; ecological momentary assessment; mobile phone

Introduction

Background

Tinnitus is an increasingly significant health concern characterized by the perception of sound in the absence of external stimuli [1]. Tinnitus is normally described as a *ringing in the ears*, but it may also take other forms such as buzzing, humming, clicking, or hissing. It has been reported by the American Tinnitus Association that approximately 15% of the general public, >50 million people in the United States, experience some forms of tinnitus, with 20 million people struggling with burdensome chronic tinnitus and >2 million cases characterized as extreme and debilitating [2]. A recent large research study conducted by Stohler et al [3] revealed an increasing incidence rate of tinnitus between 2000 and 2016. It was reported that the number of people living with chronic tinnitus is set to increase by more than half a million over the next decade, emphasizing a potentially increasing burden on the health care system. A recent observation is that the challenges associated with responses to the COVID-19 pandemic can increase tinnitus distress in case the people perceive the situation as generally stressful with increasing grief, frustration, stress, and nervousness [4]. It has been proved in previous studies that the presence of stress is highly correlated with tinnitus either initiating or worsening [5,6]. In fact, the British Tinnitus Association has reported a rapid increase in the number of people accessing their services, with a 256% increase in the number of web chats from May 2020 to December 2020 compared with the same period in 2019 [7].

Tinnitus and Cognitive Impairments

Although most patients with tinnitus can cope well with the condition, managing to minimize its impact on their life, approximately 20% of the individuals can be characterized as being severely debilitated by their symptoms [8,9]. Recently, it has been proposed to differentiate between *tinnitus* to describe the auditory phantom percept and *tinnitus disorder* for the description of the auditory component plus the associated experience [10]. Although neuroimaging evidence is emerging showing that tinnitus is associated with abnormal functioning of the central auditory system [9,11,12], epidemiological studies have revealed that the perceived sound typically associated with the condition is not the only symptom. This suggests that other pathological elements may be associated with the condition; for example, the experience of tinnitus is related to a significant decline in cognitive functions such as working memory and attention [13,14], learning and learning rate [15], and cognitive speed [16], leading to an obvious decrease in quality of life. This involvement of nonauditory impairment is reflected by the fact that tinnitus is related to abnormal functioning not only in auditory brain areas but also in nonauditory brain areas, especially the prefrontal cortex [17], which plays a crucial role in executive control and decision-making [18]. Earlier studies that investigated cognitive impairments caused by tinnitus were mainly in the domains of attentional process and memory bias, and the findings were largely based on patients' self-report behavioral and emotional responses to neuropsychological tests [15,19]. Andersson et al [20,21] were among the first to adopt experimental techniques from cognitive psychology, that is, the Stroop test, to measure selective attention in this context. Subsequent studies using similar methodologies further corroborated their findings that tinnitus depletes attention resources and results in compromised cognitive performance [16,20,22].

Computational Modeling to Capture Cognitive Processes in Decision-making

Although behavioral summary statistics used in previous experimental cognitive studies, for example, accuracy and reaction time on the Stroop test, are more objective than self-report measures, they cannot be used to understand the underlying cognitive mechanisms that generate individual-level behaviors [23]. Computational modeling presents an alternative approach to make better sense of behavioral data and enhance our understanding of the cognitive processes in people with tinnitus. The most popular and successful application of computational modeling is in the field of learning and decision-making [24], which, surprisingly, has not been explored to date in the context of tinnitus.

Decision-making is a complex mental process that requires the coordination of several simultaneous cognitive processes, including perception, attention, evidence accumulation, and motor response networks [25,26]. It now seems that the cognitive abilities involved before (eg, perception and attention) or after (eg, learning) a choice is made can have significant influence on the final step of a motor response [27]; for example, attention is beneficial for decision-making because relevant features of the environment can be preferentially processed to enhance the quality of evidence. Executive functions and memory are critical to decision-making performance under risk [28].

Thus, we hypothesize that degradation in the cognitive abilities of patients with tinnitus may affect their decision-making characteristics. To gain a better understanding of the underlying cognitive processes of people with tinnitus, the method of computational modeling will be applied on a reward-loss version of the probabilistic decision-making under volatility task. This is a task that has been used to examine how humans can track the statistics of a reward-loss environment and adapt their learning rates accordingly [29]. Participants in their study had to choose 1 of 2 shaped Gabor patches, either of which might result in the delivery of an electrical shock. In each shape, a digital number is presented indicating the magnitude of the electrical shock that might be received. In the stable task block, 1 of the 2 shapes is associated with a 75% probability of receiving an electrical shock, and the other shape generated an electrical shock on the remaining trials. In the volatile task

block, the shape most predictive of shock delivery reversed across several blocks of trials. We developed an equivalent web-based version of the task using the leprechaun story, which will be introduced in the Methods section. The computational parameters of this task can be used as a succinct representation not only for quantifying the effect of tinnitus on decision-making but also for investigating individual differences and within-individual changes in decision-making that are difficult to establish through superficial summary statistics.

The Relationship Among Tinnitus, Cognition, and Psychological Disorders

It has been documented that, apart from impairments in cognition, patients with tinnitus may experience a variety of psychological disorders such as depression and anxiety. Holgers et al [22] found that the occurrence of depression and anxiety among a population consisting of people with severe tinnitus was significantly higher than that among the general population. Similar results were obtained in the study by Fetoni et al [30], where subjective tinnitus severity demonstrated a strong correlation with psychological distress measured by the Hospital Anxiety and Depression Scale. As a result, the identification of depression and anxiety disorders is of the highest importance in the management of patients with tinnitus because these comorbidities should be specifically treated [31].

It is widely recognized that the relationships between tinnitus and psychological variables are complex; for example, it is unknown whether cognitive impairments are caused by severe tinnitus directly or whether psychological factors are also involved, given that there is growing evidence for cognitive dysfunction among people with depression and anxiety [32,33]. In other words, cognitive impairments among people with tinnitus may not simply be the result of tinnitus but the co-occurrence or mediation of high levels of anxiety and depression [34]. Alternatively, tinnitus may lead to anxiety and emotional distress that, in turn, disrupt cognitive processes. Understanding the origin and underlying mechanisms of tinnitus and tinnitus-related impairment is therefore a significant challenge for current basic research. Psychological factors as well as impairments in cognition have been considered covariates to predict self-reported tinnitus severity. Interestingly, although both were identified as significant predictors of tinnitus severity, the decline in cognition has not been explained so far by psychological covariates in people with tinnitus [20,22]. However, this is not consistent with the literature in the field of anxiety and depression where both of these disorders can lead to cognitive impairments [33,35]. In addition, it was documented that these 2 psychological disorders can lead to reduced performance in decision-making tasks [36,37]; for example, it has been reported in the study by Browning et al [29] that individuals with high trait anxiety demonstrate less ability to adjust learning rates between stable and volatile environments in a laboratory-based reward-loss probabilistic decision-making task. We developed a web-based version of this task to examine whether it is tinnitus or a psychological alteration that is related to impaired decision-making performance in people with tinnitus.

Take Tinnitus Severity Fluctuation Into Account

Another challenge encountered in the field of tinnitus research is that the perception of tinnitus loudness and distress is not constant in most cases but varies over time [38]. As a result, it is unknown whether the previous between-participants findings capture trait-like features of tinnitus or state-like features associated with fluctuating tinnitus symptoms. The second question of this study then relates to how moment-to-moment changes in tinnitus symptom experience affect decision-making performance under uncertainty. This question will be resolved by a longitudinal within-participants ecological momentary assessment (EMA) in which participants' tinnitus states in the current moment will be sampled multiple times per day via self-report questionnaires, and the decision-making task will be triggered in several sessions based on their tinnitus severity. In contrast to retrospective self-report measures where patients are required to recall and summarize their tinnitus experience in the past 1 or 2 weeks, an EMA focuses on the current moment, minimizing the potential for recall bias and increasing ecological validity. The use of EMA in tinnitus studies has increased with the development of mobile apps and the growing availability of smartphones [39-41]. We have developed a mobile app, AthenaCX [42], that can automatically send notifications to the participants at several time points during the day requesting that they complete a state questionnaire asking about their current tinnitus symptom levels.

Furthermore, an intelligent algorithm is embedded in the app to trigger the decision-making task whenever the participants perceive relatively lower or higher levels of tinnitus distress than normal for them. Leveraging these tools, we are able to examine the dynamic changes of the computational markers extracted from decision-making behaviors associated with tinnitus fluctuation, simultaneously accounting for other time-varying factors—for example, emotions and nonadherence.

Hypothesis

In summary, our first hypothesis is that people with chronic tinnitus demonstrate inferior learning adaptation in decision-making, represented by model-derived parameters, in a simulated uncertain environment compared with healthy controls, and this association is mediated by psychological disorders. An initial baseline cross-sectional study will be conducted to examine this hypothesis. Our second hypothesis is that the learning adapting ability for healthy controls will show good test-retest reliability, whereas the impairment-level of learning adapting of patients with tinnitus will exhibit higher variability and is positively correlated with moment-to-moment tinnitus severity in the longitudinal study.

Methods

Study Design

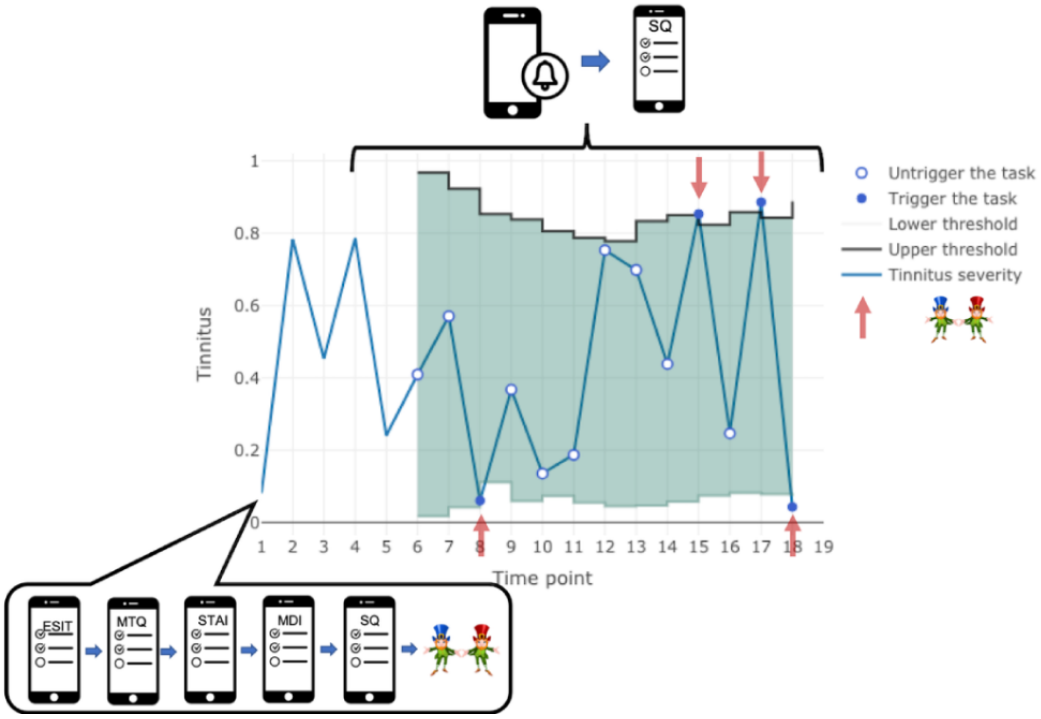
Once the participant is recruited, we will give them a unique ID and a link to download the study app AthenaCX from the Google Play Store or Apple Store. Participants will use the assigned ID to enter into the study app. After opening the app, they will be directed to read the plain language statement and the data privacy statement, which is referred to as participant

information in the app. Once they agree to the terms, they will be asked to consent to the study. All communication with interested participants will be carried out on the web. The contact information will be hashed and saved on a secure password-protected Dublin City University Google Drive folder. All assessments will be completed inside the mobile app, except for the web-based decision-making task. The collected data will be stored in the AthenaCX databases, which reside on the Amazon Web Service platform at its Western Europe data center.

The experiment starts when the participant logs in to the app and consents to participate in the study. The complete study comprises 2 phases of experiments—the cross-sectional experiment and the longitudinal experiment—lasting up to 1 month depending on the frequency of patient responses. The cross-sectional experiment takes place right after the participants log in to the app and consent to participate. In this experiment, the participants are required to finish several baseline assessments, including the European School for Interdisciplinary Tinnitus Research Screening Questionnaire [43] (ESIT-SQ; part A for participants with tinnitus as well as healthy controls and part B only for participants with tinnitus) for an evaluation of their tinnitus-related history, the State-Trait Anxiety Inventory (STAI) [44] and Major Depression Inventory (MDI) [45] for both groups to score their anxiety and depression levels, and the Mini Tinnitus Questionnaire (MTQ) [46] specifically for participants with chronic tinnitus to assess their baseline tinnitus severity, followed by an EMA questionnaire asking about their current tinnitus symptoms and emotional status. In summary, the healthy controls will finish 3 questionnaires and a state questionnaire taking approximately 15 minutes, whereas the participants with chronic tinnitus will complete the same questionnaires as well as the tinnitus-specific questions in the ESIT-SQ and an extra baseline tinnitus assessment requiring ≤10 minutes. After finishing the questionnaires, they will be directed to the web-based reward-loss version of the probabilistic decision-making task, which requires 15 minutes to finish. The self-report questionnaires and decision-making task are introduced in detail in the sections that follow.

From the second day of the participants' participation, the longitudinal-phase experiments will be activated. In the first part of this experiment, we will only observe the fluctuations of tinnitus perception and emotional status of both groups. This will be carried out as follows. The AthenaCX mobile app will automatically present to the participants the same EMA questionnaire that they completed in the baseline experiment. It is presented from 8 AM to 8 PM up to 4 times per day and is valid for 90 minutes. Unlike in the baseline experiment, the participants will not be directed to the decision-making task after the EMA survey until we obtain >5 responses of self-report tinnitus symptoms. From the sixth response, which is also the second part of this experiment, the algorithm we designed to intelligently trigger the decision-making task based on the participants' current tinnitus symptoms will be activated. In other words, the algorithm will start monitoring the tinnitus severity reported by the participants with chronic tinnitus; only when the lower or higher thresholds (which are calculated for each participant combining all their tinnitus history reports) are reached will the decision-making task be triggered. Altogether, we expect the participants with chronic tinnitus to complete the decision-making task 4 times at 4 different time points: twice when their moment tinnitus symptom is smaller than the lower threshold and twice when their moment tinnitus symptom is larger than the higher threshold. Thus, the experiment will be terminated whenever the task is completed 4 times. Another termination condition is a time limit, that is, the experiment will come to an end after 1 month irrespective of the amount of data collected from the participant. The healthy controls will need to answer the same EMA questions, except for the tinnitus-related questions, with the same frequency as the patients with tinnitus for 2 weeks, during which the task will be triggered randomly 4 times. Refer to Figure 1 for the pipeline of the experiments for the participants with tinnitus.

Figure 1. Pipeline of the experiments for tinnitus participants. ESIT: European School for Interdisciplinary Tinnitus Research Screening Questionnaire; MDI: Major Depression Inventory; MTQ: Mini Tinnitus Questionnaire; SQ: Screening Questionnaire; STAI: State-Trait Anxiety Inventory.



Study App (AthenaCX)

The study app AthenaCX is available for both Android and iPhone users. It is designed for the rapid creation and distribution of dynamic research surveys, including integrated consenting and even wearable data collection [47]. All of the surveys in this study will be delivered to the participants in this app. The demographic survey will be activated at the point of the initial download, whereas the other surveys will be activated through episodic triggering afterward; thus, only when the previous survey is completed will the next one be activated.

The ESIT-SQ Measure

The ESIT-SQ [43] is a self-report tinnitus-relevant history questionnaire, which includes 39 multiple-choice questions. It is structured in 2 parts. Part A consists of 17 questions that can be used by both individuals with tinnitus and healthy controls. Seven questions require the participant to provide details of demographics, body characteristics, education, and lifestyle. One question is about family history, and 9 questions ask medical history and presence of hearing-related and other symptoms. The last of these questions screens for presence of tinnitus lasting for >5 minutes over the past year. Participants who answer *yes* to this question will be directed to complete the 22 questions in part B, which includes 8 questions about tinnitus perceptual characteristics, 1 general question about the impact of tinnitus, 6 questions about onset-related characteristics, 4 questions about tinnitus modulating factors and associations with coexisting conditions, 1 question on objective tinnitus, and 2 health care–related questions.

The MTQ Measure

The MTQ [46] is the short version of the Tinnitus Questionnaire used to examine subjective distress related to tinnitus. It consists of 12 questions reflecting the most pertinent aspects of tinnitus distress with 3 potential answers: *true*, *partly true*, and *not true*, each yielding a score from 0 to 2. The MTQ has shown good test-retest reliability as well as high validity. The MTQ score will serve as the primary outcome measure for tinnitus severity in this study.

The STAI Measure

The STAI [44] is a commonly used measure that includes two 20-item self-report scales for assessing trait and state anxiety. *State anxiety* refers to the current feeling of the respondent, whereas *trait anxiety* refers to the general feeling of the respondent. Items on the state scale are rated on a 4-point scale from *not at all* to *very much so*; items on the trait scale are also rated on a 4-point scale, but here, the ordinal labels range from *almost never* to *almost always*. The total score of each scale ranges from 20 to 80, with higher scores indicating greater anxiety. Scores ≥30 indicate moderate anxiety, and scores ≥45 indicate severe anxiety [48]. Internal consistency coefficients for the scale range from 0.86 to 0.95. Test-retest reliability of this measure ranged from 0.65 to 0.75 over a 2-month interval [44].

The MDI Measure

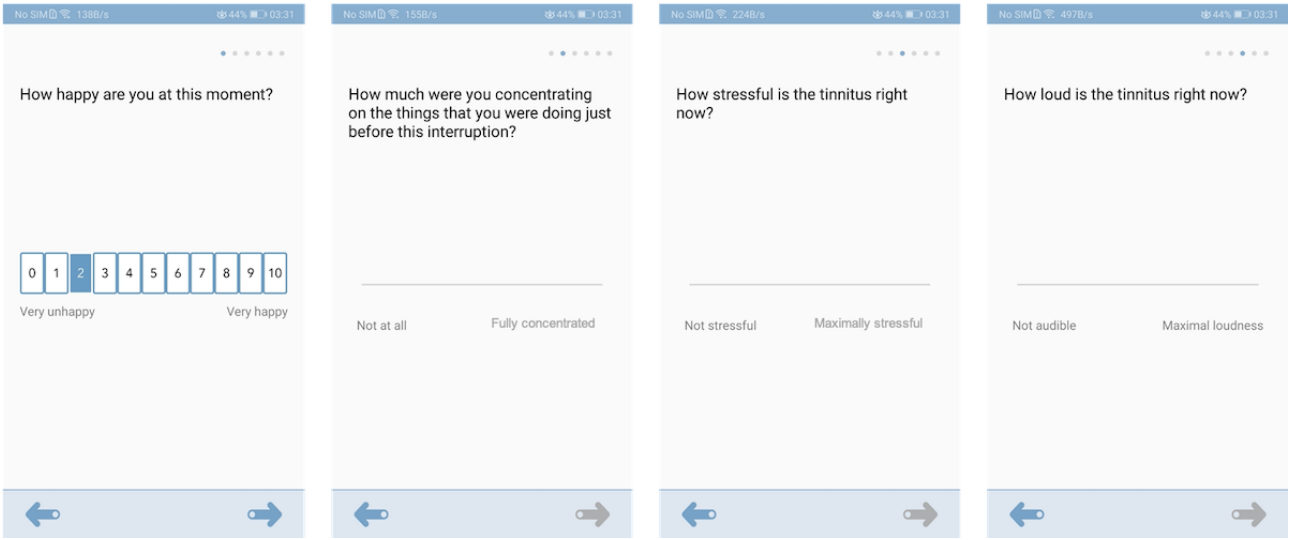
The MDI [45] is a 12-item self-report measure for depression developed by the World Health Organization's Collaborating Center in Mental Health. Items contained in the MDI reflect all symptoms of depression in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, and the International Classification of Diseases, Tenth Revision. Each item is rated on a 6-point scale from *at no time* to *all the time* to assess the presence of a depressive disorder and the severity of depressive symptoms over the past 2 weeks. The reliability of the MDI as a measure of depression severity is 0.89 based on the results in

the study by Cuijpers et al [49]. Scores on both the STAI and the MDI will be used as covariates along with tinnitus severity to examine the contribution of self-reported anxiety and depression to the performance on the cognitive decision-making task.

The EMA Survey of Tinnitus Symptoms and Emotional Status

An EMA approach is used to allow in-the-moment responses from participants. Typically, the EMA survey takes <1 minute to complete. It consists of 4 questions. The first question asks the participant to rate their emotional valence on a scale ranging from 0 to 10, representing *Very unhappy* to *Very happy*. The second question asks how much they were concentrating on the things that they were doing before the interruption. The participants can provide their answers on a visual analog scale (VAS) by moving a slider between the end points from *Not at all* to *Fully concentrated*. Technically, the VAS is implemented as a slider without a preset initial position to avoid anchoring affects. The last 2 questions are specifically for patients with tinnitus and ask about tinnitus loudness and tinnitus stressfulness. These questions are also answered using a VAS. The anchor points of the VAS asking about tinnitus loudness are *Not audible* at one end and *Maximal loudness* at the other. For the VAS asking about tinnitus stressfulness, the labels are *Not stressful* on the left side and *Maximally stressful* on the right side. In Figure 2, we have provided the interfaces of the EMA questions on the smartphone screen as an example to demonstrate the implementations of the surveys on the AthenaCX app.

Figure 2. Screenshots of the interfaces of the ecological momentary assessment questions on the smartphone screen.



The Triggering Algorithm

The decision-making tasks are triggered by the triggering algorithm developed in the study by Monacelli et al [50]. In our context, we aim to balance the burden placed on the participants—do not trigger the task too often—and data quality—collect enough data for the analysis (refer to the Statistical Analysis section). Monacelli et al [50] have shown that their algorithm performs better than both a random schedule and a rule-based approach with prefixed thresholds, which are the current state-of-the-art approaches, in achieving this goal. The algorithm adapts to the individual participants based on their reported history of tinnitus severity and adherence. It relies on 2 statistical models: tinnitus severity is modeled as an independent and identically distributed sample from a beta distribution and adherence as an independent and identically distributed sample from a Bernoulli distribution. At each interaction of the participants with the app, the algorithm estimates both the parameters of the beta distribution and the adherence rate. By using the estimates of the beta distribution and a control chart approach, the algorithm defines adaptive CIs for the tinnitus severity, which are used as adaptive thresholds for triggering the decision-making task. The significance level of these CIs is chosen by analytically solving a design optimization problem. This problem, in particular, formalizes the intent of the authors to trigger on average a prefixed number of additional tasks per participant, thus balancing the burden placed on the participants and data quality. The result is a closed-form solution for the significance level that depends only on the length of the experiment and the first time point after which the decision-making tasks can be triggered. Finally, by considering the estimated adherence rate, the algorithm updates the optimal significance level by replacing the length of the experiment with an estimate of the final number of samples collected for the individual participant. This results in an algorithm that is more careful in submitting the task to adherent participants but tries to collect data as soon as possible for those who are less adherent. This process is repeated for each interaction of the participant with the app, resulting in a web-based adaptive algorithm. A representation of the algorithm is presented in Figure 1.

As suggested in the study by Monacelli et al [50], this procedure is activated once participants have provided data via the app a minimum of 5 times, and we stop the algorithm after 5 triggers. We anticipate, based on past adherence behavior, that approximately 35% of the participant cohort will interact with the app >5 times [50]. A data quality assessment for the triggering algorithm will be performed by repeating the analysis conducted in the study by Monacelli et al [50]. Therefore, we

will consider both the F_1-scores and the utility measures, which represent, respectively, the precision of the algorithm and its effectiveness in balancing data quality and the burden placed on the participants. Plots of both the empirical cumulative distribution function and a Mann-Whitney-Wilcoxon test will be considered. It should be noted that although the triggering algorithm accounts for the uncertainty of the sample size and incorporates it into its definition of high and low values, this uncertainty cannot be overlooked in the analysis (refer to the Statistical Analysis section). Therefore, a scatterplot of the total number of samples against variables of interest such as the learning rate of the participants will be considered.

The Decision-making Task

Performance on the decision-making task is captured as an objective measure of adaptation of learning rate to volatility. In the task, participants are told that they are walking through a forest carrying 10,000 gold coins (refer to Figure 3 for screenshots of the task). As they proceed through the forest, they will come across a series of junctions. At each junction, there will be 2 leprechauns, each with distinct behaviors (therefore, we may also refer to this task as the leprechaun task). The leprechaun wearing a blue hat is referred to as the blue leprechaun, and the leprechaun wearing a red hat is referred to as the red leprechaun. The participants have to choose between the blue and red leprechauns to pass through each junction. They should choose carefully because one of the leprechauns will steal gold coins from them and run away. One of the leprechauns has a high probability of stealing gold coins from the participants, whereas the other one has a low probability. However, the probabilities of stealing gold coins, or, as we refer to them, the action-outcome contingences of the leprechauns, can be altered as part of the experimental design. In this particular experiment we have 2 blocks. In the stable block of 120 trials, the probability of one of the leprechauns stealing is consistently 75%, whereas the probability for the other leprechaun is consistently 25%. In the volatile block, which also comprises 120 trials, the stealing probability switches between 80% blue leprechaun and 80% red leprechaun every 30 trials. Figure 4 shows an example of the change of the probability of theft by the blue leprechaun throughout the task. As the participants are required to perform this task multiple times, the action-outcome contingencies of the 2 leprechauns are reversed each time the task is activated to eliminate memory effects, that is, if the structure of the task remains fixed throughout the experiments, the more times the participants play, the better they perform because they gain more experience and will be able to remember the *correct answers*.

It is not known to the participants that the task consists of 2 blocks and 120 trials (each trial is an opportunity for making a choice in the game in which the participants choose between the 2 leprechauns) per block. Each leprechaun holds a bag in their hands with a number on it that represents how many gold coins the participants will lose if that leprechaun steals from them. Throughout the task, the potential losses for choosing one of the leprechauns are randomly generated between 1 and 100 (M_1), and the losses for the other leprechaun are set to 100 – M_1.

Participants will be instructed that they should base their assessment of the most trustworthy leprechaun on their recent outcome history with each leprechaun and that their goal is to get back to their village with as many gold coins as possible. They need to learn which leprechaun on average is currently the best one to choose throughout the task, and they also need to adjust the speed of learning to reflect the stability or volatility of the environment.

Figure 3. Screenshots of the web-based leprechaun task.

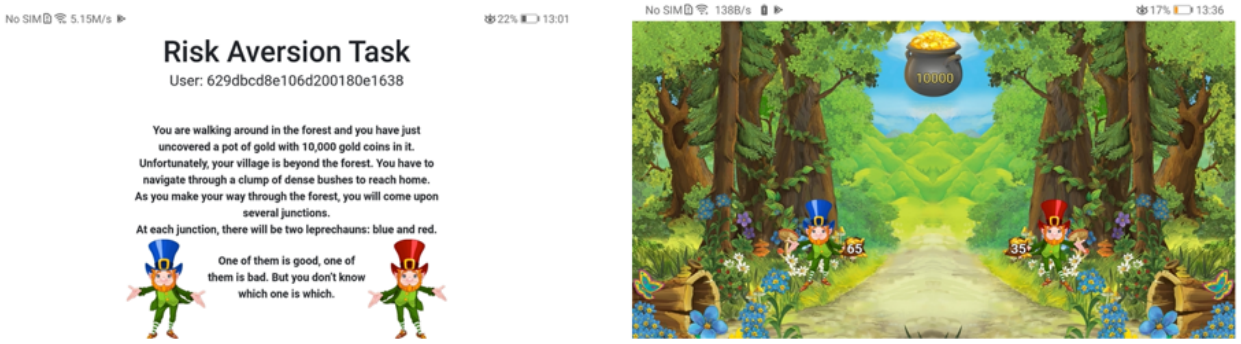
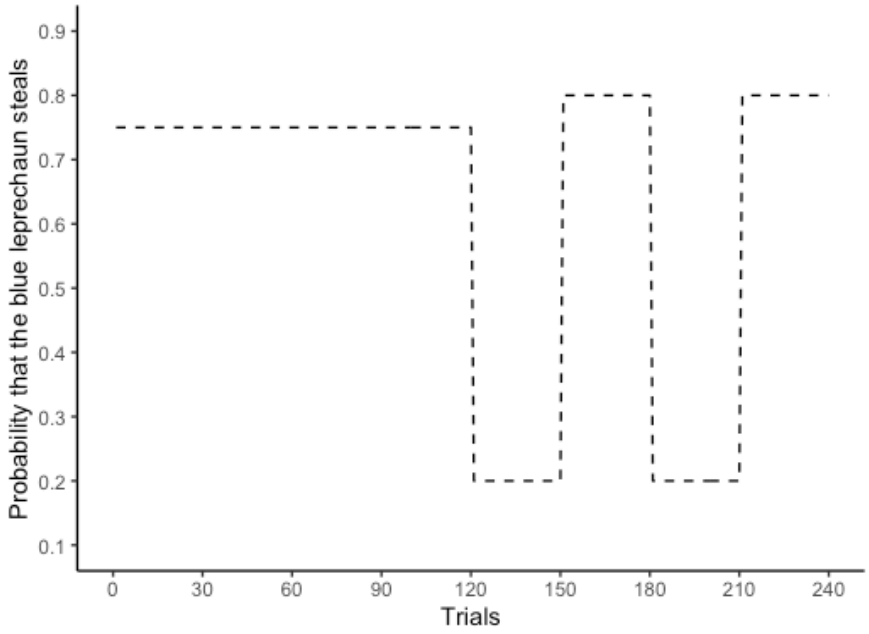


Figure 4. An example of the changes in the steal probability of the blue leprechaun.



Ethics Approval

This study has been approved by the Dublin City University research ethics committee (DCUREC/2021/070). People who are interested in participating will be instructed to access the study app (AthenaCX) where the plain language statement and consent form are presented to the participants before entering into the study. They will only be able to proceed if they provide consent.

Recruitment

Two groups, that is, patients with tinnitus and healthy controls, will be recruited in this study, and we will limit our recruitment to Ireland. Power analysis was performed to determine the sample size required to obtain significant results. The significance of the between-group difference and the correlation between adaptive learning ability and tinnitus symptoms are considered, and it turns out that the minimum sample size for satisfying both analyses is 54 with medium effect size. Thus, we will recruit 60 patients with tinnitus and 60 healthy controls. The 2 groups will be recruited through separate advertising campaigns, and both will be paid for their participation. To incentivize the participants to be adherent with the requests for data as well as to engage with the experimental decision-making task to the best of their ability, the payment is a One4all gift card; the value of the card is composed of two parts, that is, there is a basic payment (€10 [US $9.86]) plus a variable bonus (up to €30 [US $29.57]). The bonus will be determined by their response rates and performance in the decision-making task (measured by the gold coins remaining in each session) in the experiments. If the response rate to the EMA surveys is >50%, the participant is eligible to earn a bonus of €10 (US $9.86). The participants need to complete the decision-making task 4 times, each worth up to €5 (US $4.93), which means they will get up to €20 (US $19.72) for completing the decision-making task.

The patients with chronic tinnitus will be recruited through clinics and tinnitus support groups and associations; where possible, measures of hearing loss will be captured. We have established connections with The National Charity for Deafness and Hearing Loss and audiologists from Otologie Tinnitus Care (a tinnitus clinic in Dublin, Ireland). Both will help with the recruitment of patients with tinnitus. We will use an advertisement seeking people whose lives are affected by tinnitus. Eligible participants for the group of patients with chronic tinnitus will be those aged between 18 and 70 years who have experienced subjective tinnitus for ≥6 months and have access to a smartphone with internet capability. The healthy group will be recruited through our clinical partners and by posting advertisements on social media. The same doctors helping recruit patients with tinnitus will also be asked to identify likely healthy matches for the patients with tinnitus that they recruit. Thus, we will recruit the group of patients with tinnitus first, which will allow us to establish a distribution of age and gender that we will match in the subsequent round of healthy control recruitment. The healthy participants will be matched with the patients with tinnitus of the same gender and similar age with a difference of up to 5 years. Healthy participants who are interested in participating in the experiment can email us and will be recruited if they suit our study-matching needs.

All participants will need to register their interest via the link provided in the recruitment poster. We will get back to them as soon as we receive their registration information. We will forward the instructions for joining the experiment and ask each participant to meet one of the investigators on the web in case they have any questions. This step alone, while adding to the time burden for the researcher, should improve data quality and reduce the chances of multiple enrollments by the same person. We will also follow up with the participants on the fourth day to check whether they had any issues with receiving notifications and to encourage them to be more positively engaged. Please refer to Figure 5 for the workflow of the recruitment process.

Figure 5. The workflow of the recruitment process.

Statistical Analysis

Baseline Self-report Analysis

Standard descriptive statistics will be applied to describe the baseline assessments of the 2 groups, including demographic characteristics, tinnitus symptom severity, and psychological assessments. Continuous variables will be summarized by measures of central tendency and variability, whereas categorical variables will be described by measures of frequency and relative frequency. Correspondingly, a 2-tailed *t* test will be used for assessing differences in the distributions of continuous variables between the 2 groups, and the Pearson chi-square test will be applied to categorical variables.

Baseline Behavior Data Analysis

Overview

The baseline behavior data collected from the volatility decision-making task will be analyzed on three levels—basic exploratory data analysis, nongenerative computational modeling analysis, and generative computational modeling analysis—to capture the differences in decision-making under contingency volatility between the healthy controls and patients with tinnitus. The nongenerative analysis will investigate the effects of loss and the magnitude of loss on the choices during the task, whereas the generative analysis will reveal the underlying cognitive processes while participants make decisions. The details of the 3 levels are presented in the following sections.

Exploratory Data Analysis

We will first conduct an exploratory analysis of the behavioral choice data collected in the baseline experiments to capture the choice preferences of the patients with chronic tinnitus and the healthy controls. Several model-independent measures of behavior will be considered; for example, we will visualize how often participants choose the good leprechaun, that is, the leprechaun less likely to steal gold coins (ie, percentage of minimizing probability of potential losses) and how often they choose the leprechaun with the smaller stealing magnitude (ie, percentage of minimizing magnitude of potential losses). We will also explore the probability of repeating and switching an action, that is, win-stay and lose-shift, to capture fundamental aspects of learning. All of these measures will be visualized at 3 levels. At the trial level (averaging across participants), the plot demonstrates the trial-by-trial dynamic of the choice behavior. At the participant level (averaging across trials), the plot illustrates individual variation. At the overall level (averaging across both trials and participants), the plot provides the average performance of the whole group.

Nongenerative Computational Modeling Analysis

A logistic regression model will be trained to predict participants' learning dynamics. It will estimate the probability of staying versus switching based on the loss in the previous trial (main effect of the loss), current difference in loss magnitudes between the 2 options (main effect of potential loss magnitudes), and the interaction (loss × difference in loss magnitudes).

Generative Computational Modeling Analysis

To understand the underlying decision-making processes, generative computational models are developed to break performance down into several interpretable cognitive components. Several computational models have been developed and are described in the literature [29,51]. The common feature

of these models is that they all include a learning rate parameter for capturing the extent to which the outcome probability estimates are adjusted, given the unexpectedness of the previous trial's outcome; a risk preference parameter to allow for individual differences in how they weight outcome magnitude versus outcome probability; and an inverse temperature parameter to control the degree to which the expected values are used in determining the option chosen. What we refer to here as *model 1* and *model 2* in the study by Gagne et al [51] are introduced for demonstration purposes. It is worth noting here that various models will be fitted, except for these 2 models, and model comparison will be conducted to select the model that best describes the behavioral data, subject to appropriate validation processes to avoid overfitting.

Model 1 supposes that the probability P_t that a good outcome (no loss of coins) would result from choosing the blue leprechaun rather than the red leprechaun is updated on a trial-by-trial basis using the Rescorla-Wagner rule.

$$P_t = P_{t-1} + \alpha(O_{t-1} - P_{t-1})$$

in which the learning rate $\alpha \in (0, 1)$ determines how much weight the decision-maker gives to the recent outcomes when updating their expected probability. The outcome O_{t-1} is coded as 1 if the blue leprechaun is chosen and produces a good result or if the red leprechaun is chosen, followed by a bad result. O_{t-1} is coded as 0 for the opposite situation in the task. The initial outcome probability P_t is set as 0.5.

The outcome probability estimate is then adjusted to P_t' using a risk preference parameter (γ (0, 10)) to capture the relative importance of the magnitude of losses versus the outcome probability. If $\gamma<1$, it means that the participant places greater weight on the magnitude of losses, whereas if $\gamma>1$, it means that the participant places greater weight on outcome probability when performing a choice.

$$P_t' = \min\{\max[(\gamma(P_t - 0.5) + 0.5), 0], 1\}$$

The expected value for each leprechaun is then calculated through multiplying the adjusted outcome probability and loss magnitude separately, before taking the difference in expected values between the 2 leprechauns.

$$v_t = P_t' M_t^{blue} - (1 - P_t')M_t^{red}$$

Finally, the action probabilities are generated using a softmax function with an inverse temperature parameter β, which controls the degree to which the expected values are used in choosing the leprechauns.

Model 2 uses the same assumption as *model 1* in terms of updating the outcome probability (Rescorla-Wagner rule). However, in contrast with *model1*, *model2* assumes that the decision-makers combine outcome probability and outcome magnitude additively, using a mixture weight (λ). Furthermore, the difference in outcome magnitudes is nonlinearly scaled with a scaling parameter ($r \in [0.1, 10]$) to capture any potential bias that the participants have toward treating the differences in outcome magnitudes.

$$v_t = \lambda[p_t - (1 - p_t)] + (1 - \lambda)[M_t^{blue} - M_t^{red}]^r$$

This model also incorporates a choice kernel (k_t), which acts like an average window moving forward as the trials proceed. It is updated by an update rate parameter ($\eta \in (0, 1)$), which can be used to determine the number of recent choices contained in the value of the choice kernel on the current trial.

$$K_t = k_{t-1} + \eta(C_{t-1} - k_{t-1})$$

The expected value and the choice kernel are both passed through a softmax function to decide the probability that the blue leprechaun is chosen in the current trial with two separate inverse temperatures (β and β_k).

There are 3 free parameters (α, γ, and β) in *model 1* and 6 free parameters (α, λ, r, η, β, and β_k) in *model 2*. All of the generative models will be estimated with the hierarchical Bayesian method, in which we assume that the parameters of individual participants are generated from parent distributions.

The primary measure of interest in the leprechaun task is whether the participants adapted their learning rates in response to the changes of the environment (from stable block to volatile block). To take the potential within-participant correlation of the stable and volatile parameters into account in the modeling process, we assume that each participant had a stable and volatile parameter with a prior distribution defined by the multivariate normal distribution with means μ_{stable} and $\mu_{volatile}$ and covariance matrix Σ, which can be converted to a correlation matrix. The model will be implemented in Stan [52], a probabilistic programming language, so that the parameters can be estimated using Markov chain Monte Carlo algorithms. The Cholesky decomposition trick has been widely used in the Monte Carlo method for simulating systems with multiple correlated variables [53]. Thus, in the implementation, we will use this technique to decompose the correlation matrix into the product of a lower triangular matrix (Cholesky factor) and its transpose; thus, the correlation matrix of the stable and volatile parameters can be derived.

The Impacts of Baseline Tinnitus Severity and Psychological Measures

The impacts of baseline self-reports, including tinnitus, anxiety, and depression, on participants' adaptation performance on the task are then analyzed. We first extract the median values of each participant's parameters and calculate the differences between the paired stable and volatile parameters estimated in generative computational modeling analysis. The differences of each participant are then used as the outcome variable in a linear regression analysis, with baseline tinnitus severity as well as anxiety and depression scores as predictors.

Longitudinal Data Analysis

Our next question concerns whether the computational markers of the contingency volatility decision-making task of the

participants with tinnitus can be predictors for detecting moment-to-moment tinnitus symptom severity. The behavioral data of the 2 groups collected in the longitudinal experiment will be fitted to the best fitting model obtained in the baseline generative modeling analysis. Our primary analysis for the participants with tinnitus will be repeated measures linear regression, with the EMA tinnitus severity as outcome variable and the model-derived parameters that capture adaptation ability of learning as independent variables. This analysis estimates the level of tinnitus distress when a patient with tinnitus is more capable of learning the contingency volatility of the environment compared with when the same patient is less capable of learning the contingency volatility of the environment. In the second model, emotional status will be considered as another independent variable together with the model-derived parameters to predict tinnitus severity, that is, multiple regression, so that the impacts of emotional status can be examined. For the healthy controls, we will mainly focus on the test-retest reliability of their task performance.

Results

The implementation of the experiments has been completed. We have tested the workflow of the experiment, the timing of the EMA surveys, the notification functionality on various Android and iOS systems, and so on. Everything works as anticipated. For the recruitment, we designed a poster in which a link is embedded so that participants can register their interest as soon as they read the advertisement. We also developed various versions of the instructions (text, interaction-enabled, and video versions) that demonstrate how to engage with the study step by step. All of these materials have been shared with the audiologists who have agreed to help with the recruitment. The data collection effort will take place over 12 months. We will start the analysis as soon as the data collection is finished. The results are expected to be published in December 2023.

Discussion

Overview

The hypothesis of this study is that patients with chronic tinnitus demonstrate impaired adaptive learning ability in changing environments compared with a healthy population. This impairment might be exacerbated at the moment when the patients are experiencing tinnitus symptoms. This is the first study to investigate the impacts of tinnitus on decision-making and the first to acquire computational markers to investigate what differences, if any, exist between the cognitive processes of patients with tinnitus and a healthy population. In addition, by leveraging smartphone technology, this study will be the first, to the best of our knowledge, to perform many repeated measures of decision-making based on real-time EMAs of tinnitus symptoms in a real-world population consisting of patients with tinnitus, making it uniquely possible (compared with cross-sectional designs and traditional methods) to capture ongoing tinnitus vulnerability.

The findings and implications of this study will be presented to the audiologists we are working with as well as the scientific community. Identifying objective measures robustly associated with tinnitus fluctuation is important for monitoring trajectories of tinnitus development as a result of potential treatment. If the fluctuation of tinnitus symptoms is truly associated with decision-making performance, the computational phenotypes extracted have the potential to serve as objective measurements of tinnitus severity in the future. The clinical management and treatment of patients with tinnitus will benefit from these potential computational markers.

Limitations

Nevertheless, this study also includes limitations. Participants may fail to respond to the symptom survey request and therefore fail to accumulate the required number of EMA data points to feed the calculation that decides upon delivery of the decision-making task. Such neglect may arise because of competing tasks and priorities or interruptions that arise from the normal activities of daily living. The bonus payment feature has been introduced to address this issue and improve response rates. Another limitation is that it is possible that the decision-making task may never be triggered because of the probabilistic nature of the algorithm, although the triggering algorithm has been designed to overcome this limitation by adapting to individual adherence behavior.

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Data Availability

The data sets generated and analyzed during this study will be anonymized and made available via open science at Zenodo.

Conflicts of Interest

None declared.

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Abbreviations

EMA: ecological momentary assessment
ESIT-SQ: European School for Interdisciplinary Tinnitus Research Screening Questionnaire
MDI: Major Depression Inventory
MTQ: Mini Tinnitus Questionnaire
STAI: State-Trait Anxiety Inventory
VAS: visual analog scale

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Protocol

Mobile Digital Health Intervention to Promote Nutrition and Physical Activity Behaviors Among Long-term Unemployed in Rural Areas: Protocol for a Randomized Controlled Trial

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Abstract

Background: Long-term unemployed have poor nutritional and physical activity statuses, and, therefore, special health promotion needs. Particularly in rural areas, however, they often do not have access to health promotion service. Thus, new promising strategies to improve the health of long-term unemployed are needed. Hence, a digital health intervention to promote nutritional and physical health behaviors was conceived, and the effectiveness of the intervention in combination with face-to-face sessions will be evaluated in a randomized controlled trial.

Objective: The aim of this study is to elucidate the effectiveness of a mobile digital health intervention to promote the nutritional and physical activity behaviors of long-term unemployed in the rural areas of Germany.

Methods: The 9-week intervention aims to promote nutritional or physical activity behavior by improving drinking habits, increasing the consumption of fruits, vegetables, and whole grains, increasing daily step count, strengthening muscles, and improving endurance. The intervention design is based on the transtheoretical model and is implemented in a mobile app using the MobileCoach open-source platform. The effectiveness of the intervention will be elucidated by a 9-week, 2-armed, parallel-designed trial. Therefore, long-term unemployed will be recruited by employees of the German social sector institutions and randomized either to receive information brochures; the digital intervention in the form of a mobile app; and 3 face-to-face sessions regarding technical support, healthy eating, and physical activity (n=100) or to receive a control treatment consisting of solely the hand over of information brochures (n=100). The effectiveness of the intervention will be assessed using questionnaires at baseline, after 9 weeks in face-to-face appointments, and after a 3-month follow-up period by postal contact. The use of the mobile app will be monitored, and qualitative interviews or focus groups with the participants will be conducted. Incentives of €50 (US $49.7) will be paid to the participants and are tied to the completion of the questionnaires and not to the use of the mobile app or progress in the intervention.

Results: The effectiveness of the intervention in promoting the nutritional and physical activity behaviors of long-term unemployed participants will be elucidated. The adherence of the participants to and the acceptance and usability of the mobile device app will be evaluated. Recruitment started in March 2022, and the final publication of the results is expected in the first half of 2023.

Conclusions: Positive health-related changes made by the intervention would display the potency of digital health interventions to promote nutritional and physical activity behaviors among long-term unemployed in the rural areas of Germany, which would also contribute to an improved health status of the German population in general.

Trial Registration: German Clinical Trials Register DRKS00024805; https://www.drks.de/DRKS00024805

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KEYWORDS

digital health intervention; behavior changes; nutrition; physical activity; long-term unemployment; rural areas; Germany; mobile phone

Introduction

Background

As of 2020, approximately 7.2% of the total working population was unemployed around the globe [1]. This condition was exacerbated by the COVID-19 pandemic. In Germany, the rate of unemployment rose from 5.3% in prepandemic January 2020 to 6.3% in January 2021 [2,3]. Although the unemployment rate dropped again to 5.4% in January 2022, approximately 2.5 million people of the German population were unemployed, of which 40.2% were without work for >12 months [4]. There is striking evidence that unemployment is associated with poor health outcomes (reviewed in the study by Jin et al [5]). In 2011, Roelfs et al [6] meta-analyzed that all-cause mortality was 63% higher in the unemployed population than in the working population. In addition to increases in mental health diseases, such as depression, anxiety disorders [7], psychoses [8], and substance abuse [9], physical diseases also occur more often in the unemployed than in the employed [10]. These include cancer [11] and cardiovascular events [12,13]. deBoer et al [11] compared participants who had cancer in recent years with cancer-free control participants and found statistically significant higher unemployment rates in the former, particularly in those with cancers of the gastrointestinal system (relative risk of 1.41). Moreover, Gallo et al [13] showed that the unemployed had 2.4- and 2.5-fold higher risks of stroke and myocardial infarction (MI), respectively. In this regard, the risk of MI increases with increasing length of unemployment. While the relative risk of MI was 1.49 times higher in participants who were unemployed for up to 8 months than in the employed participants, it was 3.08 times higher in those who were unemployed for >16 months [14]. Gastrointestinal cancer and cardiovascular events are also known to be influenced by poor nutrition (reviewed in the study by Wei et al [15]) and physical activity behavior (reviewed in the study by Lacombe et al [16]), which are generally common among the unemployed [17,18].

Although there is no difference in health-related behavior between long-term unemployed persons in urban areas and those in rural areas, the latter have more difficult access to health promotions from, for example, primary care physicians or offers from health insurances because of a lack of financial resources, poorly developed public transportation infrastructure, and thus lower mobility [19]. This shows that strategies to reach the long-term unemployed in rural areas are especially in need. Therefore, interventions designed in a digital format might be promising strategies to promote the health of the long-term unemployed in rural areas.

In general, digital health interventions (DHIs), particularly those on mobile devices, have been shown to be effective tools for inducing health-related behavior changes [20-23]. Moreover, conversational agents (CAs), computer programs that simulate conversations, are being increasingly used as DHIs [24], including behavior change apps to promote healthy eating [25] or physical activity [26]. However, DHIs require access to technology and sufficient knowledge to use it (digital literacy). Social health inequalities may contribute to a digital gap, as next to older age and being male, lower level of education and lower annual income are associated with a lower likelihood of owning a smartphone [27]. By contrast, Rhoades et al [28] showed that more than half of the homeless population owns smartphones and uses the internet daily. Moreover, Reinwand et al [29] reported that unemployed persons in a randomized controlled study used the intervention more frequently than employed persons, probably because it was time consuming and they had more time to use it.

Objective

The aim of this study is to elucidate whether a DHI, conceived for use on mobile devices, can improve the nutritional and physical activity behaviors of long-term unemployed in the rural areas of Germany. Therefore, a customized 9-week intervention is conceptualized and implemented in a mobile app and will be tested in a randomized controlled trial (RCT). The effectiveness of the intervention will be assessed by questionnaire assessment.

Methods

Intervention Contents and Mobile App

The intervention design was planned in accordance with the intervention mapping approach [30]. The intervention content and the mobile app were designed through a user-centered approach including the needs assessment [31], a participatory design workshop with long-term unemployed (N=7), and a pretest for formative evaluation.

The intervention content is based on the transtheoretical model (TTM) for health behavior change by Prochaska et al [32,33]. The 9 weeks of the conceptualized intervention are adapted to the phases of the TTM as follows: week 1, “precontemplation”; week 2, “contemplation”; week 3, “preparation”; weeks 4 to 7, “action”; and weeks 8 to 9, “maintenance.” Before the intervention, the participants were assigned to week 1

("precontemplation"), week 2 ("contemplation"), or week 3 ("preparation") depending on their initially reported nutritional or physical activity behavior. The initially reported behavior was assessed by answering the following questions: "Do you regularly eat a balanced diet for example, foods such as fresh fruits and vegetables several times a week, or whole grains as well as dairy products sometimes and less sausage and meat?" or "Do you exercise regularly, for example, walking, biking, swimming, or going to the grocery store, that is, for at least 30 minutes each, at least 5 days per week?" If the questions were answered with "no," the participant will receive the following selections: (a) "...and I do not think about eating a more balanced diet/exercising more," (b) "...but I do think about eating a more balanced diet/exercising more," or (c) "...but I will start eating a more balanced diet/exercising more." The participant will (1) start in week 1 if the initial question is answered with "no" and then (a) is selected, (2) start in week 2 if the initial question is answered with "no" and then (b) is selected, or (3) start in week 3 if the initial question is answered with "yes" or with "no" and then (c) is selected. Therefore, the actual intervention duration varies between 7 and 9 weeks. The TTM stage is measured only once at the beginning of the intervention. However, the participants reach the next TTM stage only when they proceed to participate in the intervention. The intervention will be adaptive, and the participants must initially decide whether they want to promote their nutritional or physical behavior. Furthermore, in week 3 ("preparation"), they can choose to pursue only one of the following aims: (n1) change drinking habits, (n2) eat more fruits and vegetables, (n3) eat more whole grain products, (pa1) increase step count, (pa2) strengthen muscles, or (pa3) improve endurance, depending on whether they initially chose to promote nutritional (n1-3) or physical activity (pa1-3) behavior change. After the completion of the chosen aim, they will have the opportunity to select a new one. The intervention contents are designed in accordance with official national and international nutritional [34,35] and physical activity [36,37] recommendations. Detailed information about the intervention contents is provided in Tables 1 and 2. The language of the intervention is German.

Table 1. Intervention contents to promote nutritional behavior.

Phase of the TTM[a] (week)	Pursued goals	Intervention content	Behavior change techniques according to Michie et al [38]
Precontemplation (1)	Recognize the benefits of healthy eating and the risks of unhealthy eating and perceive conducive environmental conditions that facilitate the change of problem behavior (unhealthy eating)	(1) Benefits of healthy eating and risk of unhealthy eating, (2) information about the food pyramid, (3) information about serving size and food frequencies, (4) information about macronutrients, and (5) information about micronutrients	Self-monitoring of behavior, information about health consequences, salience of consequence, prompts/cues, and pros and cons
Contemplation (2)	Recognize the added value of healthy eating for one's own health and well-being and recognize the positive and negative consequences of current and target behavior for oneself and the environment	(1) Effects of healthy eating on digestion and well-being, (2) explanation on how to understand and use the Nutri-Score, (3) benefits of fresh foods, (4) information about food waste, and (5) information on various health parameters	Feedback on behavior, self-monitoring of behavior, self-monitoring of the outcomes of behavior, information about health consequences, salience of consequences, information about social and environmental consequences, demonstration of the behavior, pros and cons, and imaginary reward
Preparation (3)	Learning to set and pursue your own goals: (1) change drinking habits, (2) eat more fruits and vegetables, and (3) eat more whole grain products	(1) Self-reflection/self-image in relation to nutrition and nutrition habits, (2) committing to 1 out of 3 goals, (3) dealing with the weaker self, (4) building social relationships, and (5) pros and cons of the selected goal	Problem solving, action planning, discrepancy between current behavior and goal, self-monitoring of outcome(s) of behavior, feedback on the outcome(s) of behavior, social support (unspecified), verbal persuasion about capability, and pros and cons
Action (4-7)	Goal is pursued and implemented	(1) Overview, task, and information about weekly themes, recipes, and suggestions, (2) tips on planning purchasing, (3) tips to increase healthy nutrition in everyday life or leisure time, (4) motivation (push messages, positive feedback, and encouragement of participants' abilities), (5) information about various nutrition themes, and (6) daily and weekly task checks	Goal setting (behavior), problem solving, feedback and monitoring, feedback on behavior, self-monitoring of behavior, comparison of behavior, demonstration of the behavior, repetition and substitution, practice/rehearsal, behavior substitution, generalization of target behavior, graded tasks, reduce negative emotions, self-belief, and verbal persuasion about capability
Maintenance (8-9)	Consolidation of the goal and identification of counterstrategies	(1) (Self-) Reward, (2) habit-building tips, (3) role models implementing healthy nutritional behavior, (4) successfully identifying and overcoming barriers, and (5) motivation (push messages, positive feedback, and encouragement of participants' abilities)	Self-monitoring of behavior, instruction on how to perform the behavior, demonstration of the behavior, habit formation, nonspecific reward, self-reward, reduce negative emotions, and focus on past success

[a]TTM: transtheoretical model [32,33].

Table 2. Intervention contents to promote physical activity behavior.

Phase of the TTM[a] (week)	Pursued goals	Intervention content	Behavior change techniques according to Michie et al [38]
Precontemplation (1)	Recognize the benefits of physical activity and the risks of physical inactivity and perceive conducive conditions that facilitate the change of problem behavior (physical inactivity)	(1) Benefits of physical activity for different parts of the body, (2) consequences of physical inactivity, (3) opportunities for physical activity in everyday life and sport, (4) World Health Organization recommendations, (5) highlighting the positive effects of everyday physical activity, (6) invitations to try physical activity, (7) reflection on everyday physical activity and sporting activities in youth, in old age, and today, and (8) highlighting resources in the own environment	Self-monitoring of behavior, instruction on how to perform the behavior, information about health consequences, salience of consequence, and prompts/cues
Contemplation (2)	Recognize the added value of physical activity for one's own health and well-being, perceive the current state of physical activity, and recognize the positive and negative consequences of current and target behavior for oneself, the environment, and one's surroundings	(1) Effects of physical activity on well-being and environment, (2) information on various health parameters, (3) perception of well-being and feelings through self-tests, tasks, and challenges, (4) possibility to do own calculations (eg, pulse measurement), (5) perceive body signals/get to know stress limits, (6) stimulating exchange with friends/acquaintances, and (7) independent reflection on the consequences of lack of physical activity in one's own environment, now and in the past	Self-monitoring of outcome(s) of behavior, information about health consequences, salience of consequences, information about social and environmental consequences, monitoring of emotional outcomes, and reduce negative emotions
Preparation (3)	Learning to set and pursue your own goals: (1) increase step count, (2) strengthen muscles, or (3) improve endurance	(1) Self-reflection/self-image in relation to physical activity, (2) analyze strengths and weaknesses, (3) time management, (4) motivation, (5) build social relationships, (6) relaxation exercises, (7) behavioral observation and help to classify average activity and feedback, and (8) committing to 1 out of 3 goals	Problem solving, action planning, discrepancy between current behavior and goal, self-monitoring of outcome(s) of behavior, feedback on outcome(s) of behavior, information about antecedents, social support (unspecified), and verbal persuasion about capability
Action (4-7)	Goal is pursued and implemented	(1) Strategies on how to set and achieve a goal, (2) weekly and daily goals, (3) tips on different ways to increase physical activity in everyday life/leisure time, (4) motivation (push messages, positive feedback, and encouragement of participants' abilities), and (5) training plans	Goal setting (behavior), problem solving, feedback and monitoring, feedback on behavior, self-monitoring of behavior, comparison of behavior, demonstration of the behavior, repetition and substitution, behavioral practice/rehearsal, behavior substitution, generalization of target behavior, graded tasks, reduce negative emotions, self-belief, and verbal persuasion about capability
Maintenance (8-9)	Consolidation of the goal and identification of counterstrategies	(1) (Self-) Reward, (2) habit-building tips, (3) role models implementing physical active rather than inactive behavioral alternatives, (4) successfully identifying and overcoming barriers, and (5) motivation (push messages, positive feedback, and encouragement of participants' abilities)	Self-monitoring of behavior, instruction on how to perform the behavior, demonstration of the behavior, habit formation, nonspecific reward, self-reward, reduce negative emotions, and focus on past success

[a]TTM: transtheoretical model [32,33].

In addition to the theoretical model of behavior change, behavior change techniques (BCTs) are used. BCTs are active components that aim to change behaviors as a part of an intervention [38,39]. Here, the appropriate BCTs are selected in relation to the individual phases of the TTM (Tables 1 and 2).

The DHI is implemented in a mobile app using the MobileCoach intervention platform [40,41], an open-source platform for the design and deployment of DHIs based on rule-based CA. Here, the participant chooses 1 of 4 coaches before the intervention, and the intervention information is provided as text messages, graphics, and videos or by gamification and storytelling approaches by emulating human-like interactions (Figure 1). The participants receive new intervention content once a day (at midnight). Additional content is sent only after the previous day's content is completed. Push notifications are sent once a day to motivate the participants to complete the intervention content.

Figure 1. Screenshots of the mobile app. The information in the app is provided as text messages, graphics, and videos or by gamification and storytelling approaches. Screenshots taken on EMUI (version 12.0.0, Huawei).

The intervention content and mobile app were evaluated in a pretest [42]. In the pretest, the long-term unemployed participants (N=12) were asked to test the mobile app for 9 weeks, and feedback was recorded every 3 weeks. The intervention content and mobile app were modified as suggested by the participants.

Randomized Controlled Intervention Study

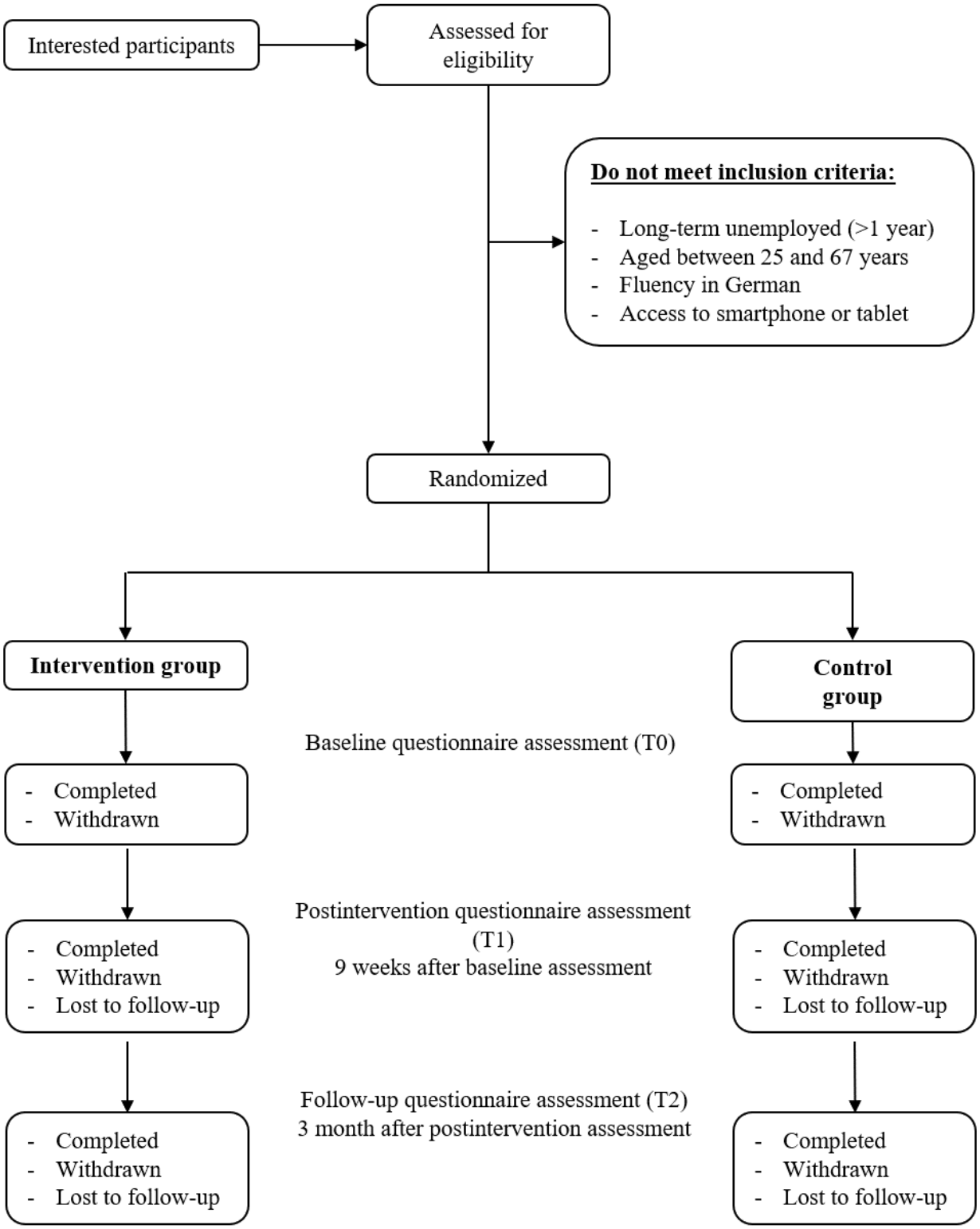
Study Design

To elucidate the effectiveness of the designed intervention, a 2-armed parallel-designed RCT is conducted with the long-term unemployed of the rural areas of Germany. The study protocol has been approved by the ethics committee of the State Medical Chamber of Baden-Wuerttemberg, Germany (number F-2019-106), and registered in the German Clinical Trials Register (DRKS00024805).

The intervention group (n=100) receives information materials (eg, brochures) regarding healthy nutrition and physical activity behavior and has access to the DHI in the form of a mobile app (refer to the section Intervention Contents and Mobile App). The intervention period is set to be 9 weeks, as this has been shown to be in the range of adequate time spans for DHIs (usually between 4 and 12 weeks) [43-46]. At baseline, after 3 and 6 weeks of intervention, the participants in the intervention group are scheduled to visit the study center located in the affiliated social sector institution to attend additional face-to-face sessions regarding technical instructions on the mobile app, healthy nutrition, and physical activity behavior, respectively. The control group (n=100) will meet at baseline at the study center to receive information material in the form of, for example, brochures (same as the intervention group) but will not have access to the DHI and will not attend the face-to-face sessions regarding technical instructions, healthy nutrition, and physical activity behavior. In addition, all participants (intervention and control group) will visit the study center after 9 weeks of intervention for a joint conclusion and to receive an incentive of €50 (US $49.7). The group allocation will not be blinded, as this is not applicable to the study design. If possible, investigators analyzing the data will be unaware of the group assignment.

Recruitment is conducted via the social sector (eg, employment societies) of the rural regions in southwestern Germany, and participant recruitment started in March 2022. Recruitment will proceed until the required number of participants is reached or until the end of 2022. The inclusion criteria are long-term unemployment (defined as >12 months), between 18 and 67 years of age, and fluency in German. In addition, the participants must have access to a smartphone or tablet with Android (minimum version 6.0) or iPhone (minimum version 9.0) operating system. As the focus of this study is on rural areas, the affiliated social sector institutions must be located in rural areas. The long-term unemployed volunteers will be allocated randomly (Figure 2) to 1 of the 2 groups by a randomization list with a block size of 4, stratified to the social sector institutions, which accomplished the recruitment.

Figure 2. Participant flow diagram. Interested participants will be assessed for eligibility, and participants not meeting the inclusion criteria will be excluded. Remaining participants will be randomized into two groups (intervention and control). The completion, withdrawal, and losses to follow-up will be monitored, and the effectiveness of the intervention will be assessed at baseline (T0), after intervention (T1), and at follow-up (T2) by questionnaire assessment.



Outcomes

The effectiveness of the DHI will be evaluated by self-reported questionnaire assessment in German at baseline (T0), after 9 weeks of intervention (T1) at the study center, and after a 3-month follow-up period (T2) by mail services. Physical activity is assessed using the International Physical Activity Questionnaire in the German short version. The International Physical Activity Questionnaire has been validated several times [47,48] and measures the duration (minutes) and frequency (days) of sitting, moderate physical activity, and vigorous physical activity during the last 7 days, which will be expressed in minutes per day.

The food frequency questionnaire (FFQ) is a revised version of the FFQ used in the German Health Interview and Examination Survey for Adults (DEGS) [49], which was validated by the study by Haftenberger et al [50]. The FFQ consisted of 68 questions regarding the consumption frequency and portion sizes of food items in the past 4 weeks. The food intakes assessed by the FFQ will be expressed as servings of the consumed food item per day, and a food-based diet quality score will be analyzed according to the study by Masip et al [51].

To elucidate the adherence of the participants, the use of the mobile app will be monitored throughout the study period, and the affinity to technological devices is assessed by questionnaires before the study. The usability and acceptance of the mobile app will be assessed according to the unified theory of acceptance and use of the technology model [52]. Therefore, qualitative interviews or focus groups with the participants will be conducted and analyzed by structured content analysis according to the method by Mayring [53] using MAXQDA (version 2022; VERBI GmbH).

Statistical Analysis

Sample size calculation was conducted using G*Power (version 3.1.9.7, Heinrich Heine University Duesseldorf). As shown in a meta-analysis by Duan et al [54], the postintervention effect sizes of nutrition- and physical activity–related outcomes in patients with noncommunicable diseases in the intervention and control groups range widely from −1.11 to 6.40 (mean 0.85, SD 1.48) and −0.13 to 4.78 (mean 0.78, SD 1.77), respectively. As we suggested a lower adherence and thus a lower effect size in the targeted group in this study (long-term unemployed), we assumed the effect to be of medium size (Cohen d=0.5). With an alpha error of .05 and a power (1-β) of .80, a total sample size of 128 participants (n=64 per group) was calculated. In addition, a previously conducted pretest showed a high dropout of participants of approximately 33% after 9 weeks of treatment, defined as participants who did not reach the “action” phase according to Prochaska et al [33]. Thus, to take further potentially high dropout rates into account, we aim to include a total of 200 participants (n=100 per group) in this study.

To investigate the impacts of the intervention on the self-reported health outcomes assessed by the questionnaire, differences between the 3 data collection times (T0, T1, and T2) and between the 2 groups (intervention vs control) will be analyzed. To test for normal distribution, all data will be subjected to the Kolmogorov-Smirnov test. In case of normal distribution and homoscedasticity of variance (Mauchly’s sphericity test), time-dependent differences will be analyzed by repeated measurement analysis of variance with post hoc comparison by Bonferroni test. In case of nonparametric data, the Friedman test will be used, and the significance level will be corrected using Bonferroni correction. If a normal distribution is given, the differences between the 2 groups at 1 time point will be compared by 2-tailed t test. Otherwise, the data will be analyzed by Mann-Whitney U test. All differences will be considered statistically significant with P values <.05. Statistical analysis will be conducted using SPSS Statistics (version 28, IBM Corporation).

Ethics Approval

This study was approved by the ethics committee of the State Medical Chamber of Baden-Wuerttemberg, Germany (number F-2019-106), and registered in the German Clinical Trials Register (DRKS00024805; registered on February 22, 2022). Written consent is obtained from all the participants before enrollment in this study.

Results

The anticipated data will show whether the blended intervention can improve the nutritional or physical activity behavior of long-term unemployed in the rural areas of Germany. Individual effects of the intervention period and differences between the intervention and control groups will be elucidated. Furthermore, data on the use of the mobile app will show the adherence of the target group. In addition, the usability and acceptance of the mobile app will be evaluated.

Study enrollment started in March 2022. Study completion is due at the end of 2022. The first study outcomes are expected to be available in the spring of 2023. The data will be published in international peer-reviewed journals.

The study is part of the project “eHealth solutions to promote dietary and physical activity behaviors among the long-term unemployed in rural areas,” which is funded by the Federal Ministry of Education and Research (BMBF) since 2019 until 2023 (after a COVID-19 pandemic–related extension).

Discussion

Principal Findings

In this study protocol, a customized DHI to promote the nutritional and physical activity behaviors of long-term unemployed is presented. The mobile app will be tested in an RCT with long-term unemployed volunteers in a parallel-armed design in 2022.

Comparison With Prior Work

Improving nutrition literacy and promoting physical activity are suggested to be successful strategies for improving the health of long-term unemployed. However, health interventions for the unemployed are scarce [55]. Moreover, they often fail to improve physical health [56,57], suggesting that either (1) the intervention design of these studies was inappropriate or (2) the intervention medium was not suitable for the targeted group. Regarding the intervention design, the intervention concept in this study is based on the TTM. The TTM is a stage-based behavior change model, which was first described for the cessation of smoking [33] and was proven to be effective by a review of Spencer et al [58]. The TTM has also been successfully used in behavior change interventions regarding nutritional (reviewed in the study by Nakabayashi et al [59]) and physical activity behaviors (reviewed in the study by Adams and White [60]), suggesting that the TTM is an effective model to change the nutritional and physical activity behaviors of long-term unemployed. However, the effectiveness in changing the behaviors is also discussed controversially [61-63], especially in regard to long-term behavior changes [60].

The intervention was conceived in the form of a DHI, which has been proven earlier to be a successful intervention medium for promoting healthier eating [25] and physical activity choices [26] in vulnerable groups. However, to date, there is no DHI specifically designed to meet the needs of long-term unemployed. Although it has been shown that mobile phone ownership is not considered a serious barrier to participate in DHIs, even for unemployed individuals [64], the accessibility to a DHI, and therefore its effectiveness, can be improved by considering support for older devices, the possibility of offline use, low digital literacy requirements, and the involvement of the targeted people in the development process [65]. Thus, the current intervention addresses health-related topics identified by the participative input of the long-term unemployed in Germany through interviews and workshops [31]. The conceived intervention is then realized by low-threshold informational content, supported by graphical files, links, and videos. A key point of the DHI is the use of a rule-based CA, which emulates an informal human-like interaction and is suggested to be encouraging and motivating [24]. Another strength of the present intervention is the blended use of an easily accessible DHI in the form of a mobile app in combination with classical face-to-face appointments. Face-to-face interventions have been proven to be more effective than interventions designed solely in a digital format [66-68]. However, DHIs are easily accessible to a wide range of the population and are associated with lower financial and time commitments, as they can be used at any time at home. Blended interventions, the combination of DHIs with face-to-face interventions, have been used frequently for the treatment of mental disorders in adults (reviewed in the study by Erbe et al [69]) and are discussed to be feasible and more effective than stand-alone interventions in the treatment of substance abuses, as they significantly reduce the participant dropout rates [70-73]. In the planned study, the conception of the intervention in a blended design is expected to decrease the participant dropout and, therefore, increase the intervention effectiveness. To minimize an increased effort to participate in face-to-face appointments, they will be located in the social sector societies near to the long-term unemployed in the rural areas of Germany, where they have, in general, daily face-to-face appointments with the employees of the social societies. However, the recruitment of social societies that are willing to assist the study by providing long-term unemployed participants and the infrastructure to carry out face-to-face appointments might be difficult, especially under the complicated circumstances due to the COVID-19 pandemic (eg, hygiene and distance rules).

Limitations

This study has some limitations. First, we did not adapt the intervention according to the multiphase optimization strategy, which maximizes the translation of research into effective practice [74]. However, we did run a pretest while developing the intervention to ensure the feasibility of the blended intervention. Second, the effectiveness of the intervention is based on questionnaires and, therefore, might be underlying a reporting bias. Further studies might be necessary to measure physiological adaptation to a healthier lifestyle, for example, by measures of health-related biomarkers, such as markers for metabolic diseases [75] or cardiovascular health [76]. Third, as the participants receive incentives, they might have been overly motivated to use the mobile app. To counteract a potential overestimation of the app use through the incentives, we instructed the participants that the incentives are only tied to the completion of the questionnaire and not to the use of the mobile app. Finally, although in previously conducted interviews (N=20), most of the long-term unemployed in the rural areas of southwestern Germany (75%) had smartphones and regularly used mobile apps on their devices (Mages-Torluoglu, J, unpublished data, February 2020), some may not and, therefore, cannot participate in this study. However, the ownership of smartphone devices is still rapidly growing [77]. Thus, we feel that a DHI with face-to-face appointments is a promising strategy to improve the health of long-term unemployed in the rural areas of Germany. At this point, it must also be emphasized that behavior change strategies may only address the secondary effects of long-term unemployment. In general, improving living conditions (eg, better financial support or social inclusion) may be a more comprehensive strategy for promoting health among the unemployed.

Conclusions

The intervention presented in this study is tailored to the needs of the long-term unemployed and is implemented in a blended intervention consisting of a DHI based on the interaction with an internet-based CA and additional face-to-face interactions. The effectiveness of the blended intervention in promoting improved nutritional and physical activity behaviors of long-term unemployed participants will be evaluated in a protocolized RCT and measured by questionnaire assessment. If we could show that the health intervention designed for the study described above is effective in promoting beneficial choices regarding nutrition (eg, eating more fruits and vegetables) and physical activity (eg, improving endurance), this would be a first and an important step in promoting the general health of the unemployed. The blended intervention is intended for implementation in community health systems and can thus contribute to an improved health status of the German population in general.

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Data Availability

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

Authors' Contributions

IW was involved in the conceptualization, methodology, and writing—review and editing. JM-T was involved in the conceptualization, methodology, writing—review and editing, and funding acquisition. CK, CW, and KS were involved in the conceptualization, supervision, and funding acquisition. ACB was involved in the conceptualization, writing—original draft, visualization, and project administration.

Conflicts of Interest

None declared.

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Abbreviations

BCT: behavior change technique
CA: conversational agent
DHI: digital health intervention
FFQ: food frequency questionnaire
MI: myocardial infarction

RCT: randomized controlled trial
TTM: transtheoretical model

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Protocol

Developing an Artificial Intelligence Model for Reading Chest X-rays: Protocol for a Prospective Validation Study

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Abstract

Background: Chest x-rays are the most commonly used type of x-rays today, accounting for up to 26% of all radiographic tests performed. However, chest radiography is a complex imaging modality to interpret. Several studies have reported discrepancies in chest x-ray interpretations among emergency physicians and radiologists. It is of vital importance to be able to offer a fast and reliable diagnosis for this kind of x-ray, using artificial intelligence (AI) to support the clinician. Oxipit has developed an AI algorithm for reading chest x-rays, available through a web platform called ChestEye. This platform is an automatic computer-aided diagnosis system where a reading of the inserted chest x-ray is performed, and an automatic report is returned with a capacity to detect 75 pathologies, covering 90% of diagnoses.

Objective: The overall objective of the study is to perform validation with prospective data of the ChestEye algorithm as a diagnostic aid. We wish to validate the algorithm for a single pathology and multiple pathologies by evaluating the accuracy, sensitivity, and specificity of the algorithm.

Methods: A prospective validation study will be carried out to compare the diagnosis of the reference radiologists for the users attending the primary care center in the Osona region (Spain), with the diagnosis of the ChestEye AI algorithm. Anonymized chest x-ray images will be acquired and fed into the AI algorithm interface, which will return an automatic report. A radiologist will evaluate the same chest x-ray, and both assessments will be compared to calculate the precision, sensitivity, specificity, and accuracy of the AI algorithm. Results will be represented globally and individually for each pathology using a confusion matrix and the One-vs-All methodology.

Results: Patient recruitment was conducted from February 7, 2022, and it is expected that data can be obtained in 5 to 6 months. In June 2022, more than 450 x-rays have been collected, so it is expected that 600 samples will be gathered in July 2022. We hope to obtain sufficient evidence to demonstrate that the use of AI in the reading of chest x-rays can be a good tool for diagnostic support. However, there is a decreasing number of radiology professionals and, therefore, it is necessary to develop and validate tools to support professionals who have to interpret these tests.

Conclusions: If the results of the validation of the model are satisfactory, it could be implemented as a support tool and allow an increase in the accuracy and speed of diagnosis, patient safety, and agility in the primary care system, while reducing the cost of unnecessary tests.

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KEYWORDS

artificial intelligence; machine learning; chest x-ray; radiology; validation

Introduction

Chest x-rays are currently the most commonly used type of x-rays, accounting for up to 26% of all radiographic tests performed [1-3]. This technique makes it possible to identify cardiopulmonary conditions, verify the correct positioning of devices such as pacemakers, gastric and thoracic tubes, or detect obstructed blood vessels, among others [4,5].

However, chest radiography is a complex imaging modality to interpret [6]. In fact, several studies have reported discrepancies in chest x-ray interpretations among emergency physicians and radiologists [7,8]. Therefore, it is of vital importance to be able to offer a fast and reliable diagnosis for this kind of x-ray, using artificial intelligence (AI) to support the clinician.

Radiology is one of the areas in which AI has had the greatest impact. Radiologists are medical professionals who use imaging technology to diagnose pathologies. Major advances in AI have enabled these professionals to make use of this tool to improve workflows and accuracy, thus reducing economic costs by avoiding unnecessary tests [5,9].

AI is a branch of computer science that aims to simulate tasks related to human intelligence, including processes such as learning and improvement through feedback or reasoning, using machines [10]. It is a tool capable of learning and analyzing large amounts of information, in different formats and at high speed, to aid in the accuracy and speed of diagnosis, facilitate and streamline clinical care, and support public health interventions, among many other applications [11,12]. The rapid growth of computer science and big data indicates that it is here to stay and will significantly change the practice of medicine [13].

The development of a computer system capable of interpreting thoracic x-rays as efficiently as a radiologist could be of great benefit in the clinical setting. The results of Rajpurkar et al's [14] study on the application of deep learning for chest x-ray diagnosis presents an algorithm (CheXNeXt), which performs comparably with professionals in detecting multiple thoracic pathologies.

Wu et al [2] compares the interpretations of 5 radiology residents with those of an AI algorithm and corroborates that these well-trained techniques can achieve performance levels similar to professionals. Furthermore, Ciceró et al [15] demonstrates that convolutional neural networks can be trained with data sets to classify chest x-rays and obtain clinically useful performance in the detection and exclusion of common pathologies.

Oxipit is one of the leading companies in medical image reading using AI, whose goal is to introduce advances in deep learning techniques into daily clinical practice [16]. The company has developed an AI algorithm for reading chest x-rays, available through a web platform called ChestEye.

This platform is an automatic computer-aided diagnosis system where the inserted chest x-ray is read and an automatic report is returned with a capacity to detect 75 pathologies, covering 90% of diagnoses. Thus, ChestEye allows radiologists to analyze only the most relevant x-rays [17,18].

Therefore, the main objective of the study is to perform a prospective validation of the ChestEye AI algorithm as a diagnostic decision support tool for the diagnosis of chest x-rays and to try to improve or optimize it if possible.

Methods

Design

A prospective study will be conducted to validate the AI algorithm, comparing the ChestEye AI diagnoses with the radiologists' diagnoses, which is considered the gold standard. The process will include the following steps:

1. The patient will arrive at the primary care center for the chest x-ray, and if he/she meets the inclusion and exclusion criteria, the health care staff will briefly explain the study and provide the informed consent form to be signed.
2. Regardless of whether the user has agreed to participate in the study or not, the reference radiologist will perform the diagnosis of the x-ray to be entered into the Primary Care Clinical Station (ECAP). This station is the computerized clinical history program used by all professionals in the primary care network of the Institut Català de la Salut (ICS).
3. If the user has agreed to participate in the study, the researchers will extract the ECAP x-ray and enter it into the AI algorithm through their web-based platform to obtain their diagnosis.
4. Finally, the performance and fit of the AI model against the gold standard (radiologists' diagnoses) will be validated and evaluated.

The AI algorithm ChestEye, from Oxipit, is an automatic and autonomous algorithm, without the involvement of the radiologist, which works through a web-based platform where the image is entered in DICOM format, and returns an image evaluation and diagnosis. The algorithm has the capacity to detect 75 pathologies, covering 90% of the diagnoses [16].

ChestEye has been previously developed and trained by Oxipit through iterative processing of large amounts of data by neural network-based AI algorithms, allowing the software to learn automatically from patterns or features in the data.

Scope, Period, and Participants

The study will be performed at the ICS Primary Care Centre Vic Nord (Osona, Catalonia, Spain), a reference center where all chest x-rays in the region are performed. It is expected that data can be obtained in 5 to 6 months, from February 7, 2022, with recruitment using consecutive sampling. In June 2022,

more than 450 chest x-rays have been collected, so it is expected that 600 samples will be gathered in July 2022.

The reference population of the prospective study will be the entire population of Osona due to undergo a chest x-ray at this center, with prior informed consent.

The study will include only anteroposterior chest x-rays performed from the beginning of the study until the necessary sample is obtained from patients with authorized informed consent and who are older than 18 years. Pregnant women and chest x-rays of inadequate quality (poor exposure, images not centered or rotated) will be excluded from the study as the AI algorithm needs high-quality images to maximize its performance.

Sample Size and Sampling Procedure

To validate the AI algorithm, a total sample of 600 x-rays will be needed, 200 of them with one of the 75 pathologies detected by the AI algorithm. The proposed sample is based on calculations used in similar research [1,14,19,20]. Furthermore, it has been calculated that with this sample size, we can estimate global accuracy considered to be around 70% with 95% confidence, 4% precision, and an anticipated replacement rate of 15%.

Data Collection and Information Sources

The ICS health care personnel performing the chest x-rays will explain the study and its objectives to the users, and will give the patient an information sheet, together with the informed consent form, to all those who meet the inclusion criteria. The ICS Central Catalonia technical service will then extract all these x-rays with their corresponding diagnosis. Each x-ray will be associated with a unique identifier to relate it to its diagnosis and eliminate any nonanonymized information. Next, the study's principal researchers will input the x-rays into the AI system to obtain the diagnoses of the models using the algorithm. Finally, the data will be analyzed by comparing the diagnoses of the practitioner and the algorithm.

Data Analysis

To validate the algorithm, the results using the AI algorithm and the diagnoses made by radiologists will be compared. With this, the confusion matrix of the algorithm will be obtained from the correctly classified positive (TP), correctly classified negative (TN), false positive (FP), and false negative (FN) x-rays. The sensitivity, specificity, classification rate (accuracy), and area under the curve (AUC) of the algorithm will be calculated from this matrix. These results can be obtained for each pathology and the classifier as a whole. Accuracy, recall, and F-measurement will also be calculated for the overall classifier and each pathology.

To evaluate the classifier for multipathology radiology, the data will be treated as a set of binary variables, one for each pathology. In this case, the AUC will be calculated using the One-vs-All method. Macroaveraging and microaveraging measures will be considered to highlight pathologies with lower prevalence. The data will be analyzed with the statistical software R (version 4.1.2; R Foundation for Statistical Computing), whose intervals will be of 95% confidence, with a significance level of 5%.

Ethics Approval

The University Institute for Research in Primary Health Care Jordi Gol i Gurina (Barcelona, Spain) ethics committee approved the trial study protocol (approval code: 21/288). Written informed consent will be requested from all patients participating in the study.

Results

Patient recruitment began in February 2022, and it is expected that data can be obtained in 5 to 6 months. On June 2022, more than 450 chest x-rays have been collected, so it is expected that 600 samples will be gathered in July 2022. Each user who agrees to participate in the study will be asked for written informed consent and will be given the project information sheet. Data collection for all participants is expected to be completed by June 2022, and the results can be published by the end of 2022.

In this way, we hope to obtain sufficient evidence to demonstrate that the use of AI in the reading of chest x-rays can be a good tool for diagnostic support. However, in the context of Central Catalonia (the Catalan region where the data was collected), there is an increasingly lower volume of radiologists, and therefore, tools need to be developed to support professionals who have to interpret these tests [21,22].

Once the algorithm has been validated, the values of sensitivity, specificity, accuracy, and AUC will be used to evaluate the results obtained and to determine whether it would be a good model to be introduced in the Catalan health system.

Discussion

Comparison With Prior Work

The protocol of this study aims to perform a prospective validation of an AI algorithm and to demonstrate that the use of AI in chest x-rays can become a good tool for supporting professionals in their diagnoses. In this context, this study may bring added value for both patients and primary care physicians as it will provide information about the effectiveness of the AI algorithm and its limitations. External validation of new AI tools is essential before implementing them as diagnostic systems.

Studies are showing that the application of AI models can be comparable to the performance of a professional in the detection of multiple pathologies [2,14,15]. However, before committing resources to AI applications in health care, the acceptance of these applications should be studied. Although some studies have shown that AI has a high potential to be useful as a diagnostic tool, it is remarkable that most patients still preferred the diagnoses done by physicians, and professionals only accepted AI models if they were used in combination with "human diagnosis" [23,24]. In this context, leading health care systems are moving toward the digitization of health care. Therefore, it is time to provide and validate tools that can enable improvement in the workflow of professionals as well as support

their diagnosis. Always consider the clinical context for the subsequent application of these tools.

Furthermore, it has to be taken into consideration that most of the AI studies conducted in health care were just proof-of-concept projects that used retrospective clinical data sets [25]. The application of AI techniques in the real clinical context is becoming more and more relevant to ensure its safe adoption in health care systems. Thus, this study will be conducted using prospective data sets, promoting the health care AI researchers' community to work closely with health care providers in a real clinical environment.

Limitations

This study has some limitations. The most relevant one is that there is the possibility of not obtaining a homogeneous distribution across the 75 possible diagnoses due to their low prevalence. In that sense, as a large number of diseases can be detected by chest x-ray, we will probably not obtain representative results for the less prevalent diseases. As class imbalance may be a limitation, the F score will be evaluated. Otherwise, the large number of more frequent pathologies may overestimate the quality of the algorithm (accuracy, sensitivity, and specificity). Another possible limitation is that a small amount of sample is likely to be lost due to inadequate image quality, as chest x-rays of inadequate quality will be excluded.

Conclusions

If the results of the model validation are satisfactory, the model can be implemented as a support tool and can increase diagnostic accuracy and speed, patient safety and agility within the primary care system, and reduce unnecessary testing costs.

Data Availability

Our manuscript is based on confidential and sensitive health data. However, to support scientific transparency, we will publish deidentified data for reviewers or for replication purposes. The data will be deposited and made available in our publicly accessible Mendeley repository.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
AUC: area under the curve
ECAP: Estació Clínica d'Atenció Primària (Primary Care Clinical Station)
ICS: Institut Català de la Salut

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Protocol

A Conversational, Virtual, Avatar-Led Cognitive Behavioral Therapy App Intervention for Improving the Quality of Life and Mental Health of People With Epilepsy: Protocol for a Randomized Controlled Trial

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Abstract

Background: Epilepsy is a common neurological disorder affecting about 1 in 100 people in the United Kingdom. Many individuals experience a lower quality of life as a result of their epilepsy diagnosis and are more likely to develop mental health problems, such as anxiety and depression. Medical interventions for this client group tend to focus on the treatment of seizures, whereas mental health disorders often remain undiagnosed and untreated. Early identification and treatment of mental health difficulties in people with epilepsy are vital to ensure better outcomes and improvements in quality of life.

Objective: The aim of this exploratory randomized controlled trial is to evaluate whether an 8-week cognitive behavioral therapy–based intervention delivered through a mobile app—ThinkNinja for Epilepsy—is a clinically effective tool to improve quality of life, mental health, and emotional well-being in a large sample of people with epilepsy and anxiety or comorbid anxiety and depression.

Methods: The study aims to recruit 184 individuals, 18 to 65 years of age, with a self-reported diagnosis of epilepsy and anxiety or comorbid anxiety and depression. Participants will be randomly assigned to the ThinkNinja for Epilepsy app condition (arm A) or the waiting-list control group (arm B). Participants in arm A will receive access to the ThinkNinja for Epilepsy app first. After 8 weeks, participants in arm B will receive the same full access to the ThinkNinja for Epilepsy app as the participants in arm A. This design will allow an initial between-subjects analysis between the two conditions as well as a within-subject analysis including all participants. The primary outcome is participants' quality of life, measured by the 10-item patient-weighted Quality of Life in Epilepsy questionnaire. The secondary outcomes include measures of anxiety, using the 7-item Generalized Anxiety Disorder assessment; depression, using the 9-item Patient Health Questionnaire; medication adherence, using the Medication Adherence Questionnaire; and impression of change, using the Patient Global Impression of Change questionnaire.

Results: Recruitment for this study began in March 2022 and was completed in October 2022. We expect data collection to be finalized by May 2023 and study results to be available within 12 months of the final data collection date. Results of the study will be written up as soon as possible thereafter, with the intention of publishing the outcomes in high-quality peer-reviewed journals.

Conclusions: This study aims to determine the clinical efficacy and safety of the ThinkNinja for Epilepsy intervention at improving the quality of life, mental health, and emotional well-being of people with epilepsy. The findings from our study will hopefully contribute to addressing the critical gap in universal provision and accessibility of mental health and emotional well-being support for people with epilepsy.

Trial Registration: ISRCTN Registry 16270209 (04/03/2022); https://www.isrctn.com/ISRCTN16270209

International Registered Report Identifier (IRRID): DERR1-10.2196/40261

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KEYWORDS

epilepsy; mental health; anxiety; depression; quality of life; cognitive behavioral therapy; digital therapy; smartphone; mobile phone; app

Introduction

Background

Approximately 1 in 100 people in the United Kingdom have a diagnosis of epilepsy, with around 87 people being diagnosed every single day. This level of prevalence equates to approximately 500,000 people in the United Kingdom having an official diagnosis of epileptic seizures [1]. Many individuals are subsequently diagnosed with anxiety after their epilepsy diagnosis and also experience lower quality of life [2-4]. The fear of having a seizure is reported to be one of the most common causes for anxiety in those with epilepsy [5].

Research has found that epilepsy is comorbid with anxiety and depression, and that people with epilepsy are more likely to experience these mental health issues than the general population [6]. It is estimated that the lifetime prevalence of depression in people with epilepsy is around 55%. Comorbid anxiety and depression affect 20.2% and 22.9 % of people with epilepsy, respectively [7]. Depression and anxiety co-occur in 16% to 19.9% of cases, depending on studies [8,9]. People with epilepsy are also at increased risk for suicidal ideation and behaviors [10,11]. It has been hypothesized that psychiatric comorbidities in people with epilepsy might be the consequence of a potential common underlying biological etiology [11], a possible side effect of antiepileptic drugs, and the psychological impact and hopelessness resulting from living with a chronic health condition [12,13].

Astonishingly, there is still little research into this issue, its possible causes, or possible treatment solutions. Medical interventions for this client group tend to focus on the treatment of seizures, though it is equally important that doctors can recognize and address symptoms of anxiety and depression. Depression can increase the frequency of epileptic seizures by means of sleep deprivation. Panic disorder and phobic disorders, such as agoraphobia, are common in epilepsy patients. These are often the result of poor seizure control or the fear of having a seizure [14]. People with epilepsy and anxiety tend to have more severe seizures and a lower quality of life [15]. Effective epilepsy management should incorporate the early detection of psychological disorders and the promotion of appropriate interventions [2] in order to improve the quality of life of people with epilepsy [16,17].

Smartphone apps for mental health have seen considerable growth in recent years [18]. However, few apps have been specifically developed for people with epilepsy, much less an app focusing on the mental health, emotional well-being, and quality of life of people with epilepsy. The majority of the smartphone apps developed for epilepsy are for seizure management and seizure diaries [19].

Cognitive behavioral therapy (CBT) is one of the most thoroughly investigated and effective alternatives to medication for mental health issues, such as anxiety and depression [20,21], and it is recommended in England's National Institute for Health and Care Excellence (NICE) clinical guidelines [22-24]. Although internet-based CBT programs have existed for some time, their sometimes-inadequate design and usability have inhibited their popularity and advancement [25,26].

In a recent systematic review (F Lecce, CR Smith, and FR Burbach, unpublished, 2022), we identified six digital mental health interventions for people with epilepsy, but only one of them—Emyna—was a fully automated epilepsy-specific CBT-based program. Emyna is a 180-day internet intervention that requires no clinician support and is accessed via a secure, password - protected website from a computer or smartphone. In a recent clinical trial in Germany, Meyer and colleagues [27] examined the effectiveness of this fully automated internet-delivered treatment in reducing symptoms of depression and anxiety and improving quality of life in a sample of 200 people with epilepsy and comorbid depression. The authors found that participants experienced significantly greater improvement in depression, anxiety, and quality of life compared to the control group and concluded that the intervention was effective when used adjunctively to usual care.

Aims of This Study

In this exploratory randomized controlled trial (RCT), we will evaluate whether an 8-week CBT-based intervention, delivered through ThinkNinja for Epilepsy (Healios Ltd), is a clinically effective tool for improving the quality of life, mental health, and emotional well-being in a large sample of people with epilepsy.

We hypothesize the following:

1. There will be an improvement in participants' self-reported quality of life scores, as measured by the 10-item patient-weighted Quality of Life in Epilepsy questionnaire (QOLIE-10-P) [28], as a result of the ThinkNinja for Epilepsy intervention.
2. There will be an improvement in participants' self-reported anxiety, depression, impression of change, and medication adherence, as measured by the 7-item Generalized Anxiety Disorder assessment (GAD-7) [29], the 9-item Patient Health Questionnaire (PHQ-9) [30], the Patient Global Impression of Change questionnaire (PGIC) [31], and the Medication Adherence Questionnaire (MAQ) [32], respectively, as a result of the ThinkNinja for Epilepsy intervention.
3. There will be a positive association between the level of engagement with the app and the primary and secondary outcomes.

Methods

Ethics Approval

The study was approved on August 20, 2021, by the Cambridge East Research Ethics Committee (REC reference No. 21/EE/0128). Initial recruitment will occur via social media, and interested participants will complete a brief online screening questionnaire and provide their informed consent before being randomized and given access to the app via our secure clinical platform. Data will be directly collected via the app, and clinical scales will also be completed via our secure platform. Healios is registered with the National Health Service (NHS) Data Security and Protection Toolkit standards for patient data and achieves the required level-2 information governance standards for provision of clinical services on behalf of the NHS. Healios complies with the UK General Data Protection Regulation requirements regarding the collection, storing, and processing of clinical and study data. At the end of the study, all data will be pseudonymized prior to statistical analyses. Participants will not be compensated for their participation in the study. This study was registered at the ISRCTN Registry (16270209) on March 4, 2022.

Study Setting

The study intends to recruit 184 participants. Individuals interested in taking part in the research have to be residents in the United Kingdom, aged between 18 and 65 years, and have a self-reported diagnosis of epilepsy. Recruitment of participants will be conducted via advertisements on epilepsy charity websites and mailing lists as well as social media platforms, such as Facebook and Twitter. Participants will be able to download ThinkNinja for Epilepsy on their smartphones and use it independently, with additional support provided by the research team where needed. It is expected that participants will use the ThinkNinja for Epilepsy app in their own private time.

Study Design

Participants will be randomly assigned to a waiting-list control group or will receive full access to the ThinkNinja for Epilepsy smartphone app. A mixed study design will allow for an initial between-subjects analysis between the two condition arms—those who receive the app straight away versus those who wait for access—as well as a within-subject analysis of those who complete the intervention; this includes those who receive the intervention straight away as well as those who receive it after the waiting period. The study adheres to relevant ethical guidelines from the British Psychological Society [33]. In addition, the completeness, content, and quality of the study protocol is reported in line with the Standard Protocol Items: Recommendations for Interventional Trials guidelines [34].

Eligibility Criteria

All individuals who meet the inclusion criteria will be eligible to participate. Inclusion and exclusion criteria are outlined in Textbox 1. Participants will have a self-reported diagnosis of epilepsy received at least 6 months before applying, and they will be encouraged to share photographs of their current medication, letter, or report from their health care provider. There will be no restrictions for participants to access any other form of psychological services during the study; however, they will be asked to disclose this information while completing the measures throughout the study. Participants will require access to a personal Apple iOS or Android smartphone and will be able to download the ThinkNinja for Epilepsy app from the iTunes store or Google Play. The app is completely free for participants to download using Wi-Fi, and there are no in-app purchases. However, downloading the app via data roaming may incur additional charges as per the user's contract fees; therefore, the use of Wi-Fi is encouraged.

Textbox 1. Study inclusion and exclusion criteria.

Inclusion criteria

- Adults aged 18-65 years
- UK resident
- Fluent in English
- Scoring ≥5 on the 7-item Generalized Anxiety Disorder assessment (GAD-7; mild anxiety) at screen-in
- Willing and able to receive notifications and SMS text and email messages
- A confirmed epilepsy diagnosis (6 months minimum time since diagnosis; suspected cases are not permitted); diagnosis to be confirmed, ideally by participants submitting photographs of their current medication, letter, or report from their health care provider
- Stable epilepsy medication and anxiety or depression medication regimens (antiepileptic, antidepressant, anxiolytic drug, etc); stable medication regimen for this study refers to no change in medication in the last 4 weeks; questions to cover this at all data collection time points; should participants change medication during the study period, this will not affect their inclusion, however, this will be explored in the analysis

Exclusion criteria

- Scoring <5 on the GAD-7 at screen-in
- Having a score of ≥20 on the 9-item Patient Health Questionnaire, indicating severe depression at screening, or if they answer, "more than half of the days" or "nearly every day" to the question "Over the last 2 weeks, how often have you been bothered by thoughts that you would be better off dead or of hurting yourself in some way?"
- Sensitivity to mobile phone screen exposure
- Currently receiving counseling or psychological therapy; however, they will not be excluded if they seek support during the study; questions in measures to reflect this
- Individuals involved in current or ongoing research
- Pregnant or gave birth in the past 12 months
- Diagnosis of a severe mental illness (eg, severe depression including suicidal ideation, schizophrenia, bipolar disorder, psychosis, personality disorder, posttraumatic stress disorder, and substance misuse)
- Severe learning disability and individuals requiring a carer for their epilepsy
- Does not have access to a smartphone (ie, iPhone with iOS 13 or greater capabilities or an Android phone with OS 7 or greater capabilities)

Recruitment

Potential participants will be able to click a link in the advertisement, which will lead them to a short contact form collecting their name, date of birth, home address, and email address. Personal information will be stored in our secure system. The GAD-7 will be used to screen potential participants' suitability for inclusion, with scores of 5 or greater as the cut point for mild anxiety. The PHQ-9 will also be used as a screening questionnaire. If we identify severe depression (score ≥20) or significant suicidal risk, potential participants will be excluded from the study and advised to seek professional help via the NHS. Significant suicidal risk is identified if they answer, "more than half of the days" or "nearly every day" to the PHQ-9 question "Over the last 2 weeks, how often have you been bothered by thoughts that you would be better off dead or of hurting yourself in some way?" We will also include contact details for national crisis support helplines in the return email to ensure that participants are aware of the support they can receive from national helplines. The GAD-7 and the PHQ-9 are well-researched measures with sound psychometric properties [35]. The same measures will also be used throughout the study at the specified time points (T) to assess any change in participants' self-reported anxiety and depression scores.

To mitigate risk to implementation, we aim to complete baseline measures and enrollment with all participants over a 2- to 4-week period. Opt-in consent forms will first be distributed to all participants.

Participant Classification

Data will be input into the R Minirand program (version 0.1.3; R Foundation for Statistical Computing) for randomization, and participants will be assigned to either the ThinkNinja for Epilepsy app arm (condition A) or the wait-list control arm (condition B) using minimization techniques. The prognostic factors over which the data will be minimized include age, sex at birth, and education level. Each prognostic factor will be minimized over two distinct categories: age (over 40 and under 40), sex at birth (male and female), and education level (below degree level and degree plus). Prognostic factors will have equal weighting in randomization. As there is not a requirement to blind this trial (ie, both clinicians and patients will be aware of whether they receive treatment or not), a deterministic approach is satisfactory; therefore, the significance level on which participants will be randomized is $P>.99$.

Intervention

Healios has developed a CBT-based app called ThinkNinja for Epilepsy. ThinkNinja for Epilepsy is designed to support users' individual situations and to address mental health challenges

with weekly mini modules. These are guided by an automated virtual assistant, the Wise Ninja, combined with interactive screens that are designed to cover an 8-week period, delivered at the user's pace. Each week of the program includes three sessions, and users have to complete each session before being able to progress to the next one. Every week, new content is released and three more sessions become available to the user, allowing them time to digest information, develop their understanding, and practice coping and CBT skills to manage their epilepsy and mental health. Moreover, the structured epilepsy-specific 8-week program provides tools for monitoring epileptic seizures as well as ways of helping individuals understand and improve their mental health and emotional well-being (Table 1).

The first week includes an overview of the program and psychoeducation regarding epilepsy and mental health. Participants are then introduced to the "seizure diary" and are helped to think about triggers and warning signs for seizures. Week 2 introduces the main principles of CBT, and participants are encouraged to watch two short videos about anxiety and low mood. Participants learn about "automatic thoughts" and how these can impact on their mood. They learn to assess their own thoughts and how these might not always be accurate or helpful. Week 3 explores maladaptive coping strategies (ie, safety behaviors) and how to spot them. In week 4, participants further develop their CBT skills and learn about the importance of facing their fears, set daily quests, and practice using positive statements. Users are also introduced to some relaxation skills, including breathing exercises and "grounding" techniques. In weeks 5 and 6, participants learn ways of challenging difficult thoughts. They are encouraged to evaluate their beliefs and cognitive biases and begin to develop alternative thoughts via the "thought diary." They are also introduced to further relaxation and mindfulness exercises. Week 7 focuses on practicing alternative thoughts and stress reduction techniques. Week 8 involves reflecting on the progress made and relapse prevention as well as thinking about how to share this with their support network.

Table 1. Overview of the 8-week program.

Week	Session 1	Session 2	Session 3
1	Introduction and resources	My epilepsy diary	Setting goals
2	Introduction to CBT[a]	Anxiety and low mood videos	Thinking traps
3	Safety behaviors	The spotlight	Unhelpful coping
4	Formulation	Hot cross bun	Grounding techniques
5	Challenging thoughts	Thought challenger	Relaxation
6	Snapshots (gratitude journal)	Thought diary introduction	Thought diary 1
7	Thought diary 2	Breaking it down	Confidence boost
8	Moving on	Keeping calm	Staying well

[a]CBT: cognitive behavioral therapy.

As part of augmenting the 8-week structured self-management program, within the app, there are two "step-up" levels to allow the user to access further clinical support via interaction with a trained clinician. Details of the step-up levels are as follows:

1. Step-up level 1 is a continuation of the CBT intervention and is a text-based feature enabling a trained mental health coach to perform live problem-solving, perform assessment of need, and signpost additional support where required, all via a text-chat interface within the app. Participants may request a text-based chat with a clinician through a designated button on the home screen. Text support will be available to participants Monday to Friday, 9 AM to 6 PM, with all requests responded to within a maximum of 24 hours. For the 8-week duration of the active participation section of the study, participants will have access to the step-up level-1 feature, if necessary.
2. Step-up level 2 is a video-based, brief, goal-focused continuation of the CBT intervention involving up to three live video-based sessions with a clinician to learn skills to manage symptoms of anxiety and low mood using CBT techniques. The level-2 step-up is only possible via accessing level 1 and is determined by the clinician based on a needs assessment. Step-up level 2 will be available to participants for the 8-week duration of the active participation section of the study.

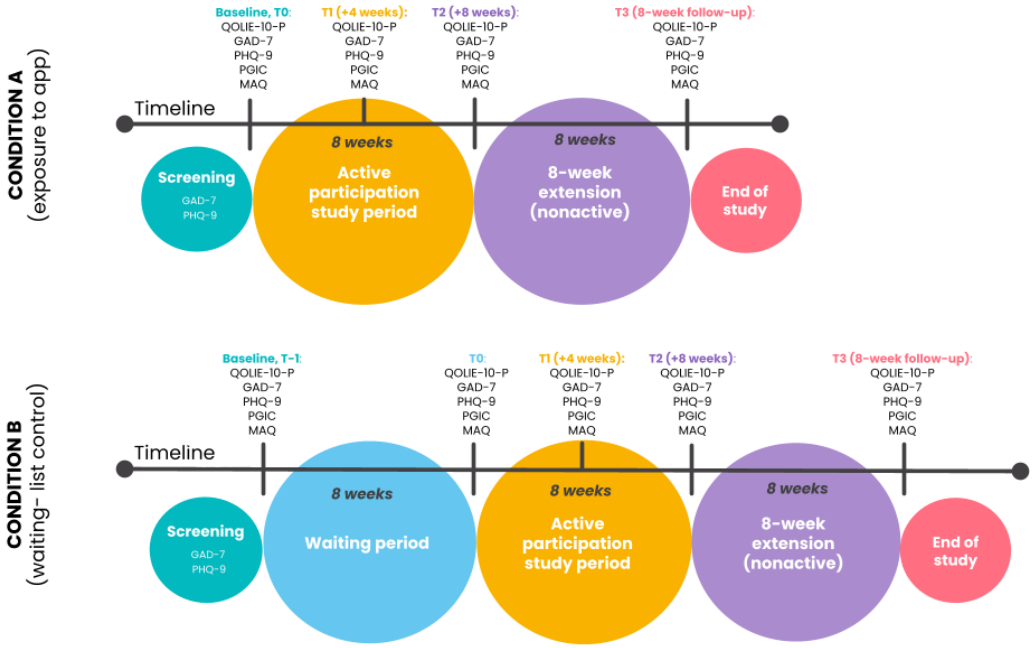
ThinkNinja for Epilepsy was created with a range of external inputs. Healios CBT therapists and clinical psychologists developed the CBT clinical architecture of the app, in order to ensure clinical accuracy in accordance with the NICE clinical guidelines, as well as appropriate tone and language. The CBT architecture was then approved by independent UK psychologist experts as suitable for supporting both mental health and emotional well-being, as well as supporting symptoms of anxiety and low mood. Epilepsy field experts, such as neurologists, neuropsychiatrists, and clinical psychologists, were then consulted during the creation of the epilepsy-specific content in order to ensure that the app could be as valuable as possible to persons with epilepsy. As part of the co-design with users, four user focus groups—18 participants across three face-to-face groups and one online group—were conducted to provide input into app design concepts covering look, feel, and tone suitability. During the app technical build process, an online group of 6 users was set up to provide weekly input into each weekly development "sprint" of new app features, covering the tone and language of the content as well as the interactivity and usability of the app. Real-time feedback incorporated into the

app on a weekly basis ensured that the development phase of the project had continued input from independent individuals.

Outcomes and Variables

Figure 1 shows details of the measures and the time points at which they will be collected. The primary outcome is the QOLIE-10-P score.

Figure 1. Condition A and B timelines. GAD-7: 7-item Generalized Anxiety Disorder assessment; MAQ: Medication Adherence Questionnaire; PGIC: Patient Global Impression of Change questionnaire; PHQ-9: 9-item Patient Health Questionnaire; QOLIE-10-P: 10-item patient-weighted Quality of Life in Epilepsy questionnaire; T: time point.



Data will be collected at baseline (T0, plus T–1 for wait-list participants), T1 (4 weeks after commencement of the ThinkNinja for Epilepsy intervention), T2 (8 weeks after commencement of the intervention), and T3 (8 weeks following completion of the active period of the study) via participant-completed questionnaires.

The secondary outcomes include anxiety (GAD-7), depression (PHQ-9), patients' global impression of change (PGIC), and self-reported medication adherence (MAQ). All measures to be collected at T–1, T0, T1, T2, T3, and weekly were chosen due to their suitability, reliability, validity, and established sensitivity to change for people with epilepsy and for evaluating changes in quality of life, anxiety, and depression levels. The measures chosen are also balanced with consideration to minimizing burden on both participants and researchers and maximizing data quality. All T–1, T0, T1, T2, T3, and weekly measures will be completed online and will be self-reported by the participants. In addition, demographic characteristics, including age, gender, and ethnicity, will be self-reported by participants at baseline [36].

At each time point, bespoke questions will also be included to cover any change in medications and any psychological support services the participant may have accessed during the study, such as services from their local NHS, including mental health services covering counseling or therapy. These will be self-reported by the participant. To minimize potential self-reporting inaccuracies, the participant will be asked to recall any additional support over the previous 3 months at T–1, T0, T1, T2, and T3, instead of recalling any additional support over the full study period at completion.

Other measures captured within the app at various frequencies via user input and app tracking mechanisms are as follows:

1. Usage data to determine fidelity of the intervention and how closely the participants complied with the recommended guidance, covering which elements of the app they use the most and for how long they use different elements of the app.
2. Goal-based achievement for those participants who set goals.
3. Mood and anxiety scores and activity ratings throughout the study.
4. Skill practice implementation data.

Study Procedure

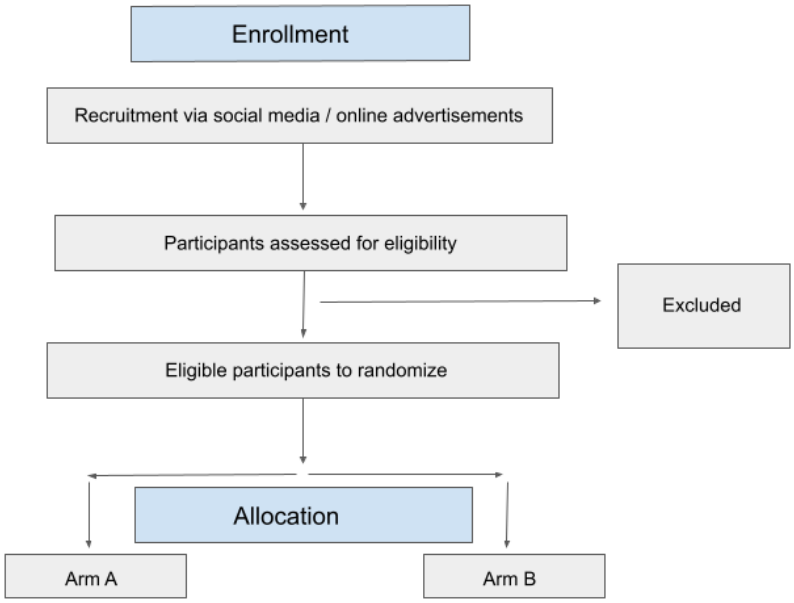
Participants randomly assigned to condition A will receive access to the ThinkNinja for Epilepsy app first. Participants will receive guidance on the expected frequency and duration of app use and will be encouraged to use the app two to three times per week for the duration of the 8-week study period. After the active 8-week period of the study is completed, participants may use the app on their own accord, as much as they like, for the remaining 8-week duration of the study.

Step-ups will only be available for the 8-week active participation period of the study. Participants will be reminded via push notifications to use the app if they have not used it in the previous 3 to 7 days. Although participants will be able to disable app notifications as is standard through their device's

operating systems settings menu, we will request that they remain enabled for the duration of the study in order to facilitate communication with the research team. Participants assigned to condition B will receive the same full access to the ThinkNinja for Epilepsy app as the participants in condition A after 8 weeks. The study procedures and timing are summarized in Figures 1 and 2.

We considered performing weekly tracking of anxiety and mood for the control arm participants but, on balance, decided that for this exploratory study, the potential adverse effects on engagement due to perceived burden outweighed the advantages of collection of weekly data. The weekly measures will be collected as part of the CBT-based intervention, as is common in the delivery of CBT; this will allow us to monitor clinical change and potential risk as part of the intervention. Participants will be able to report any app technical issues via a Healios study email address and telephone number. The research team will make every effort to locate participants lost to follow-up using text and email.

Figure 2. Participant flow. Arm A participants will receive access to ThinkNinja for Epilepsy app first. Arm B participants will be the waiting-list control group.



Sample Size

A formal sample size calculation was based on assumptions of QOLIE-10-P means and SDs from earlier studies [37,38]. It was performed using a 2-tailed *t* test of equal means at a significance level of .05 and a power of 80% for an estimated medium effect size (Cohen *d*=0.5). All calculations were done using the software nQuery (version 7.0; Statsols) [39]. We intend to recruit 184 people—92 participants in each arm—so that we can accommodate a dropout rate of 30%.

The chi-square method was used to determine the power for structural equation modeling (SEM) [40] using the associated online power calculator [41]. It was determined that with a sample size of 184 (see above) and a *P* value of .05, the proposed 11-parameter SEM analysis would be powered at 0.705 (70.5%).

Data Analysis

The analysis will be performed in two phases. The first phase of analysis will occur after completion of the 8-week (T2) outcome measures, when all participants in arm A have completed the 8-week program and can be compared to the waiting-list control participants (arm B). The second phase of analysis with the pooled data will occur after the completion of the 8-week follow-up period (T3) outcome measures for all participants.

The following patient cohorts will be used in the analysis:

1. The per-protocol study cohort will include all allocated participants with at least 80% completed questionnaire data, including a completed QOLIE-10-P score, at baseline (T0 ThinkNinja for Epilepsy group and T–1 wait-list group) and at 8 weeks (T2 ThinkNinja for Epilepsy group and T0 wait-list group).
2. The intention-to-treat study cohort will include all allocated participants.

Available information on screened participants who were not randomized will be summarized.

Descriptive statistics will be produced for the distribution of all variables, including baseline demographic variables, app use, and engagement variables, as well as for each outcome variable at each time point. The change in each outcome from baseline will be reported in terms of mean and SD. An analysis of reliable and clinical change will be produced for the GAD-7 and PHQ-9 scores in order to determine the percentage of those who had clinical and reliable change (ie, clinical recovery) after taking part in the intervention.

The primary outcome analysis (ie, quality of life) will be performed for the overall cohort, both unadjusted and adjusted for baseline characteristics, app use, and app content variables. We will be comparing changes in quality of life (ie, QOLIE-10-P scores) from baseline to completion of the 8-week program.

The secondary outcome analysis will constitute analyzing the change in GAD-7 (ie, anxiety) and PHQ-9 (ie, depression) scores. In addition, we will be reporting on the results of the MAQ and PGIC, using descriptive statistics.

In addition to this, a sensitivity analysis that uses both the primary and secondary outcomes will be performed. To explore both between-subjects (ie, arm A vs arm B) and within-subject (ie, T0 vs T1 vs T2 vs T3) differences, a series of repeated-measures (2 × 4) analyses of variance (ANOVAs) will be performed in the first instance with both the primary outcome measure (ie, QOLIE-10-P score) and the secondary outcome measures (ie, GAD-7, PHQ-9, PGIC, and MAQ scores) as dependent variables. All of these ANOVA tests will be powered at 0.80 (P=.05). The output from this series of ANOVAs will permit the necessary sensitivity analyses to be completed.

Further exploratory subgroup analyses will be performed for the following:

1. Change in primary and secondary outcomes for subgroups defined by baseline characteristics and demographics, such as age and gender.
2. Change in primary and secondary outcomes stratified by app use, videoconference use, and text support use.
3. Engagement variables: low versus high frequency and duration of app use.

Responder and nonresponder groups will be identified on the basis of changes in primary and secondary outcomes, and these groups will be characterized in terms of baseline characteristics, demographics, and app use variables. Descriptive statistics will be produced, and a regression model will be performed to identify variables associated with responder status. An SEM model will then be developed where baseline characteristics will be independent variables, app use and content variables will be mediating latent variables, and quality of life will be the dependent variable. Regression coefficients will be reported with 95% CIs. These analyses will be performed as an intention-to-treat analysis, using all randomized participants with imputation of missing end-of-study (T2) observations, with the exception of the sensitivity analyses, which will be per-protocol analyses.

Results

Recruitment for this study started in March 2022 and was completed in October 2022. Considering that participants who were randomized to arm B will take 16 weeks to complete the study (Figure 1), we expect data collection to be finalized by May 2023 and study results to be available within 12 months of the final data collection date. Results of the study will be written up as soon as possible thereafter, with the intention of publishing the outcomes in high-quality peer-reviewed journals.

Discussion

Overview

This exploratory RCT aims to investigate whether an 8-week CBT-based intervention—ThinkNinja for Epilepsy—delivered through a smartphone app is clinically effective in improving the quality of life, mental health, and emotional well-being of people with epilepsy and concurrent mental health difficulties. We hypothesize that there will be an improvement in participants' self-reported quality of life, anxiety, depression, impression of change, and medication adherence as a result of the 8-week CBT-based intervention, with the outcomes being positively associated with participants' levels of engagement with the app.

Despite the link between epilepsy and mental health difficulties being well known, current medical interventions tend to focus on seizure management. As a result, mental health difficulties in the context of epilepsy are too often overlooked and untreated, with detrimental outcomes on people's quality of life.

CBT is a well-researched psychological intervention that has proved to be effective in reducing symptoms of anxiety and depression in people with epilepsy, and it is recommended in the NICE guidelines [42].

More recently, digital mental health interventions, including CBT-based programs, have become quite popular and have proved to be effective in managing and preventing mental health disorders in people suffering from chronic health conditions. Sasseville et al [43] recently conducted a rapid literature review aimed at determining the effectiveness of digital mental health interventions for people with a concomitant chronic disease. The authors concluded that digital mental health interventions are effective and safe for people with chronic health conditions, but further studies are required in order to provide precise recommendations to specific clinical populations.

To the best of our knowledge, only a few digital interventions and smartphone apps are currently available for people with epilepsy; these typically offer tools to manage seizures, such as seizure diaries [19], with only a few focusing on mental health [27].

ThinkNinja for Epilepsy appears to be the first CBT-based digital mental health smartphone app that is specifically designed to support people with epilepsy. The findings from our study will hopefully contribute to addressing the critical gap in the universal provision and accessibility of mental health and emotional well-being support for people with epilepsy.

Limitations

We note the following limitations to the proposed study. First, participants will know that they will be able to start the intervention after an 8-week waiting period if they are randomized to the waiting-list control arm. We considered that this would potentially result in either improved mood and motivation or the opposite. This cannot be controlled for, but we will capture further baseline data (T0) when the waiting-list participants move to the active arm and start the intervention. We will also explore this in our qualitative evaluation upon completion of the study. Second, this study is based in the United Kingdom; therefore, the results of this study may have reduced generalizability to other cultures where mental health support is limited due to issues such as social stigma. Moreover, recruitment of participants will take place via advertisements on social media platforms, such as Facebook and Twitter, as well as on epilepsy charities' websites. This may result in

selection bias toward motivated participants who are likely to be better educated about their condition and able to afford mobile technologies. These types of participants may be more likely to benefit from technology-based interventions compared to patients who do not engage with social media. Therefore, care should be taken when generalizing the results of this study to the wider epilepsy population. Our study will only include participants with a self-reported diagnosis of epilepsy, as they are volunteers recruited through charities and social media platforms. We acknowledge this as a limitation and, if this study is successful, we would envisage our next trial to be held within primary care and specialist neurology services, with all referrals being made by NHS clinicians. Similarly, self-reported questionnaires will be used to assess outcomes.

We also acknowledge that participants' ability to access other forms of psychological services during the study is a potential limitation. However, they will be asked to disclose this information while completing the measures throughout the study and it will be accounted for in our analyses. Participants may not wish to disclose this information, but this is an unavoidable limitation of this study.

Conclusions

This study is a preliminary investigation into an underdeveloped area with significant potential for future scaling of psychological interventions for people with epilepsy. This study will attempt a sophisticated analysis of factors related to engagement and outcomes, which will inform future research and app intervention development. We envisage that this study will lead to further investigation of the ThinkNinja for Epilepsy app within clinical services.

Acknowledgments

This study was funded by UCB, a pharmaceutical company.

Data Availability

The study described in this protocol will gather confidential and sensitive data. However, to support scientific transparency, data can be made available upon request to the corresponding author.

Conflicts of Interest

All the authors are employees of Healios Ltd and do not have any financial interests in the ThinkNinja for Epilepsy app.

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Abbreviations

ANOVA: analysis of variance
CBT: cognitive behavioral therapy
GAD-7: 7-item Generalized Anxiety Disorder assessment
MAQ: Medication Adherence Questionnaire
NHS: National Health Service
NICE: National Institute for Health and Care Excellence
PGIC: Patient Global Impression of Change questionnaire
PHQ-9: 9-item Patient Health Questionnaire
QOLIE-10-P: 10-item patient-weighted Quality of Life in Epilepsy questionnaire
RCT: randomized controlled trial
REC: Research Ethics Committee
SEM: structural equation modeling
T: time point (in the context of T–1, T0, T1, T2, and T3)

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Protocol

Effectiveness of Gamification in Knee Replacement Rehabilitation: Protocol for a Randomized Controlled Trial With a Qualitative Approach

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Abstract

Background: Exergames can provide encouraging exercise options. Currently, there is limited evidence regarding home-based exergaming in the postoperative phase of total knee replacement (TKR).

Objective: This study aimed to investigate the effects of a 4-month postoperative home-based exergame intervention with an 8-month follow-up on physical function and symptoms among older persons undergoing TKR compared with home exercise using a standard protocol. In addition, a concurrent embedded design of a mixed methods study was used by including a qualitative component within a quantitative study of exergame effects.

Methods: This was a dual-center, nonblinded, two-arm, parallel group randomized controlled trial with an embedded qualitative approach. This study aimed to recruit 100 patients who underwent their first unilateral TKR (aged 60-75 years). Participants were randomized to the exergame or standard home exercise arms. Participants followed a custom-made exergame program independently at their homes daily for 4 months. The primary outcomes at 4 months were function and pain related to the knee using the Oxford Knee Score questionnaire and mobility using the Timed Up and Go test. Other outcomes, in addition to physical function, symptoms, and disability, were game user experience, exercise adherence, physical activity, and satisfaction with the operated knee. Assessments were performed at the preoperative baseline and at 2, 4, and 12 months postoperatively. Exergame adherence was followed from game computers and using a structured diary. Self-reported standard exercise was followed for 4 months of intervention and physical activity was followed for 12 months using a structured diary. Qualitative data on patients' perspectives on rehabilitation and exergames were collected through laddering interviews at 4 and 12 months.

Results: This study was funded in 2018. Data collection began in 2019 and was completed in January 2022. The COVID-19 pandemic caused an unavoidable situation in the study for recruitment, data collection, and statistical analysis. As of November 2020, a total of 52 participants had been enrolled in the study. Primary results are expected to be published by the end of 2022.

Conclusions: Our study provides new knowledge on the effects of postoperative exergame intervention among older patients with TKR. In addition, this study provides a new understanding of gamified postoperative rehabilitation, home exercise adherence, physical function, and physical activity among older adults undergoing TKR.

Trial Registration: ClinicalTrials.gov NCT03717727; https://clinicaltrials.gov/ct2/show/NCT03717727

International Registered Report Identifier (IRRID): RR1-10.2196/38434

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KEYWORDS

knee arthroplasty; serious game; gamification; therapeutic exercise; rehabilitation; physical therapy; Kinect; mixed methods; randomized controlled trial

Introduction

Background and Rationale

People with osteoarthritis (OA) often remain sedentary after total knee replacement (TKR) [1,2], predisposing them to noncommunicable diseases and disabilities with advancing age. Exercise is a recommended core treatment in the clinical guidelines for musculoskeletal disorders and a cornerstone of standard care for patients with OA [3,4]. People with knee OA should follow similar doses of exercise (frequency, intensity, time, type, volume, and progression) as physical activity (PA) recommended by public health authorities to have a positive effect on physical function [5]. Although engagement in PA is difficult for the general population, it is even more challenging for people with OA. They are often physically inactive and highly sedentary because of pain and disease progression [6].

Typically, TKR surgery is performed after years of progressive pain, swelling, stiffness, and decreased range of motion in the joint. The rate of TKRs for severe OA is increasing substantially [7,8], and it is one of the most frequently performed elective surgeries [9]. Fast tracking for TKR involves optimizing the treatment protocol to reduce the primary treatment period and thus reduce the use of institutional care [10]. The primary treatment period after TKR was approximately 3 days, and for 75% of the patients, the discharge destination was home [10]. Emphasis is placed on providing postoperative physiotherapy in hospitals to enable the patient's independence in activities of daily living (ADL) before discharge. In addition, hospital physiotherapists supervise active home exercises to improve knee range of motion, muscle strength, and weight-bearing while walking. High-intensity outpatient physical therapy directly after discharge improves the functional performance of patients who had undergone TKR [11]. Nonetheless, rehabilitation after discharge is mainly the patient's responsibility.

A study by Valtonen et al [12] found that although the operation reduces pain effectively, even 10 months after the knee replacement surgery, the knee extension torque and power in the operated lower limb remained weaker than those in the nonoperated side. This asymmetry limits patients' ability to negotiate stairs [12]. Questionnaires administered to patients 5 years after TKR have shown that their expectations regarding postoperative PA were not fulfilled to the same extent as their expectations regarding pain relief [13]. PA levels remain below the recommended levels, and sedentary behavior continues after TKR [1]. However, meeting preoperative expectations is a significant determinant of overall patient satisfaction following lower limb joint arthroplasty [14].

In the long term, PA would be crucial for the aging population undergoing TKR by reducing the risk of chronic noncommunicable diseases and disabilities in ADL. Exercise adherence is an essential predictor of the long-term effectiveness of exercise therapy both within and after the intervention period [15]. Gamified exercise, or exergaming, is a new approach to increase exercise adherence. Increased exercise adherence using exergames has been reported in several studies involving different patient groups [16,17].

Objectives

This study explored the effectiveness of home-based exergame rehabilitation on physical function and symptoms after TKR. This "Gamification in Knee Replacement Rehabilitation, randomized controlled trial" (BEE-RCT) is part of the "Business Ecosystems in Effective Exergaming" (BEE) project. The primary objective of this study was to examine the effectiveness of a 4-month gamified home exercise program on physical function, disability, and symptoms following TKR surgery. We hypothesized that people assigned to the exergame arm would have better functional status and lower levels of symptoms than those assigned to the standard home exercise arm.

Furthermore, we will assess exercise adherence and game experience in the gamified home-based rehabilitation arm of the study following TKR surgery and the maintenance of intervention benefits 1 year after TKR surgery. In addition, using a mixed methods approach, we aim to investigate the complex interrelationship between gamified rehabilitation, exercise adherence, PA, physical function, and symptoms in older adults after TKR surgery.

Methods

Trial Design

This was a 4-month dual-center, two-arm, parallel group randomized controlled trial that determined the effectiveness

of exergame-based home-based rehabilitation by comparing it with standard home exercise after TKR. The 4-month intervention period was followed by the 8-month follow-up period. Participants' perspectives on rehabilitation and exergames were explored using an embedded qualitative approach. Figure 1 illustrates the flow of this study.

Figure 2 presents the enrollment schedule, interventions, outcome assessments, and interviews. The participants' functioning, disability, and symptoms were assessed preoperatively *at* t_0 (baseline) and postoperatively *at* t_1, t_2, *and* t_3 (2nd, 4th, and 12th month, respectively). Individually arranged assessments were conducted in the exercise laboratory at the Turku University of Applied Sciences and the exercise laboratory at the University of Jyväskylä. Research data were collected before TKR surgery at baseline and during the RCT intervention and follow-up periods. The baseline assessment (t_0) was performed within 2 weeks before the planned day of surgery. During the baseline assessment visit, participants provided written informed consent, after which the research physiotherapist measured the outcomes, performed randomization, and guided home exercising according to the allocation group. The postoperative assessments (t_1,t_2, and t_3) were performed within +5 or −5 days of the postoperative 2-, 4-, and 12-month time points. During the postoperative assessment visit, the research physiotherapist measured the outcomes (t_1,t_2, and t_3) and guided the PA of standard care and the gym work out for strength training (t_2).

Figure 1. Flowchart of the Gamification in Knee Replacement Rehabilitation, randomized controlled trial. TKR: total knee replacement.

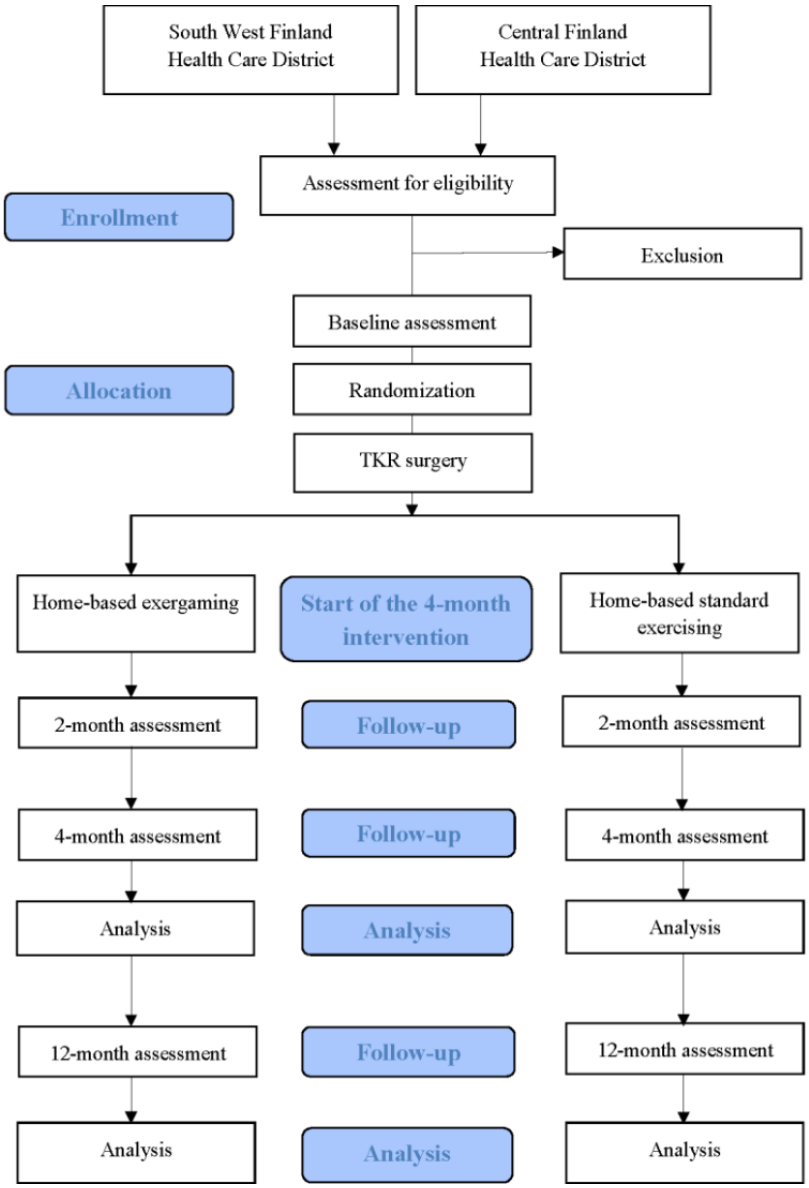

Figure 2. The schedule of enrollment, interventions, assessments, and interviews in the Gamification in Knee Replacement Rehabilitation, randomized controlled trial.

	Study period					
	Recruit-ment	Base-line	Opera-tion	Intervention		Follow-up
Timepoint	$-t_1$	t_{01}	t_{02}	t_1	t_2	t_3
Months from baseline	-2	0	0	2	4	12
Enrollment						
Eligibility screen	X					
Initial survey		X				
Informed consent		X				
Random allocation		X				
Interventions						
Exergame-based training at home			◆—	——	—◆	
Usual postoperative exercising at home			◆—	——	—◆	
Assessments						
Primary outcomes: Oxford Knee Score and Timed Up and GO Test		X		X	X	X
Secondary outcomes: 10-m Walking test, Short Physical Performance Battery, Isometric knee extension and flexion strength, Knee range of motion, Knee pain, World Health Organization Disability Assessment Schedule 2.0, and Knee Injury and Osteoarthritis Outcome Score		X		X	X	X
Outcomes related to exercising: Game User Experience Satisfaction Scale, Positive System Usability Scale, and Exercise time and dose (Self-reported and registered by the game computer through intervention period)				X	X	
Other outcomes: Satisfaction with the operated knee, and Physical activity (through study completion)				X	X	X
Interviews					X	X

Study Setting

The study participants were Finnish patients with knee OA who lived in the Southwest and Central Finland Health Care Districts and had undergone TKR surgery at the Turku University Hospital in the City of Turku or the Central Finland Hospital in the City of Jyväskylä. These hospitals perform approximately 1700 (Turku, 1200 and Jyväskylä, 500) knee joint arthroplasties per year. After discharge from the hospital, patients performed therapeutic exercises independently in their homes for 4 months with either exergame (intervention group) or standard postoperative exercises (control group). The intervention group participants followed the standard postoperative home exercise program when they could not use exergames, such as during vacations in another locality or abroad. For 1 year after surgery, the participants maintained a record of PA.

Eligibility Criteria

The study participants were men and women aged 60-75 years who had undergone TKR surgery. They were recruited during their preoperative outpatient visits at the Turku University Hospital and Central Finland Hospital. Inclusion criteria for enrollment in the study were as follows: (1) aged 60 to 75 years; (2) first primary, unilateral TKR; (3) diagnoses of primary knee arthrosis (International Classification of Diseases 10th Revision codes M17.0 and M17.1); (4) mechanical axis of the limb in varus; (5) model of the TKR is posterior stabilizing or cruciate-retaining prosthesis; and (6) normal vision with or without eyeglasses. The exclusion criteria were as follows: (1) diagnosed memory disorder or cognitive impairment; (2) neurological conditions (such as Parkinson disease, multiple sclerosis, or stroke); and (3) fractures, rheumatoid arthritis, or other biomechanical disruptions in the affected lower limb within 1 year before surgery. Inclusion criterion for age was set to have a sample presenting a vast majority of patients who had

undergone TKR without trauma background or increased number of comorbidities and to control high variability in skills of technology use.

Recruitment

During the preoperative outpatient hospital visit, the surgeon, with either a physiotherapist or a research nurse, assessed the eligibility of study patients. If a patient was eligible, a physiotherapist or research nurse described the study to the patient and asked for written permission for the research's initial preoperative contact. The patient was informed of the study course during the initial phone contact. The date of the preoperative baseline assessment was agreed upon by interested patients who did not report conditions that could affect the safety of physical testing and exercise. These conditions included chest pain during exercise or other physical exertions, excessive shortness of breath, cardiac medication, seizures or unconsciousness, fainting, or dizziness. In the baseline assessment, eligibility was reassessed based on the initial survey. The patient provided written informed consent to participate in the study if eligible.

Random Allocation

After the preoperative baseline measurements, the study participants were randomly allocated one by one to the exergame and standard home exercise groups. A person unrelated to the study had previously used a computer-generated randomization procedure using blocks of 2 and 4 in random order and according to the place of recruitment (Jyväskylä or Turku), gender and baseline Timed Up and Go (TUG) test with time ≤10 seconds (indicating faster performance in patients who had undergone TKR [18,19]). A person unrelated to the study had concealed group allocation cards in opaque sealed envelopes into 4 separate sets of stratification (slow men, slow women, fast men, and fast women) per place of recruitment. After the baseline measurement of each participant, the research physiotherapist of the exercise laboratory opened the next envelope from the appropriate set of envelopes, complying with the allocation stratification, and assigned the participant to the exergame or standard home exercise group according to the group allocation card in the envelope.

Interventions

Exergame

The exergame group played 11 different Unity (Unity Technologies) exergames (Turku University of Applied Sciences, Finland) developed in the BEE project. Exergame development was based on a standard postoperative rehabilitation program for TKR. The exergames were played using a motion sensor (Kinect 2.0, Microsoft Corporation) connected to a laptop (Micro-Star International) and controlled with a tablet (Lenovo). Training software (GoodLife Kiosk Trainer, GoodLife Technology) and television screens offered implementation in the homes of the study participants (Figure 3). Exergaming content and progression were built for players using PhysioTools Online (PhysioTools) exercise library software, enhanced with exergames. The player controls the games using movements similar to the standard postoperative home exercise program. The research physiotherapist instructed the participants in the exergame group to play exergames progressively several times a day for 16 weeks after discharge from the hospital (Multimedia Appendix 1). In addition, the participants were recommended to follow the standard postoperative home exercise program when they could not use exergames, such as during vacations in another locality or abroad.

Figure 3. Exergame solution in rehabilitation after total knee replacement in the home setting.

The initial guidance for setting up the exergame system, using applications, and testing 2 games (the Bubble Runner and Cave Game) took place at the exercise laboratory baseline visit immediately after randomization. Face-to-face individual guidance was provided for 15 to 20 minutes by the same research physiotherapist who had conducted the baseline assessment. In addition, the study participants received a written manual on exergame equipment, setup, applications, and exergaming. The participants independently set up the exergame equipment in their homes.

Exergames were categorized according to exercise target: knee extension and flexion, knee flexion or squatting, weight shifting from side to side, stretching, and functional exergames (Multimedia Appendix 1). The knee extension-flexion games (the Cave Game and Intruders) and stretching game (the Cannon) were played in a sitting position, whereas the other games (the Rowing Game, Pick Up, Squat Pong, Bubble Runner, Hat Trick, Brick Breaker, Hiking, and Toy Golf) were played in a standing position. Detailed information on each exergame's solution explaining the game's course and the strategies and metrics used is provided in Multimedia Appendix 1.

The first week of the exergame protocol (Multimedia Appendix 1) was initiated on the third day after surgery. The exergames of each week were prescribed to be played in the order presented in Multimedia Appendix 1. The protocol specified 4 to 5 exergames for each intervention week. The participants were instructed to play the games prescribed several times a day. Weekly, the exergame protocol became more demanding as games became more challenging, and playing time, number of repetitions, sets, and intensity in games increased. In weeks 5-12, exergames that had once been in the exergame protocol but were not planned for the current week were further available for play as additional exergames of the week. In the last 4 weeks of the exergame protocol (weeks 13-16), the exergames were the most demanding versions, with the highest exercising doses.

Control

The control group underwent a standard postoperative home exercise program initially instructed by a physiotherapist in the hospital where the surgery was performed (Multimedia Appendices 1-3). The research physiotherapist instructed the control group participants to follow this standard program several times a day for 16 weeks starting after discharge from the hospital. Similar to the exergame group, guidance was provided at the exercise laboratory baseline visit immediately after randomization. Face-to-face individual guidance was provided for 5 to 10 minutes by the same research physiotherapist who had conducted the baseline assessment.

Postoperative Usual Care

Both groups received standard care after TKR (Multimedia Appendices 2 and 3). Standard care included a clinical visit to hospital physiotherapists or orthopedists at an average of 2 months after surgery. In addition, the artificial joint status and ability to function were monitored regularly with electronic surveys and, if necessary, conventional radiography. Surveys were taken 2 to 3 months after surgery, 1 year after surgery, and will be taken every 5 years thereafter. In addition, PA guidance based on PA recommendations [20] was also provided as a part of standard care. At the 4-month postoperative research assessment visit, the research physiotherapist briefly, in approximately 5 minutes, counseled the participants of both groups about the PA guidance of standard care and provided written gym instructions for strength training (Multimedia Appendix 1).

Outcome Measures

Overview

Research physiotherapists responsible for collecting descriptive data and outcomes pre- and postoperatively were trained. Preoperative descriptive data were gathered by an initial survey, by interviewing study participants, and from medical records with the permission of the study participants. The selection of outcomes (Figure 2) adapted the recommended tests of physical function in people with knee OA [21] and were collected during exercise laboratory visits in Turku or Jyväskylä, according to the participant's residential area. Before data collection, participants were asked about their current perceived well-being (normal, tired, or unwell) to ensure safe exercise laboratory measurements. The outcomes were collected in a permanent order during both pre- and postoperative visits. The questionnaires were collected first, followed by height and weight measurements to calculate BMI. The questionnaires were collected using the pen and paper method in the following order: Oxford Knee Score (OKS), Knee injury and Osteoarthritis Outcome Score (KOOS), World Health Organization Disability Assessment Schedule (WHODAS 2.0), and satisfaction with the operated knee. In addition, on the 2- and 4-month visits, after previous questionnaires, the Positive System Usability Scale (P-SUS) and Game User Experience Satisfaction Scale (GUESS) questionnaires were collected from participants in the intervention group. Subsequently, the assessments were performed for all participants in the following order: knee pain (visual analog scale [VAS]), knee range of motion, Short Physical Performance Battery (SPPB), TUG test, 10-meter walking speed, and isometric knee extension and flexion strength. Sitting balance was measured using a prototype measuring device (SmartChair, Tohoku University) in the TUG and SPPB sit-to-stand tests. Finally, interviews were conducted. Data regarding exercise time and dose throughout the intervention period and PA through study completion were gathered by self-reported structured diaries and exergame time and dose data by game computers. The outcome assessments and interviews are described in detail in the *Primary Outcomes*, *Secondary Outcomes*, and *Qualitative Data* sections.

To minimize the amount of missing data owing to the COVID-19 pandemic, the principal investigators approved changes to the data collection method. Consequently, all data to be collected using the pen and paper method were collected by mail from the participants during the lockdowns and from the participants who, on their own, did not visit the exercise laboratory after the lockdown. The change to the data collection method did not require a modification of the ethical statement or hospital permission.

Primary Outcomes

Changes in knee function and pain were assessed using the OKS questionnaire [22]. OKS is a short, reproducible, valid, and sensitive questionnaire used to assess clinically important changes after TKR surgery [23]. Each of the 12 items was scored from 0 to 4, with 4 being the best outcome. When summed, the overall scores ranged from 0 to 48 points, with higher scores indicating better function and lower knee pain.

The TUG test was used to assess changes in mobility [24]. The TUG test was performed twice at maximum speed, with the shoes on. Time in seconds was measured using a stopwatch. Both results were recorded, and a better result (shorter time in seconds) was used. A lower TUG test time indicated better mobility.

Secondary Outcomes

Walking was assessed with a 10-meter walking test [25] performed 4 times with shoes on: twice with normal speed and twice with fast speed with a 2-meter flying start. Possible use of walking aids was also recorded. The time in seconds was measured using photocells. All results in seconds were recorded and reported as the walking speed (m/s). Better results at normal and fast speeds (higher value of m/s) were used. Higher speed in the 10-meter walking test indicated better walking performance.

Lower extremity performance was assessed using the SPPB test [26], which includes 3 subtests: static balance in 3 different positions, 4-meter walking time, and 5 repetitions of sit-to-stand. The balance test was performed without shoes. The walking test was performed at normal speed, and the sit-to-stand test was performed at fast speed, and both these tests were performed with shoes on. The possible use of a walking aid during the test was also recorded. All subtest results were recorded in seconds and scored from 0 to 4 points, leading to a maximum of 12 points. Higher SPPB test scores indicate better lower extremity performance.

Muscle strength was assessed with isometric knee extension and flexion forces collected using a Metitur Good Strength dynamometer in Jyväskylä (Newton [N]) and a Con-Trex Multijoint dynamometer (Newton-meter [Nm]) in Turku. Knee extension and flexion forces were measured from each lower limb in the sitting position, with the knee angle at 60° of flexion. The measurement sequence was as follows: (1) knee extension, (2) knee flexion force from the nonoperated lower limb, (3) knee extension, and (4) knee flexion force from the operated lower limb. The participants performed 4 warm-up and training contractions with moderate force, after which 4 contractions with maximal force were measured. Thereafter, the performances were repeated until the force improved to <50 N during the knee extension contraction and <20 N during the knee flexion contraction. One contraction lasted approximately 3 seconds, and there was a 30-second break between contractions. All maximal force results were recorded. In addition, after completion of the sets of contractions of the lower limb (eg, knee extensions and flexions of the operated lower limb), the participants were asked if the pain impaired their performance. The direction of painful performance (ie, extension, flexion, or both) and pain intensity on a scale of 1 to 10 were recorded. The best results for knee extension and flexion forces (Nm or N) were used. For analysis, N values were calculated as Nm with the formula Force (N) × lever arm length of the leg (m) and normalized based on body weight (Nm/weight). A higher value in the isometric knee extension and flexion tests indicated better muscle strength.

The range of knee joint flexion and extension was measured using a universal goniometer [27,28]. Measurements were performed on the operated knee in the supine position. First, active and passive knee flexion were measured, followed by active and passive knee extensions. The results were recorded in degrees; a smaller result in extension and larger result in flexion indicated a better joint range of motion.

Knee pain was assessed using the pen and paper version of the VAS [29] by asking participants to rate the average knee pain over a week. The VAS ranges from 0 to 100, indicating no knee pain and the worst possible knee pain, respectively.

Disability was evaluated using the self-reported WHODAS 2.0 questionnaire [30] including 12 items. The scale ranges from 0 to 4 per item, indicating values from “no difficulty” to “extreme difficulty,” and the total score ranges from 0 to 48 points. A lower total score on the WHODAS 2.0 indicated better function.

The KOOS questionnaire [31] includes 5 subscales: pain, other symptoms, quality of life, ADL, and sport and recreation function. The 5-point Likert scale ranged from 0 to 4 for each subscale. The maximum score on each subscale was 100 points. A higher score on the KOOS questionnaire indicated less knee pain and associated problems.

Exergame experience was evaluated using the GUESS [32] and the 10-item P-SUS [33] questionnaires. GUESS includes 9 subscales that assess usability or playability, narratives, play engrossment, enjoyment, creative freedom, audio esthetics, personal gratification, social connectivity, and visual esthetics. The questions were scored from 1 to 7, indicating values from “strongly disagree” to “strongly agree.” In addition, a score of 8 indicates “not applicable.” P-SUS questions were scored from 1 to 5, indicating values from “strongly disagree to “strongly agree.” A higher score on the GUESS and P-SUS questionnaires indicated a more positive experience of the exergames played.

Outcomes related to exercise adherence were collected using a self-reported structured diary and a game computer. Participants filled in the exercise diary daily for the exergame and standard home exercise adherence (number and duration of exercise sessions in minutes). This will be summed as days, sets, and minutes of exergaming and standard exercising per week. Minutes per week will be calculated as metabolic equivalent hours per week [34-36]. In addition, exergame adherence was measured based on the game computer data gathered during each exergame session (name of exergame, duration, timestamp, and game score). Adherence from game computer will be calculated as days, sets, and minutes of performed exergaming per week. Longer exercise duration, that is, minutes per week, indicated a higher level of commitment to exercise. In addition, adherence throughout the intervention period will be reported

as the percentage of completed exercise days compared with the total number of days.

PA was measured using a structured PA diary, which the participants completed daily from baseline to 12 months. The diary form sought data on each activity's mode, intensity, and duration. Leisure time PA and PA related to daily errands or commuting are reported separately. PA will be calculated as the metabolic equivalent hours per week and month by multiplying each marked activity by self-evaluated intensity (1, light; 2, moderate; and 3, vigorous), according to Ainsworth et al [34].

Satisfaction with the operated knee was assessed using the following question: "How satisfied are you with your operated knee?" Response options were "very satisfied," "satisfied," "dissatisfied," and "very dissatisfied."

Qualitative Data

Individual interview data on patients' perspectives on rehabilitation and exergames were collected 4 and 12 months after the operation. Face-to-face interviews were recorded, and laddering notations were used. Owing to the COVID-19 pandemic, phone interviews were conducted as necessary. All participants were invited to participate in the interviews. The laddering interview technique supports the understanding of the user's perspective [37]. The technique is based on the personal construct theory [38], which emulates human beings' mental models. The laddering interviewing technique operationalizes the personal construct theory by providing a means to investigate system attributes, consequences (reasoning) for system use, and values or goals that drive its use [37]. The laddering interview process by Tuunanen and Peffers [39] was followed. First, participants were given a list of stimuli (Multimedia Appendix 4) intended to suggest ideas about possible recovery experiences of participants to enable brainstorming [37]. Second, the interviewees were asked to select 2 stimuli that they perceived as the most important to them. The interviewer proceeded to ask the participant to explain why each experience was important by asking questions such as "why" and "why that would be important." The ladder data were recorded as attribute-consequence-value chains, as presented by Tuunanen and Peffers [39]. The interview recordings are also transcribed to later enable other qualitative approaches in the analysis.

Adverse Events and Dropouts

Adverse events that the study participants reported spontaneously were recorded. The type of harm and its onset time, intensity, and frequency were recorded, and the possible causal relationship with the intervention was assessed. The date, informant, and reason for dropout were recorded for the study participants who discontinued the study. In addition, we assessed whether the interruption was because of an adverse event, the participant's state of health, personal will, or whether the participant was not reached.

Blinding (Masking)

Participants and trial personnel were not blinded after the point of assignment to interventions following baseline measurements because of the nature of the interventions and outcomes assessed. Participants knew which group they belonged to because the group-specific exercise routines were followed immediately after randomization, and gaming equipment was provided to those randomized to the intervention group. Trial personnel, in turn, were able to deduce the group from the questionnaires related to the game experience gathered during 2- and 4-month visits from participants randomized to the exergame group.

Promotion of Participant Retention

Participant retention was promoted with phone contact before the 2-, 4-, and 12-month measurements to ensure participation. Data collection was supported by mailing questionnaires to participants when they did not come to the exercise laboratory for 2-, 4-, and 12-month measurements owing to personal reasons or pandemic constraints. The outcomes collected by mail were OKS, VAS, WHODAS 2.0, KOOS, satisfaction with the operated knee, GUESS, and P-SUS scores.

Data Management

The management of the collected and generated data was documented in the Data Management Plan (DMP) document. The data were pseudonymized and stored securely in locked cupboards or protected network drives. Unidentifiable data were shared with the investigators involved in the study. Processes to promote data quality include the documented data collection protocol and training of data handlers. All research results will be made public through conference presentations or journal publications. Individual study participants will not be identifiable based on public research results. A data monitoring committee was not needed because of the short duration of the trial and the known minimal risks.

Sample Size

The intended sample size (n=100) of the BEE-RCT was based on the primary outcome, the OKS [22]. Assuming a mean difference of 5 (SD 8) points [40] in a change in the OKS between the groups at 6 to 12 months [40,41], a sample size of 42 in the intervention and control groups was required to detect differences between groups at an α of .05 and reach power of 80%. The dropout rate was estimated to be 10%; consequently, a minimum of 100 participants were needed to be recruited. In 2020, the COVID-19 pandemic decreased the number of elective surgeries, such as TKR, and there were lockdowns in exercise laboratories. Due to this, recruitment slowed in the spring of 2020 and was completely stopped for 3 months because of lockdowns. Consequently, the trial failed to recruit the intended sample size of participants.

Data Analysis Plan

Repeated measures of the changes in primary and secondary outcomes will be compared between the exergame and standard home exercise groups using intention-to-treat analysis, mixed effects models, and an unstructured covariance structure. Fixed effects included group, time, and group × time interactions. In the primary analysis, repeated measurements will be taken at different time points, including at baseline and at 2 and 4 months. Mixed models allow for the analysis of unbalanced data sets without imputation; therefore, all available data with

the full analysis set will be analyzed. In response to the impact of COVID-19, the number of participants is expected to be insufficient for per-protocol analysis. The maintenance of intervention benefits for 12 months will be analyzed using similar mixed effects models as secondary analyses.

A concurrent embedded design of a mixed methods study was used by including a qualitative component within a quantitative study of exercise effectiveness. In the mixed methods approach, quantitative data analysis is mainly descriptive to support the interpretation of qualitative findings. For physical function measures, categorization based on a clinically meaningful level or change from baseline will be used to further integrate the qualitative data. With the qualitative interview data, primarily thematic coding and clustering of the concepts arising from ladder chains are planned [37]. The ladder data will be coded and categorized by 2 researchers and checked until a complete consensus is achieved between them. Integration of quantitative and qualitative data will focus on developing a framework using the identified clusters and structuring them by adopting the interpretative structure modeling technique [42].

Ethics and Dissemination

Ethics Approval

The Ethics Committee of the Southwest Finland Health Care Districts has reviewed and made a statement for the BEE-RCT study (Dnro 66/1801/2018, June 19, 2018) according to the Medical Research Decree. In addition, the Turku University Hospital and Central Finland Central Hospital provided permission for the study.

This study follows the guidelines of the Finnish National Board on Research Integrity [43], the ethical principles of the University of Jyväskylä, and good scientific practice and valid legislation. The ethical issues of this study concern humans as participants, the use and storage of the data, and principles related to intellectual property rights.

We conducted a pilot study with laboratory loading measurements before RCT to ensure safe and reasonable exergaming for patients recovering from TKR [44]. The universities insured the participants of the duration of laboratory measurements and trips directly related to them.

Consent or Assent

This project involved human participants, and informed consent was obtained along with the BEE-RCT. The research physiotherapist obtained consent before the baseline measurements. Consent follows the ethical principles of research in the human, social, and behavioral sciences and data protection legislation. It was ensured that the potential participants had fully understood the information and did not feel pressured or coerced to provide consent. Participants could deny or cancel their participation at any time without any consequences. The patient's consent or refusal to participate did not affect the treatment they received.

Confidentiality

All personal and collected data were treated as confidential at all stages of the study and were stored separately. All personal data were stored in a highly secure Deltagon CollabRoom environment. The electronic data were saved with metadata in university network drives, which are protected by usernames and passwords. The participant ID list that connects the study participants and research data will be disposed of after 15 years. Institutions hold the ownership of registry data. Data collected in this research will be owned by the University of Jyväskylä, the Turku University of Applied Sciences, and the University of Oulu. The intellectual property rights policy of each university will be followed, and ownership has been agreed upon when creating the DMP.

Declaration of Interests

This project is part of the BEE collaboration project and is partly funded by companies. The data will be processed and published without any commercial interest or input. Funders did not interpret the results of this project or participate in writing and publishing the research results. The BEE publication committee supervises and conforms to the authorships and contributions to each planned publication. The principal investigator will own all the results concerning collaborations with commercial entities. Commercial collaborations already own the rights to their products, and this will not be disputed.

Access to Data

Researchers from the University of Jyväskylä, the Turku University of Applied Sciences, and the University of Oulu will have access to the final data. The right to access data is managed according to the joint controller agreement of universities.

Dissemination Policy

Metadata entries will be published via the University of Jyväskylä Converis research information system. Individual written feedback was provided to the participants from participant-level data. The feedback included individual results of primary and secondary outcomes measured at baseline and after the intervention and follow-up periods. The trial results will be reported via scientific publications and congress presentations. In publications, the recommendations of International Committee of Medical Journal Editors for authorship eligibility will be followed [45].

The DMP for this project supports the reuse of data. However, as the data consist of confidential personal information, their use is strictly restricted to research purposes explicitly mentioned in the project plan. The project metadata will be found via the Converis research information system. Metadata, complete with a full description of methods, will be published as data sets are saved in the Jyväskylä University Digital Repository. Data are available to external collaborators upon agreement on the terms of data use and publication of results.

Protocol Version and Amendments

This study refers to protocol version 3 on March 16, 2020. Before data collection, PA diaries replaced activity monitors to measure PA. Important modifications in response to extenuating circumstances, such as COVID-19, have been reported following the CONSERVE-SPIRIT extension for reporting trial protocols and completed trials [46] (Multimedia Appendices 5 and 6).

Results

The first participant was recruited in November 2018 and randomly allocated to the intervention or control group in March 2019. The intervention was initiated in March 2019. Owing to the COVID-19 pandemic, trial recruitment was paused from March 16, 2020, to May 31, 2020. Recruitment was completed in December 2020, and 52 participants provided informed consent. Of these participants, 88% (46/52) completed at least one postoperative measurement (t_1, t_2, and t_3). The trial ended in January 2022, when the last recruited participant completed the 12-month follow-up measures and interviews (t_3). Primary results are expected to be published by the end of 2022.

Discussion

Principal Findings

The randomized controlled multicenter trial BEE-RCT will provide new knowledge about the gamification of therapeutic exercise and changes in physical function, disability, and symptoms after TKR surgery. First, we hypothesize that patients with TKR who were assigned to the exergame group would demonstrate better functioning and lower level of symptoms when compared with those assigned to the standard home exercise group. Second, we hypothesize that exercise adherence would be higher in the exergame group and that there would be an association between adherence and positive user and game experience. Using a mixed methods approach, we expect to better understand the complex interrelationship between gamified rehabilitation, exercise adherence, PA, physical function, and symptoms in older adults after TKR surgery.

In therapeutic exercises, training adherence dictates the effectiveness of exercise interventions in real life. Traditionally, printed instructions have reminded patients who had undergone TKR to follow the recommended rehabilitation process at home. Knee replacement reduces pain effectively; nevertheless, engagement in exercise and PA is especially difficult for people with OA who remain sedentary after TKR [47,48]. In light of these results, new solutions for rehabilitation technology are welcome to support people in their behavior change process after surgery. More recently, remote technologies such as mobile apps, wearable sensors, and gamified solutions have been developed to assess, guide, motivate, and receive feedback during the rehabilitation process.

Comparison With Prior Work

In BEE-RCT, we will explore the effects of custom-made exergames played in home settings. At the same time, previous studies of virtual reality tools after TKR have emphasized supervised interventions with standard commercial games [49] or without gamification [50]. Home-based rehabilitation will become even more essential after the COVID-19 pandemic, as the landscape of clinical outpatient rehabilitation changes from in-person visits to a greater reliance on remote services and digital rehabilitation [51].

Technological developments have enabled the digitalization of rehabilitation services. Traditionally, physiotherapists do not have valid and resource-effective methods to follow home exercise adherence or progression of patients after TKR. In BEE-RCT, the effects of postoperative home exercises and compliance will be studied thoroughly. The game computer gathered information on home exergame adherence, offering the advantage of objectively measuring which parts of the intervention participants were truly engaged in at home. This type of data provides the possibility of a large data set of exercise adherence, and it can be a valid measure of exercise behavior. In the future, new forms of data may be tested, and theories of intervention implementation and behavior change may be developed [52].

Strengths and Limitations

The data collection for the BEE-RCT was implemented during the COVID-19 pandemic affecting people and society. Within the allotted time, fewer participants were recruited than was initially planned. Therefore, the study is likely not powered to reveal differences in primary outcomes between the exergame and usual home exercise groups. However, the strength of the BEE-RCT is the intervention planned for the home environment and continued without disruption during the pandemic. After the COVID-19 lockdown, few of the recruited participants considered that coming to the postoperative exercise laboratory assessments would pose a high risk of developing the disease, and therefore, they did not want to come for the scheduled visits. However, we collected all questionnaires, interviews, and intervention data. When interpreting the results, it should be considered that blinding participants and professionals did not exist except at baseline assessment before randomization.

In addition to effectiveness, any new technology must be feasible, appropriate, and meaningful before implementing evidence-based rehabilitation. By using a mixed methods approach and integrating quantitative and qualitative data, BEE-RCT will produce an in-depth understanding of older people's experiences of their recovery process after TKR and the meanings of gamification. With a 1-year follow-up of physical function and PA combined with data from repeated interviews on patient experiences, we can explore complex interrelationships between gamified rehabilitation, exercise adherence, PA, physical function, and symptoms in older adults after TKR surgery.

Conclusions

Building on a multidisciplinary approach, this project can generate new knowledge and relevant results for digital rehabilitation services and technology development. A dual-center randomized controlled trial will add data to the evidence regarding the effects of exergame interventions. A mixed methods design and novel laddering approach will generate data on the complex phenomena of PA and rehabilitation after TKR.

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Authors' Contributions

All authors contributed to the conceptualization of this study. AH was the principal investigator in Jyväskylä, and KM was the principal investigator in Turku. EA, MJ, and NK drafted the protocol. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Exercise protocols in Gamification in Knee Replacement Rehabilitation, randomized controlled trial (BEE-RCT).
[DOCX File , 133 KB - resprot_v11i11e38434_app1.docx]

Multimedia Appendix 2
The guidebook of the Turku University Hospital for patients who had undergone knee replacement (in Finnish).
[PDF File (Adobe PDF File), 540 KB - resprot_v11i11e38434_app2.pdf]

Multimedia Appendix 3
The guidebook of the Central Finland Hospital, Jyväskylä, for patients who had undergone knee replacement.
[PDF File (Adobe PDF File), 746 KB - resprot_v11i11e38434_app3.pdf]

Multimedia Appendix 4
Laddering interview stimuli.
[PDF File (Adobe PDF File), 90 KB - resprot_v11i11e38434_app4.pdf]

Multimedia Appendix 5
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOC File , 153 KB - resprot_v11i11e38434_app5.doc]

Multimedia Appendix 6
CONSERVE-SPIRIT Extension (CONSORT and SPIRIT extension for randomized controlled trials revised in extenuating circumstances).
[DOCX File , 29 KB - resprot_v11i11e38434_app6.docx]

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Abbreviations

ADL: activities of daily living
BEE: Business Ecosystems in Effective Exergaming project
BEE-RCT: Gamification in Knee Replacement Rehabilitation, randomized controlled trial
DMP: Data Management Plan
GUESS: Game User Experience Satisfaction Scale
KOOS: Knee injury and Osteoarthritis Outcome Score
OA: osteoarthritis
OKS: Oxford Knee Score
PA: physical activity
P-SUS: Positive System Usability Scale
SPPB: Short Physical Performance Battery
TKR: total knee replacement
TUG: Timed Up and Go
VAS: visual analog scale
WHODAS 2.0: World Health Organization Disability Assessment Schedule

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Protocol

Digital Phenotyping Data to Predict Symptom Improvement and App Personalization: Protocol for a Prospective Study

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Abstract

Background: Smartphone apps that capture surveys and sensors are increasingly being leveraged to collect data on clinical conditions. In mental health, this data could be used to personalize psychiatric support offered by apps so that they are more effective and engaging. Yet today, few mental health apps offer this type of support, often because of challenges associated with accurately predicting users' actual future mental health.

Objective: In this protocol, we present a study design to explore engagement with mental health apps in college students, using the Technology Acceptance Model as a theoretical framework, and assess the accuracy of predicting mental health changes using digital phenotyping data.

Methods: There are two main goals of this study. First, we present a logistic regression model fit on data from a prior study on college students and prospectively test this model on a new student cohort to assess its accuracy. Second, we will provide users with data-driven activity suggestions every 4 days to determine whether this type of personalization will increase engagement or attitudes toward the app compared to those receiving no personalized recommendations.

Results: The study was completed in the spring of 2022, and the manuscript is currently in review at JMIR Publications.

Conclusions: This is one of the first digital phenotyping algorithms to be prospectively validated. Overall, our results will inform the potential of digital phenotyping data to serve as tailoring data in adaptive interventions and to increase rates of engagement.

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KEYWORDS

digital phenotyping; digital phenotype; mental health; depression; anxiety; smartphone; app; college student; university student; young adult; engagement; digital health; mobile health; mHealth; health app; Technology Acceptance Model; adoption

Introduction

While COVID-19 restrictions begin to end, the crisis in college mental health continues to expand. Recent large-scale studies suggest that the mental health impact of depression and anxiety for college students continues even in mid-2022 [1]. Digital mental health technologies, especially smartphone apps, are a leading tool to help provide more services to students [2]. Numerous college mental health centers already recommend mental health apps, and many programs are aimed specifically at college students [3]. Despite the clear potential of apps to provide easy-to-access and interactive mental health resources, their impact to date has been limited [4]. One leading barrier has been a lack of engagement; many people quickly abandon apps after only a few days [5]. In this paper, we propose a scalable and data-driven approach to customize daily and weekly app content based on predictive models that enable both personal and automated care.

Smartphone apps are well suited to personalize care as they can gather information related to real-time mental health. Often

known as digital phenotyping or smartphone sensing, it is possible, for example, to use signals from a smartphone's accelerometer to infer sleep behaviors and geolocation to infer mobility patterns. Reviews and research on digital phenotyping in college students suggest that, while digital biomarkers do exist [4], their effect size is likely small. In our prior research [6], we have combined these digital biomarkers with brief smartphone surveys to build predictive models of stress, anxiety, and depression. While we have validated these models retrospectively on different data sets of college students, to date there have been no studies exploring their prospective validity and if customizing an app to offer tailored preventive resources may reduce mental health symptoms. Overall, this work aims to prospectively evaluate a model for participant improvement across the study and compare groups that receive personalized interventions via a digital navigator, automated worker, or neither to explore the Technology Acceptance Model (TAM) in college students.

Methods

First, we will provide general details about the study, and then, we will address how we plan to achieve these two goals.

Participants, Technology, and App Use

This study will use the open-source mindLAMP app developed by the Digital Psychiatry lab at Beth Israel Deaconess Medical Center to collect survey and sensor data from college student participants [7]. mindLAMP is an app that facilitates survey, digital phenotyping (see below), and app-based intervention all in one platform that runs on Apple and Android smartphones. In this study, GPS, accelerometer, and screen state data will be collected. In addition, the app will be used to administer surveys and provide cognitive games, mindfulness, and other activities. Like earlier iterations of this study, college students will be recruited via social media to complete a screening survey on REDCap [8]. Given that in-person recruitment remains challenging around COVID-19, online recruitment via social media is practical [9]. To participate, students must be 18 years or older, score 14 or higher on the Perceived Stress Scale (PSS) [10], be enrolled as an undergraduate for the duration of the study, own a smartphone able to run mindLAMP, be able to sign informed consent, and pass the run-in period outlined below. We will not exclude students based on any comorbidities. We aim to recruit at least 100 students to start the study in line with our prior pilot studies and the sample sizes used to generate the model we are testing. Given that the effect size of any personalization efforts remain largely undefined, formal power analysis is more challenging; although, we note that this study is larger than prior digital phenotyping studies for college mental health, which have a mean sample size of 81 [11].

Participants will be sent log-in information for the app and will enter a run-in period. During these 3 days, participants will be asked to complete a survey each day. This run-in period will serve to screen out participants whose devices are not able to capture digital phenotyping data or do not engage with the app at all, and give the study coordinators time to verify that informed consent is signed and dated correctly. The run-in period is designed to help improve overall digital data coverage that is important for validation of the predictive model [12]. After these 3 days, participants who have completed the required surveys and have sufficient GPS data will be moved to the enrollment period of the study. Participants who have not completed the required surveys will be emailed by the study worker automation and given 24 hours to complete these tasks before being automatically discontinued.

Metrics

Participants will be asked to complete a longer survey each week on the app that includes the Patient Health Questionnaire-9 (PHQ-9) [13], Generalized Anxiety Disorder-7 (GAD-7) [14], PSS [10], UCLA Loneliness Survey [15], Pittsburgh Sleep Quality Index [16], Digital Working Alliance Inventory (DWAI) [17], and TAM-related questions (Table 1) [18].

On the first day of the study, participants will also be asked to complete the Prodromal Questionnaire-16 [19] (Multimedia Appendix 1A). Participants will have a daily survey each morning on the app that asks about sleep duration and sleep quality, and has questions from the PHQ-9, GAD-7, and PSS (Multimedia Appendix 1A). Participants will be compensated for completing the weekly surveys: US $15 for completing one survey between the first and eighth days, US $15 for completing at least one survey between the 8th and 21st days, and finally US $20 for completing at least one more survey between the 21st and 28th days. Students will be paid via Amazon gift card codes.

Throughout the study, engagement will be monitored to ensure that a minimum amount of data is being collected. To promote engagement, the study worker will reach out to participants via email if they have not completed any activities in the past 3 days and encourage them to complete the scheduled activities. If participants have not completed any activities in 5 days, they will be discontinued.

Table 1. Questions to explore the TAM. Some questions are part of both the DWAI and the TAM model. All answers are on a Likert scale (0, strongly disagree; 1, disagree; 2, neither agree nor disagree; 3, agree; and 4, strongly agree).

Component of TAM[a] and questions	From DWAI[b]
Usefulness	
The app supports me to overcome challenges.	Yes
The app allows me to easily manage my mental health.	No
The app makes me better informed of my mental health.	No
The app provides me with valuable information or skills.	No
Ease	
The app is easy to use and operate.	Yes
Attitude	
I trust the app to guide me toward my personal goals.	Yes
I believe the app tasks will help me to address my problems.	Yes
The app encourages me to accomplish tasks and make progress.	Yes
I agree that the tasks within the app are important for my goals.	Yes
Behavioral intention	
I want to use the app daily.	No
I would want to use it after the study ends.	No

[a]TAM: Technology Acceptance Model.

[b]DWAI: Digital Working Alliance Inventory.

Activities

All participants will be scheduled for different therapeutic modules each week. The activities are listed in the app under the participant's daily task feed. The components of the study are shown in Figure 1.

These modules include content created specifically for college students. For the first week, all participants will be scheduled for gratitude journaling. In the second and fourth weeks, participants will learn about different types of thought patterns and practice recoding and rationalizing their thoughts (Multimedia Appendix 1B). Screenshots of the app modules are shown in Figure 2.

We have evaluated improvement (change in GAD-7 scores) in a prior study [20], which is shown in Figure 3. Each participant's change in GAD-7 is shown by a line going from their start-of-week to end-of-week score. Overall, it is difficult to determine in this small data set if one module is better than the other. However, it seems that participants with higher GAD-7 scores may not improve as much with mindfulness as compared to cognitive distraction games. Thus, in the third week, participants will be scheduled for either mindfulness or cognitive distraction games based on whether they had low (≤10) or high (>10) GAD-7 scores on the initial weekly survey. Participants who do not complete this initial survey within the first week will be discontinued.

Figure 1. Activities throughout the study. Following a 3-day run-in period, participants will complete different module activities each week. GAD-7: Generalized Anxiety Disorder-7.

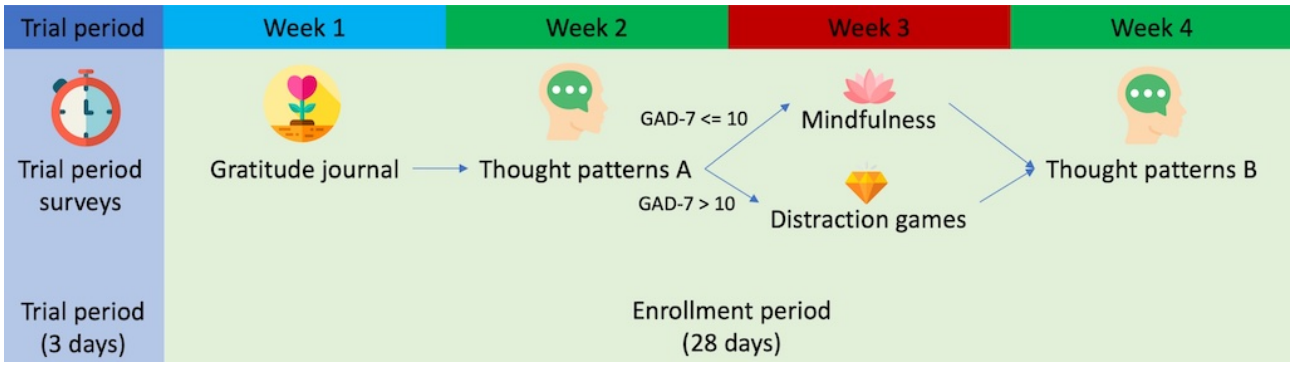


Figure 2. Screenshots of activities in the mindLAMP app including (A) gratitude journal (week 1); (B) the thought patterns learn tip (weeks 2 and 4); (C) a thought patterns activity example (week 2); (D) thought patterns, asking the user to reframe their thought (week 4); (E) a breath activity (week 3); and (F) the spatial span game (week 3).

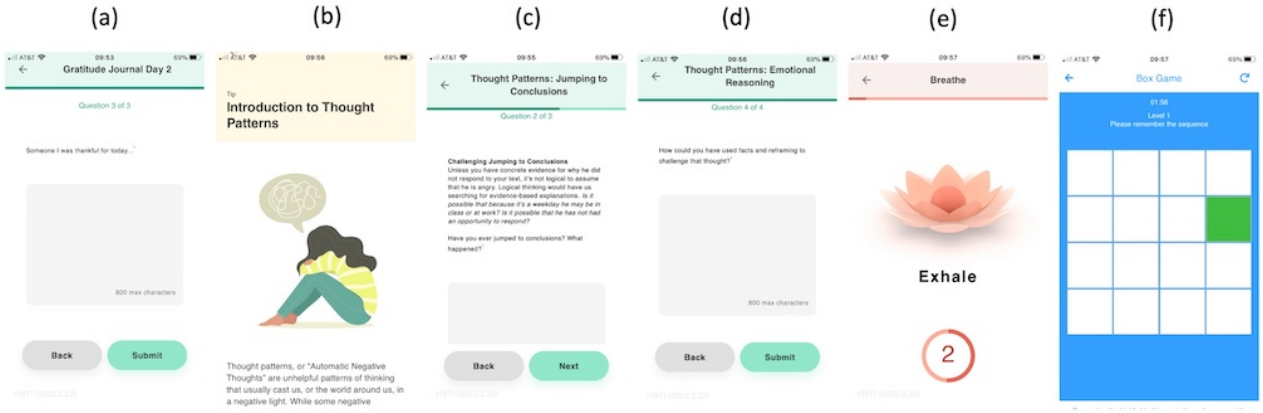
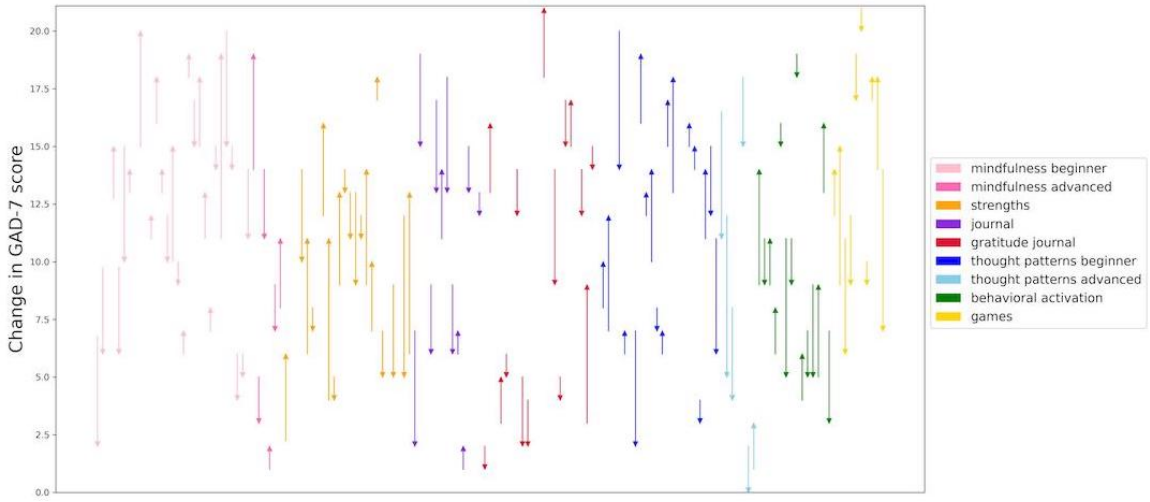


Figure 3. Improvement across different modules from earlier studies. The change in score is shown via the direction of the arrow and the magnitude of the change is shown by the length of the arrow. This highlights the nature of the data used to produce the recommendation model tested in this study. GAD-7: Generalized Anxiety Disorder-7.

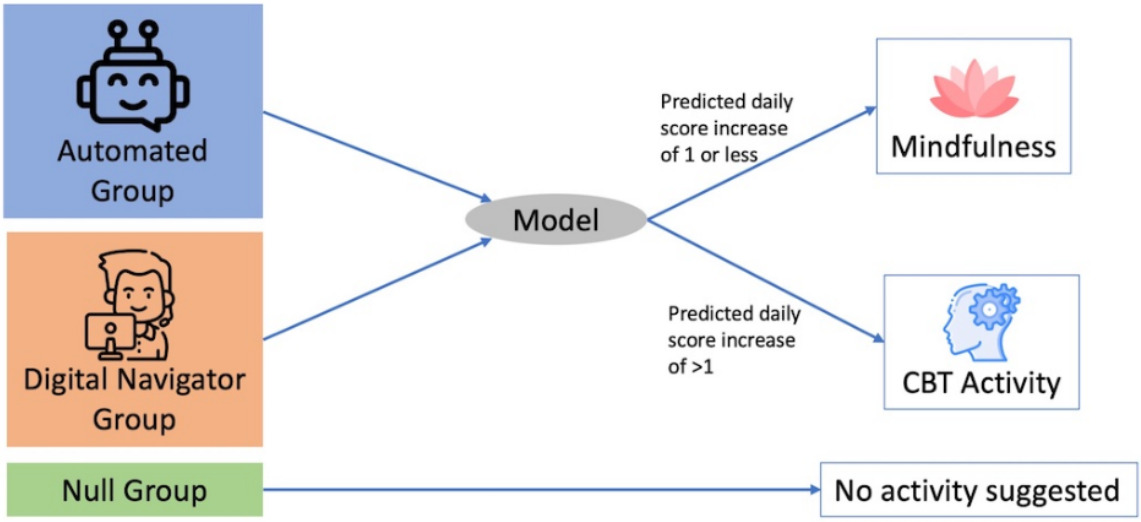


Engagement Theory and Study Design

To address our second aim exploring engagement, we adapted the TAM as a theoretical framework [18]. The TAM is the most widely used model to study engagement around digital health technologies. In the TAM, both perceived ease of use and perceived usefulness influence attitude toward technology, which in turn impacts behavioral intention to use (B) and actual system use. In this study, attitude toward technology will be measured by the DWAI [17]. The predictive models offering tailored resources should increase perceived usefulness and thus attitude toward technology and actual engagement compared to a control group receiving a scheduled set of resources.

However, increasing perceived usefulness may not be enough, as recent studies suggest the need for a social, or at least human, interaction to drive engagement. It is currently unclear if this interaction would have the largest effect on perceived usefulness, attitude toward technology, or behavioral intention to use, and thus, we will perform an exploratory analysis around this question. The study will be split into three groups. For those in the first group, digital navigators [20] will provide human support and reach out every fourth day to suggest a different module based on whether the algorithm (described below) predicts future symptom worsening or improvement. In this study, navigators are research assistants who have been trained in our 10-hour curriculum on how to provide technical and engagement support for people using health apps [21]. They will use email to communicate with participants, although we automated much of the role for this study as outlined below. For those assigned to the automation arm, modules will be suggested every fourth day by the automated study worker bot via email. Our automation platform will generate emails, and those assigned to the bot group will receive that email, while those assigned to the digital navigator group will have theirs reviewed and signed by such. Finally, for those assigned to the third arm, or the null group, there will be no modules suggested or automation/digital navigator interaction. Study staff will be available to answer any study questions from all participants. The reason for activities being suggested every 4 days is to allow participants to practice the suggested skills and resources, and allow a window for these to impact symptoms. Upon enrollment, participants will be sequentially assigned to one of three groups: the automated group, the digital navigator group, or the null group (Figure 4).

Figure 4. The study will be split into 3 different groups. Activities will be suggested based on model predictions. CBT: cognitive behavioral therapy.



Machine Learning Model for Engagement Intervention

We present a logistic regression model trained on the passive data features of a prior study of college students to predict whether daily survey scores would increase by one or more (any decrease in mental health). The model will be used to predict every fourth day if there will be an increase in reported symptoms. The model is used to demonstrate the feasibility of applying a data-driven approach to activity suggestions. On these days, students in the digital navigator group and the automated group will receive a suggestion via email for an additional activity to complete from either a digital navigator or the automation worker bot, respectively. On days with an expected increase, a cognitive behavioral therapy–based exercise will be assigned, and on days without an expected increase, a mindfulness exercise will be assigned. These activities will be pulled sequentially from a predefined list and will be different from the weekly activities (Multimedia Appendix 1C). In addition, participants will be asked to complete a 3-question survey about their attitude and behavioral intention toward the app after completing the survey (Multimedia Appendix 1A) as a measure of engagement.

The model was fit using data from the second iteration of the college mental health study using leave-one-patient-out cross-validation on the difference between each of the passive data features from 2 days ago to the previous day to predict a score increase of one or more from the previous to the current day. The implementation of the passive data features used in the model can be found on GitHub [22]. The Scikit-Learn LogisticRegression model was used with a 1:1 ratio of 0.5 [23]. Class weights were balanced, and all input features were standardized. The final model coefficients (Table 2) are an average of the coefficients of each model. The area under the curve (AUC) over all the combined cross-validated folds was 0.648.

Table 2. Passive data model coefficients, means, and SDs.

Feature	Coefficient	Mean (SD)
Entropy	–0.07705803	4.132491e-3 (4.193345e-1)
Home time	–0.74001826	–4.256811e5 (2.199408e7)
Screen duration	0.12002379	8.479066e4 (1.127670e7)
GPS data coverage	0.2187653	–2.222512e-3 (2.301561e-1)
Step count	0.11418704	–4.385282e2 (5.877810e3)

Symptom Improvement Model

To achieve our first aim, we present an additional logistic regression model to predict if participants will improve by at least 25% by the end of the study on the weekly surveys from the average of all features over the course of the study. The model was trained on data from the first iteration of the college study [8] and tested on the second iteration of the college study to test model generalization. The AUC scores are shown in Table 3. The features used in the model and a table of nonzero model coefficients can be found in Multimedia Appendix 1D.

Both previous versions of the study recruited college students to participate in a 28-day study taking daily and weekly surveys. Differences included the time the study was performed (version 1 collected data from December 2020 to May 2021, and version 2 collected data from November to December 2021) and the module activities (version 1 had no assigned activities, and version 2 had four set modules: thought patterns, journaling, mindfulness, and cognitive distraction games).

Table 3. Model performance for the improvement model. Results are shown for the second college data set from a model trained on the first college data set.

Survey	Area under the receiver operating characteristic curve
Patient Health Questionnaire-9	0.647
Generalized Anxiety Disorder-7	0.738
Perceived Stress Scale	0.640
UCLA Loneliness Scale	0.835
Pittsburgh Sleep Quality Index	0.634

End of the Study

The activity schedule will finish after 28 days in the enrollment period. However, if participants have not completed their final weekly survey, they will be given up to 4 additional days to complete this survey and receive compensation. At 32 days, all remaining participants will be marked as completed, and their sensor data collection will be turned off.

Study Automation and Data Coverage

To enable scalable research, we will build upon the digital study infrastructure used in our prior studies [12]. All parts of the study will be automated via workers implemented in Python. We have added new features to the codebase, including a worker that will update a Google Sheet with study information such as the status of different participants in the study, payment form completion, and which activities have been assigned. In addition, automated Slack notifications will be sent to the team to help manage the study (Figure 5). These improvements will provide an easy way for the study team to track study progress.

Passive and active data coverage will additionally be monitored throughout the study via Slack notifications sent to the study team and graphs on the data portal (Figure 6). Graphs will include participant GPS, accelerometer, and screen state coverage over the past week, days since the last activity, previous week's module completion, and previous week's daily/weekly survey counts. These graphs will allow researchers to monitor for any study-wide data collection issues and track overall participant engagement at a high level.

In addition to these researcher-facing metrics, participants will receive a weekly progress email telling them their streak, number of weekly and daily surveys completed, and module completion to promote engagement. The code for the study workers can be found on GitHub [24].

Figure 5. Slack notifications from the study worker: (A) lists levels of available gift codes for payment and (B) reports the number of participants in each phase of the study.

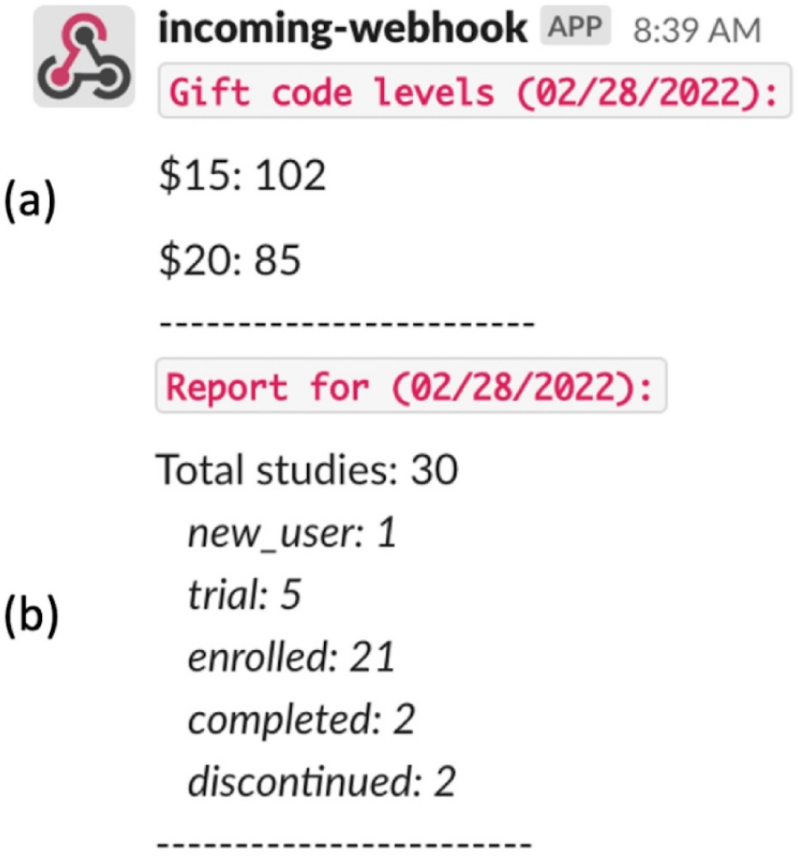
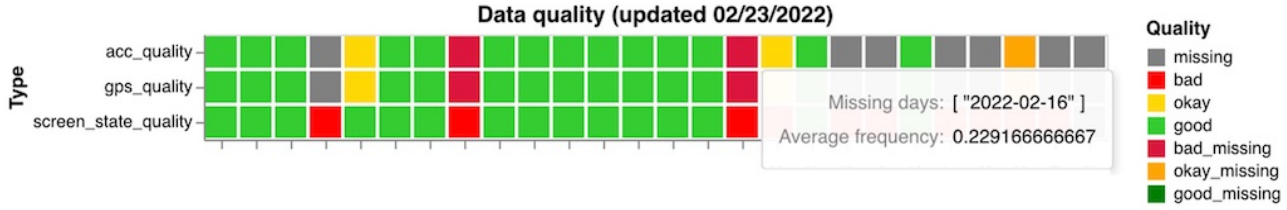


Figure 6. Passive data coverage graphs. Rows show accelerometer coverage (acc_quality) GPS coverage (gps_quality) and screen state coverage (screen_state_quality). Further details can be found on Github [22].



Safety

For any participants who indicate thoughts related to self-harm or suicide as noted by a score of 3 on question number nine of the PHQ-9, an alert will be sent to study staff by the automated study worker, and the principal investigator or covering licensed clinicians will reach out to the student within the same business day to conduct a safety assessment. If the student cannot be reached via phone or email after 24 hours, we will notify the local student mental health services. At the same time a participant records an elevated thought of self-harm or suicide, the app also displays a reminder that it is not a replacement for emergency care and that study staff cannot respond in real time, and provides links and phone numbers to resources.

Ethics Approval

This study was approved by the Beth Israel Deaconess Medical Center institutional review board (protocol 2020P000310). Data is not available to share, but the smartphone app and feature processing code are.

Results

The first key goal of this work is to prospectively evaluate a model predicting improvement across the study. Second, we aim to analyze the effectiveness of suggesting personalized modules to participants. We will compare the improvement of the automated and digital navigator groups to see if there is a significant effect of having a person versus artificial intelligence delivering information. We will also compare the automated and digital navigator groups with the null group to see whether suggested modules and interaction during the study increases engagement or improvement. As a secondary outcome, we will perform an ANOVA analysis to compare the TAM questions across the three study groups, acknowledging that this type of analysis is novel and that the results of individual questions will be challenging to compare to prior literature. The study was completed in the spring of 2022, and the results will be published with JMIR Publications.

Discussion

The results of this study will inform both data science and clinical engagement questions around digital college mental health. First, by prospectively testing our algorithms on a unique sample, we can determine both their reliability and validity. Second, by assessing engagement outcomes with digital navigators versus automations versus a control group, we can learn how to best increase the use of apps and build mechanistic understanding using the TAM.

While many smartphone digital phenotyping biomarkers and algorithms have been proposed across the mental health field and even specifically for college mental health [11], none have ever been prospectively validated. In our prior research, we have been able to retrospectively validate findings, used to inform this study's methods, on older data sets [6,8].

Beyond their predictive ability, the results around the validity of the digital phenotyping biomarkers hold potential for advancing adaptive interventions [25]. A key component of adaptive interventions is the tailoring variable that is used to customize treatment at each decision time point [26]. While most tailoring variables are static (eg mood score above a predetermined threshold at a certain time), digital phenotyping biomarkers could serve as more dynamic tailoring variables that would enable more personalized treatments. Given that smartphones themselves can serve as platforms to offer these adaptive interventions, the results around optimal tailoring variables are highly relevant.

The digital navigator group, as well as the control group, offer useful comparisons that must be considered. Digital navigators are increasingly used to increase engagement although at the price of greater scalability. Still, most apps today are not supported by either digital navigators or algorithms, so comparing outcomes to a control group can help assess any potential benefit. Additionally, it remains difficult to determine which activities are best for participants or which interventions should be assigned in real time in response to passive data changes. This challenge makes it difficult to truly personalize app recommendations. However, it may be the case that providing expert or data-driven suggestions to the participant introduces a placebo effect that improves engagement and attitude toward the app regardless of the actual usefulness of the activity. Although difficult to explore in this study, comparing different app activities is an interesting area of future work.

Further secondary outcomes related to the TAM can also help inform mechanistic-based understanding of engagement. While many prior studies, including our own, have examined outcomes like usability, fewer have explored why apps are engaging. Even if our results are negative around engagement, learning how TAM scores change over time and correlate to rates of app use will inform how future versions of mindLAMP can be improved.

There are limitations to this protocol. For secondary outcomes regarding automated interventions, given that our model here has a low AUC, the results will have to be interpreted with caution. While our study is designed to prospectively validate the symptom algorithm, it is not powered around the secondary engagement outcomes. This is in part due to the effect size for

different engagement strategies like digital navigators and personalization remaining poorly defined. Thus, our results can help inform future study design.

Like our prior studies, our research is fully reproducible. We offer details of our recruitment process and procedures in this paper that outlines details of our recruitment, screening, and data coverage procedures [12]. The mindLAMP app remains open-source software currently deployed at over 50 clinical sites worldwide, and our algorithms are also publicly accessible via GitHub [27]. This enables others to validate and expand upon our work transparently. While not a study outcome, the decentralized clinical trial mechanism used in this study offers a practical example of how digital phenotyping research can be done in a remote yet scalable manner.

Data Availability

Data from this study is not available given the personal identifiable nature of the information. However, the mindLAMP app and processing code are freely available.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Additional figures and supplementary material.
[DOCX File , 33 KB - resprot_v11i11e37954_app1.docx]

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Abbreviations

AUC: area under the curve
DWAI: Digital Working Alliance Inventory
GAD-7: Generalized Anxiety Disorder-7
PHQ-9: Patient Health Questionnaire-9
PSS: Perceived Stress Scale
TAM: Technology Acceptance Model

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Protocol

A Web-Based Self-help Intervention for Coping With the Loss of a Partner: Protocol for Randomized Controlled Trials in 3 Countries

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Abstract

Background: The death of a partner is a critical life event in later life, which requires grief work as well as the development of a new perspective for the future. Cognitive behavioral web-based self-help interventions for coping with prolonged grief have established their efficacy in decreasing symptoms of grief, depression, and loneliness. However, no study has tested the efficacy for reducing grief after losses occurring less than 6 months ago and the role of self-tailoring of the content.

Objective: This study aims to evaluate the clinical efficacy and acceptance of a web-based self-help intervention to support the grief process of older adults who have lost their partner. It will compare the outcomes, adherence, and working alliance in a standardized format with those in a self-tailored delivery format and investigate the effects of age, time since loss, and severity of grief at baseline as predictors. Focus groups to understand user experience and a cost-effectiveness analysis will complement the study.

Methods: The study includes 3 different randomized control trials. The trial in Switzerland comprises a waitlist control group and 2 active arms consisting of 2 delivery formats, standardized and self-tailored. In the Netherlands and in Portugal, the trials follow a 2-arm design that will be, respectively, complemented with focus groups on technology acceptance and cost-effectiveness analysis. The main target group will consist of adults aged >60 years from the general population in Switzerland (n≥85), the Netherlands (n≥40), and Portugal (n≥80) who lost their partner and seek help for coping with grief symptoms, psychological distress, and adaptation problems in daily life. The trials will test the intervention's clinical efficacy for reducing grief (primary outcome) and depression symptoms and loneliness (secondary outcomes) after the intervention. Measurements will take place at baseline (week 0), after the intervention (week 10), and at follow-up (week 20).

Results: The trials started in March 2022 and are expected to end in December 2022 or when the needed sample size is achieved. The first results are expected by January 2023.

Conclusions: The trials will provide insights into the efficacy and acceptance of a web-based self-help intervention among older adults who have recently lost a partner. Results will extend the knowledge on the role of self-tailoring, working alliance, and satisfaction in the effects of the intervention. Finally, the study will suggest adaptations to improve the acceptance of web-based self-help interventions for older mourners and explore the cost-effectiveness of this intervention. Limitations include a self-selective sample and the lack of cross-cultural comparisons.

Trial Registration: Switzerland: ClinicalTrials.gov NCT05280041; https://clinicaltrials.gov/ct2/show/NCT05280041; Portugal: ClinicalTrials.gov NCT05156346; https://clinicaltrials.gov/ct2/show/NCT05156346

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KEYWORDS

bereavement; cognitive behavioral therapy; CBT; cost-effectiveness; electronic mental health; grief; technology acceptance

Introduction

Background

The death of a partner is a very stressful critical life event in later life. It involves a dissolution of social and emotional ties, which requires the acceptance of the loss as well as the development of a new identity and a new perspective for the future. It involves the adaptation of daily routines, which can be even more challenging when social, physical, and financial resources decrease in later life [1]. Grief and psychological distress after the loss of a partner are normative reactions. For most individuals, grief intensity weakens to a manageable degree within several weeks or months after the loss (eg, [2,3]). However, some individuals are less able to cope with bereavement and show symptoms of prolonged grief or adaptation problems [4-7]. Approximately 10% of mourners develop prolonged grief, which is a psychological disorder characterized by separation distress; frequent or disabling cognitive, emotional, and behavioral symptoms such as avoidance of reminders of the loved one; difficulties moving on with life; and functional impairment [8-10]. A recent study comparing the prevalence of prolonged grief disorder based on 2 criteria sets, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, American Psychiatric Association [11] and International Statistical Classification of Diseases and Related Health Problems, 11th Edition, World Health Organization, 2019 [12], found a lower prevalence of the disorder (4.4% and 3.3%, respectively) than the previous studies. However, this study highlighted a higher prevalence of symptoms: difficulty accepting the loss was the most frequent single symptom (14%-25%), and grief-related impairment was common (10%-16%). Crucially, this study showed that >60% of participants with probably prolonged grief disorder used health care services [13]. Therefore, supporting mourners and promoting a healthy grief process is key to preventing further health problems.

Web-Based Grief Interventions

Several web-based interventions have been developed as a complement to face-to-face grief counseling or therapy [14-18]. A recent meta-analysis, while summarizing the evidence for web-based interventions for mourners, found that all the cognitive behavioral therapy (CBT)–based interventions showed moderate effects (g=0.54) for symptoms of grief and large effects (g=0.86) for posttraumatic stress disorder, with effects being stable over time [19]. Furthermore, an additional systematic review and meta-analysis with similar aims managed to replicate said results, showing that all 9 assessed randomized controlled trials decreased symptoms of grief after bereavement [20]. However, this meta-analysis clarified that most of the interventions assessed focused on the loss of a child. Only 2 interventions focused on the loss of the partner and on prolonged grief [14,15]. From these, only 1 study aimed at supporting the grief process of older adults [14]. This suggests that the bereavement of older adults when they lose their partners is overlooked, especially considering the potential for developing prolonged grief and other symptoms. Indeed, older adults seem to be underrepresented in web-based CBT interventions in general, as suggested by a meta-analysis testing whether computerized CBT treatments are potential tools to decrease depression in later life [21]. Despite being pervious to challenges related to low digital literacy, web-based interventions aimed at older adults present several benefits such as high accessibility, flexibility, and privacy as well as low costs [22]. Such benefits are expected to outweigh these potential barriers.

CBT techniques such as exposure, cognitive reappraisal, as well as integration and restoration as treatment components have been demonstrated to have good results in web-based self-help interventions for complicated grief after bereavement [17,18]. Furthermore, a study compared exposure on the web with behavioral activation treatment [15], showing that both interventions reduced complicated grief, posttraumatic stress, and grief rumination, but only exposure showed an effect on depression and brooding levels relative to the control group. Most web-based interventions provide standardized modules in a given order. However, the need to achieve better outcomes by adapting treatment planning to each individual has been guiding research in face-to-face CBT interventions (eg, [23]). It also fostered the development of modular intervention formats, which proved to be effective (eg, [24,25]). Rather than following a standardized fixed order, in this type of intervention, modules are implemented according to individuals' specific symptoms and specific needs at each time (eg, [25]). Following this principle, self-tailored, web-based CBT interventions (iCBT)

may lead to promising results as modular face-to-face approaches. A study addressing comorbidity in depression compared self-guided iCBT with standardized (nontailored) iCBT and revealed that both delivery formats of the intervention improved measures of depression, anxiety, and quality of life. This study also revealed that the self-tailored treatment was more effective than the standardized treatment among participants with more severe symptoms at baseline and more comorbidity [26]. However, most of the research tends to compare web-based interventions (regardless of being self-tailored or standardized) with other therapeutic formats, such as care-as-usual or discussion groups, as it is described in a meta-analysis testing the role of self-tailoring in web-based interventions [27].

The Web-Based Self-help Intervention

The development and evaluation of the web-based self-help intervention for mourners is embedded in the Optimizing the Mental Health and Resilience of Older Adults That Have Lost Their Spouse via Blended, Online Therapy (LEAVES) project [28], a European project, funded by the Active and Assisted Living Programme focused on the development of a web-based self-help program that supports older adults dealing with the loss of their partner and with adapting to the new life situation. The web-based self-help intervention is based on 2 theoretical models describing crucial factors for an adaptive adjustment to bereavement: the 4 tasks of mourning [29] and the dual-process model of coping with bereavement [30,31]. It follows the most relevant CBT elements that cognitive behavioral interventions for prolonged grief are often based on (1) exposure (eg, telling the story of the loss), (2) cognitive reappraisal or restructuring of individual dysfunctional thoughts (eg, guilt or anger) associated with the loss, (3) integration and restoration including self-care and social re-engagement, and (4) behavioral activation [32,33]. As described earlier, previous web-based grief interventions have been testing the benefits of these elements (eg, [15]), although these studies did not combine the 4 elements in a single intervention, as it is the aim of this web-based self-help program. The content of the intervention is based on the LIVIA self-help program for coping with prolonged grief after the loss of a spouse [14,34,35]. LIVIA, as a text-based intervention on the web, without sophisticated interaction with users, proved its efficacy for mourning older adults from a general Swiss population sample with a mean age of 59 years, who had lost their partner at least 6 months ago. It confirmed that the intervention is also efficacious for milder grief symptoms and thus may prevent grief-related disorders. Compared with the waitlist control group, the intervention resulted in significant reductions in grief (Cohen d=0.81), depression (Cohen d=0.59), and psychopathological distress (Cohen d=0.39) as primary outcomes and reductions in embitterment (Cohen d=0.37) and loneliness (Cohen d=0.37) and an increase in life satisfaction (Cohen d=−0.41) as secondary outcomes. These gains were maintained over 3 months. Improvements were similar among participants with low, medium, or high levels of grief at baseline.

The content of the LIVIA program, based on the elements of exposure, cognitive reappraisal, and restoration, has been complemented with an Activities section for behavioral activation, as well as a conversational virtual agent that guides users through the self-help program. In distinct modules, the program provides users the opportunity to cope with their grief in a thorough process from confrontation with the loss to practicing new coping strategies and routines focused on the adaptation to a new life.

Research Goals

This study has five research goals: (1) to test the efficacy of the web-based self-help program in 3 countries, which includes comparing the active arms with a control group; (2) to examine which delivery format (standardized vs self-tailored) leads to better clinical outcomes; (3) to investigate the mechanisms of change underlying the intervention effects and to examine the roles of predictor variables and mediators; (4) to assess technology acceptance from the perspective of older adults in grief; and (5) to estimate the cost-effectiveness of the web-based service for providers to support the business models and marketing strategies during the implementation of the service. Thus, it provides a comprehensive evaluation of the web-based self-help program.

Main Research Hypotheses

The main research hypotheses include the following:

1. We hypothesize that the intervention will significantly decrease grief symptoms (primary outcome) as well as depression symptoms and perceived loneliness (secondary outcomes) compared with the control group.
2. Considering that the self-tailored delivery format provides participants with the opportunity to meet their specific needs at any time, we hypothesize that the self-tailored intervention will lead to higher satisfaction with the intervention and to a higher decrease in grief, depression symptoms, and perceived loneliness than the standardized intervention.
3. We hypothesize that the overall helpfulness of the modules, gains in mastery experiences, self-esteem, insights, the matching of the needs of the user (session outcomes), and a better working alliance mediate the effect of the treatment.
4. Comparing the 2 active arms, we hypothesize that the self-tailored intervention will lead to better session ratings and a higher working alliance than the standardized intervention, thus leading to better outcomes after the intervention.

To better understand the intervention effects, exploratory analyses will test whether age, time since loss, and the severity of grief symptoms affect treatment outcomes. Technology acceptance and cost-effectiveness analysis are exploratory and have no a priori hypotheses.

Methods

Study Paradigm

The intervention's efficacy will be tested in Switzerland, Portugal, and the Netherlands, in 3 different trials. Besides the main goal of testing efficacy, each trial will allow meeting different complementary research goals and, consequently, will follow different designs. In the study conducted in Switzerland,

the complementary goal will consist of a thorough efficacy evaluation, including the comparison of a standardized with a self-tailored intervention. It consists of a 3-arm randomized controlled trial with 2 active arms (standardized vs self-tailored) and a waitlist control arm and will explore clinical mediators and predictors of the intervention's effect. Following the principle of parsimony, the trials in the Netherlands and Portugal will follow variations of the main clinical design using a 2-arm randomized controlled trial comparing the intervention with a control group; whereas in the Netherlands trial, whose complementary research goal is to understand technology acceptance, the self-tailored intervention will be compared with a waitlist group. The focus on technology acceptance will be implemented through the conduct of focus groups. In Portugal, where the complementary goal will be to conduct a cost-effective analysis, the study will compare the standardized intervention with a care-as-usual group. The study in Portugal will also include qualitative methodology for the assessment of the barriers to and facilitators of using the web-based self-help program. Testing the web-based self-help intervention in 3 countries is not intended to guide cross-cultural comparisons but to inform different complementary research goals. The web-based intervention will be named differently in the 3 countries: SOLENA in Switzerland, EuLuto in Portugal, and LEAVES in the Netherlands.

Participants

The main target group is older mourners from the general population (adults aged >60 years) who have lost their partner and seek help in their grief process. Specific inclusion criteria are (1) experience of partner bereavement; (2) seeking help or willingness to accept help to cope with grief symptoms, psychological distress, or the psychosocial adaptation to a life without the deceased; (3) access to an internet connection and adequate equipment; (4) mastery of the country's first language; and (5) an informed consent by the participant. General exclusion criteria are (1) that the loss occurred <1 month before enrolling in the study, (2) severe psychological or somatic disorders that need immediate treatment and hinder the continuous work on the web-based self-help program, (3) acute suicidality, (4) no emergency plan that specifies a health care professional or service who participants can turn to if they find themselves in crisis, and (5) cognitive or physical inability to follow the procedures of the study. Considering that this research does not have an age-related hypothesis, the trials do not impose an age limit for the participants.

Sample Size

Sample size was determined by a power analysis based on a probability level of 0.05 and a power of 0.80 with G*Power [36], which is based on the results of the evaluation of LIVIA [14]. As in LIVIA, we expected a large effect size of Cohen d>0.80 for the decrease in grief as primary outcome, measured by the Texas Revised Inventory of Grief (TRIG), in the comparison of the intervention with a waitlist control group or care-as-usual control group. For the comparison of the standardized intervention with the self-tailored interventions, we expect a small to moderate effect (Cohen d=0.30) in favor of the self-tailored version. Power analyses for a repeated measures ANOVA with a within-between interaction for 3 groups in Switzerland estimated a sample size of at least 85 participants. For the 2-arm designs in Portugal and the Netherlands, we anticipate a dropout rate of 15% and, consequently, efforts will be made to recruit more primary end users than indicated by the power analysis.

For the target group of primary end users, older mourners, the aim is to include at least 85 participants in the study conducted in Switzerland with an allocation of 35:35:15 for the 2 active arms and the waitlist control group, respectively; at least 80 participants in Portugal with an allocation of 40:40; and at least 40 participants in the Netherlands, with an allocation of 20:20.

Recruitment

Recruitment will vary across implementation countries to ensure a recruitment method that is adjusted to the specific study design of each country, sample characteristics, and country culture. Potential participants from the general population will receive an invitation to register in the study via newspaper, social media, internet, pastoral care, social care, or personal contacts from health care professionals. For each implementation country, an assessment of the recruitment strategy will be conducted 1 month after the start of the trial to decide whether the recruitment contingency plan will be implemented.

Randomization

All eligible participants are randomly assigned to the active arm of the study (including the 2 active arms, standardized or self-tailored intervention format for the trial in Switzerland) or to the control or care-as-usual groups, depending on the implementation country. Participants assigned to the active arms will receive a participant code that gives them access to the self-help program and will be asked to use it for 10 weeks. Participants in the waitlist control group will start using the program 10 weeks after randomization. In Portugal, participants in the care-as-usual group can use the program after 20 weeks of follow-up, if requested.

For the 3 trials, the block-wise randomization was performed by an external programmer not involved in the trial using a random allocation sequence. The trials are unblinded. In Switzerland, the participants register on the study website and fill out the baseline questionnaire. Then, a member of the study team conducts the screening telephone call and allocates the participants to the 3 arms based on randomization numbers provided by the external programmer. In the Netherlands and in Portugal, participants are directly contacted by the teams responsible for implementing the study. Contacts are made based on their own professional lists. In the 3 countries, participants receive the intervention link after their eligibility has been confirmed in a phone call or an individual interview, depending on the implementation country.

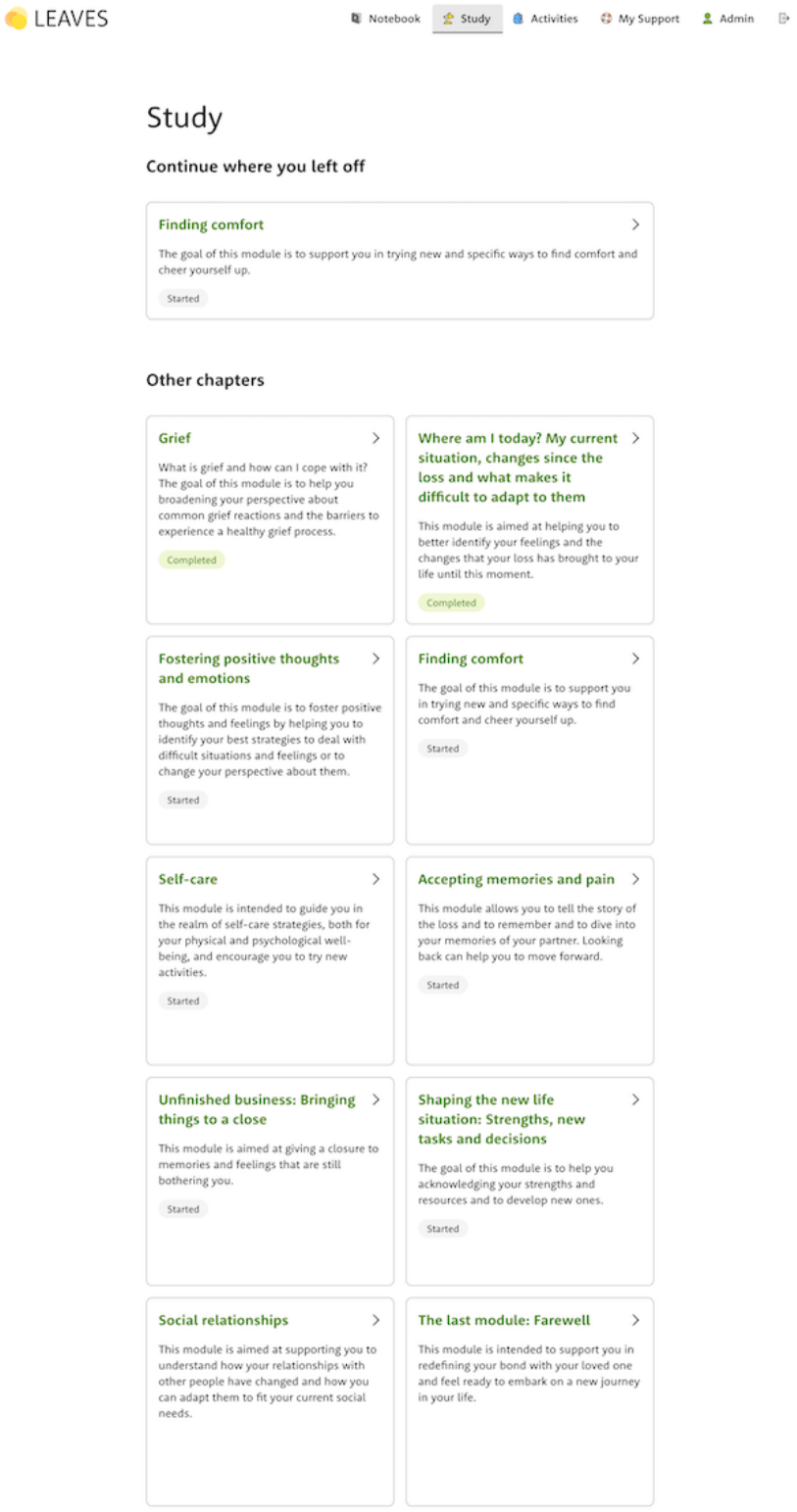
Description of the Intervention

Content

The content of the intervention was designed to follow the content structure of LIVIA [14,34]. However, unlike LIVIA, the content will be provided to participants through a conversational virtual agent, Sun, who guides the user through

the *Study* section (the CBT intervention itself; Figure 1). During the onboarding and the completion of study modules, users will be invited to use the other sections of the intervention: Notebook, Activities, and My Support. The Notebook is where users can find their notes from the study modules and are provided with a shortcut for the most important exercises. The Activities section provides suggestions for activities that encourage mourners to try new daily tasks or routines aimed at promoting mental and physical well-being. Finally, in My Support, participants can find a reminder of the hotlines or people they can contact to ask for additional support, alongside a summary of their best strategies to find support, which corresponds to some of the exercises completed in the study modules.

Figure 1. Screen of the web-based self-help program showing the first 6 modules and the available functionalities (right top corner).



The main section of the intervention is the *Study* section which comprises 10 modules that address topics intended to support either the acceptance of the loss or the restoration and adaptation to a new life. The modules are divided in several submodules, which correspond to specific subtopics or different types of exercises. The first 2 study modules include general information about (1) the impact of the loss of a partner and grief reactions and (2) an assessment of the current personal situation. Modules 3 to 5 focus on resources and restoration-oriented tasks for fostering positive thoughts and emotions as well as self-care. Modules 6 and 7 consist of loss-oriented interventions for accepting memories and pain and for addressing unfinished businesses, events that the mourner may see as unresolved. Modules 8 and 9 again include restoration-oriented tasks focusing on creating a new life without the partner and social relationships. The last module, module 10, addresses the redefinition of the relationship with the deceased person.

The modules and submodules include (1) readings—that is, texts based on scientific knowledge about grief-related topics that provide the background and rationale for the modules; and (2) exercises encouraging mourners to actively reflect on their lives, their grief, and what was learned in the readings, besides applying their new knowledge to their daily life and regularly practicing the new coping strategies and routines. Within the *Study* section, the conversational agent introduces the modules and submodules, guides users through them, wraps up the modules and submodules, and suggests the completion of the self-reflection items, where participants are asked to assess how helpful the completed submodule was.

The content is delivered in 2 formats, corresponding to the 2 active arms of the trial conducted in Switzerland. In the standardized intervention format, the presentation of the modules is based on a fixed order, in which the next modules are only accessible after the former was completed. In the self-tailored intervention, only modules 1 and 2, focusing on information about grief reactions and an assessment of the current personal situation, respectively, are mandatory and are required to be completed at the start. The remaining modules become available after the completion of module 2, and from then on, the participants can decide on which module they want to work on next.

The German content of LIVIA was translated and further developed in English by the clinical team of the project. Subsequently, all content was translated from English to German, Dutch, and Portuguese by the research teams of each country with expertise in adult health care. The translated content was implemented in the web-based platform and tested by primary end users (older mourners) in user-experience tests. On the basis of the test results, changes were made in the English version by the clinical team of the project, followed by the respective translations. This iterative process of content development, translation, and testing ensured that the content is consistent among the implementation countries and is adapted to each cultural language specificities, without losing its clinical validity.

Mood Self-check

Participants will be asked every other week to complete a set of questions to self-check their mood and perceived progress in the program. This will also enable the program to assess whether participants are experiencing intense psychological distress. In addition, based on users' answers in this self-check questionnaire, participants can be suggested to seek further support if high and prolonged distress in the mood self-assessment is reported or if they do not perceive that any progress was made while using the self-help program.

Participants' Guidance During the Trial

During the 10 weeks of the intervention, users will be able to receive guidance, which varies depending on the country-specific research goal, target population, and structure of the research team. In Switzerland, participants will receive via email a short weekly feedback and support from a trained coach, whereas users in Portugal will be contacted via telephone every other week on the grounds of technical support and troubleshooting. This guidance is intended to acknowledge and motivate participants for their work with the self-help program and to provide a weekly structure for the use of the program. Moreover, it will ensure the identification of potential technical problems and create the opportunity for participants to ask further questions. This guidance will also be based on participants' self-reported mood and therapeutic progress within the program. In the Netherlands, where the complementary research goal is to assess technology acceptance, guidance will follow a passive format in which participants will be able to contact the intervention's team via email or telephone in case they need further support.

Measures

Overview and Measurement Times

All clinical outcomes are self-report measures and will be completed on the web or within the program. In the trials conducted in Switzerland and the Netherlands, for the active arms, measurements of primary and secondary outcomes will take place (1) before users start using the program at baseline; (2) after the intervention, 10 weeks after the start of the program; and (3) at follow-up, 20 weeks after the user starts the program, which will measure the stability of the outcomes over time. For the waitlist control groups, the measurement times will occur at baseline (week 0), after 10 weeks waiting to start the intervention, after completing the intervention (week 20), and at follow-up (week 30). In the trial conducted in Portugal, the active arm and control group, care as usual, will occur at baseline, 10 weeks after starting the intervention, and at follow-up, 20 weeks after starting the intervention.

As no cross-cultural comparisons are planned, measures will be adapted to each country's trial. The measures used in the 3 different countries depend on the measures available for each language, which will result in the use of equivalent measures when it is not possible to use the same. Primary and secondary outcomes will allow for testing the efficacy.

Primary Outcome: Grief Symptoms

In the 3 implementation countries, grief will be assessed with TRIG (eg, [37]). TRIG is a widely used measure to assess the severity of grief. A recent factor analysis identified 3 factors for emotional response, thoughts, and nonacceptance regarding a loss. TRIG assesses the severity of grief from 1=completely true to 5=completely false.

Secondary Outcomes

Depression Symptoms

In the 3 implementation countries, depression symptoms will be assessed by the Patient Health Questionnaire-9, a self-administered version of the Primary Care Evaluation of Mental Disorders diagnostic instrument for common mental disorders. The Patient Health Questionnaire-9 scores each of the 9 diagnostic criteria for major depression in the Diagnostic and Statistical Manual, Fourth Edition. For each item, the answer format is a scale from 0=not at all to 3=nearly every day [38].

Perceived Loneliness

Perceived loneliness will be measured with the de Jong Gierveld Loneliness Scale [39,40] in Switzerland and the Netherlands. These will use the revised and shortened version of the scale with 6 items that resolve into social and emotional subscales [41]. In the Portuguese trial, perceived loneliness will be measured by the University of California, Los Angeles Loneliness Scale [42]. This scale has 18 items that measure subjective feelings of loneliness and social isolation.

In the trials conducted in Switzerland and in the Netherlands, primary and secondary outcomes will be determined after the intervention and after 10 weeks of using the intervention for the active arms and after 10 weeks of waiting to use the intervention for the control group. In Portugal, primary and secondary outcomes will be determined after 10 weeks of starting the trial, for both the active arm and the care-as-usual groups.

Potential Mediators and Change Mechanisms

Working Alliance

In the Swiss trial, the working alliance will be measured by the Working Alliance Inventory (WAI) [43,44], which is a measure of the therapeutic alliance, a key variable that accounts for treatment outcomes and users' satisfaction across interventions (eg, [45]). The items of the WAI adapted for guided internet interventions were derived from the WAI - short revised [46] and adapted to internet intervention programs with therapist support [44,47,48]. The task and goals subscale will be the one used, as it measures agreement with tasks and goals of the program (therapy), which includes 12 items to be rated on a 5 - point scale, from 1=never to 5=always. The working alliance will be assessed at weeks 2, 5, 8, and 10 after starting the intervention.

Session Outcomes: Self-reflection Survey

In the 3 implementation countries, session outcomes, as possible change mechanisms, will be measured by a questionnaire with a 5-item short version based on the Bern Patient Questionnaire [49]. This measure includes the rating of the overall helpfulness of the module and the matching of participant's needs and presented content, as well as gains in self-esteem, mastery experiences, and insight. Items are rated on a scale ranging from 3=not at all to 3=yes, exactly. Participants will be asked to complete the session outcomes items (self-reflection survey) after the completion of each submodule or module. In addition, these items related to the whole intervention will be assessed after the intervention.

Mood Monitoring

In the 3 implementation countries, mood monitoring will be measured by the mood self-check tool developed for this intervention, which assesses grief and depression symptoms, social withdrawal, and perceived progress within the intervention. Starting from the beginning of the web-based self-help intervention, the program will trigger an automatic message every other week asking participants to complete the mood self-check. Although this mood self-check is not part of the evaluation, it will inform the guidance of participants.

User Satisfaction

In the 3 implementation countries, user satisfaction will be measured by the Patient Satisfaction Questionnaire adapted for web-based interventions [50,51]. The Patient Satisfaction Questionnaire is a self - report measure that explores patients' overall satisfaction with the treatment. It includes 8 items that are rated on a 4 - point scale from 1=low satisfaction to 4=high satisfaction.

Use Data

Adherence will be measured through use, which will consist of the number of log-ins, completion of modules and submodules, and visits to the program's pages. Use data will be assessed continuously while using the self-help program.

Context Measures and Sociodemographic Variables Assessed at Baseline

Context and predictor variables include age, gender, education, nationality, marital status, duration of relationship until the loss, time since the loss, and details about the loss (death due to illness, violence, suicide, or accident). These data will be collected in the 3 implementation countries.

Technology Acceptance

The trial conducted in the Netherlands is aimed at thoroughly investigating the technology acceptance of the intervention, specifically focusing on perceived usefulness (self-devised) and effort expectancy (based on the study by De Veer et al [52]), measured at baseline. The usability (based on the study by Holden [53]) and user experience using the AttrakDiff instrument (User Interface Design GmbH) [54] will be assessed midintervention. Finally, after the intervention (week 10), usability and user experience will be measured again, and participants will be asked to complete a measure of acceptance (self-devised) and effort (based on the study by De Veer et al [52]). In addition, at this phase, we will add open questions to assess the use and appreciation of mood self-check monitoring and respective feedback messages and critical incidents. As a follow-up, focus groups will be conducted to better understand the perceived benefit of the web-based self-help program. Focus

groups will address usability and technical acceptance, answer which intervention elements need improvement, and assess the potential use of the intervention in daily and working routines.

The research team agreed to share all the materials used in the study, including the scales used (if open access) and the focus group scripts upon request to the corresponding author.

Data Collection, Management, and Analyses

Data will be assessed using web-based questionnaires programmed in REDCap (Research Electronic Data Capture; Vanderbilt University) [55,56] or Qualtrics (Qualtrics) [57]. Data integrity will be enforced according to referential data rules, valid values, range checks, and consistency checks. Checks are applied at the time of data entry into a specific field. In addition, data on the use of the self-help sessions are collected within the platform. All data will be saved in an anonymous manner, only identified by a code that is not related to the participant's identity. Data will be divided over 3 databases, an anonymized database containing data entered by the user into the platform (eg, exercises), an anonymized database containing use data logs, and a database that contains personal identifiers and the link to the internal anonymized identifier. After the end of the study, the last database will be deleted so the complete data set is anonymous. The platform and all data will be stored on International Organization for Standardization 27001–certified servers and will make use of secured connections. All data will be treated according to the guidelines of Dutch law and good clinical practices of the Swiss Federal Act on Research Involving Human Beings. Only the researchers directly involved in the study will have access to the data. Finally, it is important to note that this research collects data that allow identification of severe distress or mental health symptoms, including suicidal ideation. Following the public health guidelines on the management of personal data collection, this intervention is designed to flag the participants who show suicidal ideation or severe mental health crises that can be addressed in the guidance.

Statistical Analyses

Dropout is defined as participants who withdraw actively from the study after randomization or fail to fill out the postintervention questionnaires despite 2 reminders. For technology acceptance, noncompliance is defined as not filling out the biweekly mood self-check questionnaire despite 2 reminders. Noncompliant participants are also defined as those who, despite not actively quitting the study, do not complete the 2 mandatory study modules (module 1 and module 2) within 10 weeks. Nevertheless, these participants will be a part of the intention-to-treat analysis, as they have been randomized. Adherence will be assessed with the number of modules completed and use data.

All rating scales will be checked for reliability (Cronbach α) and multicollinearity (correlation analysis). Results will be reported on scale averages, as well as multiple 2-way correlations. Analyses will be conducted according to the intention-to-treat paradigm. First, we will analyze the extent of missing data, explore the missing data patterns, and determine the type of missing data (missing completely at random, missing at random, or not missing at random). If the missing mechanism is missing at random, multilevel mixed effects regression analyses will be used, which allow a different number of measurement points per participant and are thus less sensitive to missing data.

Multilevel mixed effects models with repeated measures data will be conducted to evaluate the efficacy of the intervention after 10 weeks and the stability of the effects after a further 10 weeks. Restricted maximum likelihood estimation will be used, which is recommended for small group samples and yields asymptotically efficient estimators for balanced and unbalanced designs. Mixed effects models have several advantages. These consider the dependency of the data and account for the correlation of the repeated measures within individuals. Furthermore, mixed effects models use all available data of each participant and estimate parameters of missing values. Models for each outcome variable will be computed. The pre-post comparisons of all outcome measures will include time as a within-group variable, the intervention format as a between-group variable, and an interaction term time by a group for cross-level interactions. To test the stability of the effects from the postintervention period to follow-up, only time will be included as a within-group factor in the mixed effects models. Cohen *d* will be calculated as effect size for all observed outcome variables. Furthermore, a Reliable Change Index will be computed as a measure of clinical change. Complementary analyses will test whether variables such as age, time since loss, and the severity of grief symptoms have an effect on the outcome by including them as predictors in the regression models. To analyze the longitudinal interplay of predictor variables and test mediation analyses, structural equation models will be conducted. Analyses will be conducted using SPSS Statistics (IBM) [58] and Mplus [59] software.

To explain technology acceptance, a backward regression analysis will be conducted. All qualitative data will be analyzed thematically, following the guidelines by Braun and Clarke [60], whereas reporting will be done according to the consolidated criteria for reporting qualitative research standards [61].

Cost-effectiveness Analysis

Incremental cost-effectiveness ratios of the intervention will be estimated, in terms of cost-per-point improvement in the grief scale (primary outcome) in the depression scale or in the loneliness scale (secondary outcomes), during the intervention and follow-up periods. A provider perspective will be adopted to mimic the *real-life*, posttrial, costs of the tool. Costs will include both technological (equipment costs and cost of using the platform) and human costs (training and time spent by staff delivering the intervention) associated with providing the intervention. To measure human costs, each coach will fill in a time sheet where they detail the number of minutes spent on each activity (eg, guidance or email reminders) for each user. Time is then multiplied by the hourly wage rate (including employer charges). To reflect statistical uncertainty (ie, sampling variation) with regard to both costs and effects, incremental cost-effectiveness ratio estimates will be accompanied by nonparametric bootstrapped SEs [62]. These analyses will be

conducted separately by country, as the context and costs involved differ.

Qualitative Evaluation of Implementation and Engagement

In Portugal, an additional qualitative study will be conducted to assess the barriers and facilitators to implementation, adoption, and engagement with the web-based self-help intervention. This study will be conducted separately with the primary and secondary end users (health care professionals) after the end of the intervention. Topic-guided interviews will be developed using the capability, opportunity, motivation, and behavior model [63] approach to assess barriers and facilitators in relation to aspects of competence, opportunity, and motivation to use the intervention. Thematic saturation will be used to determine the sample sizes, with a minimum of 10 interviews planned with each sample.

Ethics Approval and Trial Registration

All participants will give written informed consent. In the 3 countries, a short telephone call will be conducted to assess whether participants meet the eligibility criteria. In Portugal, participants will have their eligibility fully checked in person, at baseline, with the presentation of the informed consent, after which the initial evaluation will continue. In Switzerland and Netherlands, eligible participants will receive a link to complete the primary and secondary outcomes for the baseline measurement.

Medical ethics approval has been obtained by the Medical Ethical Committee of Northwestern and Central Switzerland (Business Administration System for Ethics Committees number 2021-02221) and the Ethical Committee of Unidade Local de Saúde do Baixo Alentejo (EDOC/2021/48762). For the study in the Netherlands, the Medical Ethical Committee Oost-Nederland ruled that the study was exempt from obtaining medical ethical permission, as the main topic of the intervention and study (mourning) is not a medical condition (file numbers 2021-13268 and NL79937.091.21). The Portuguese and Swiss trials were registered at ClinicalTrials.gov (NCT05156346 and NCT05280041, respectively).

This study will be conducted in line with the Declaration of Helsinki, and no participant will be randomized unless written informed consent is available for that participant. Participants can withdraw from the trial at any time and will be informed and assured of such right. This study follows the principles of data protection and management described in the European Union's General Data Protection Regulation. The trials were classified as having no or low risk; therefore, no protective measures for adverse events were mandatory. In the case of adverse events, the responsible ethics committees will be informed. Data monitoring committees are not required by the ethics committees. The ethics committees have the right to perform an audit at any time.

Results

The trials started in March 2022 and are expected to end in December 2022 or when the needed sample size is achieved. The first results are expected by January 2023.

Discussion

Expected Findings

In 3 different trials, the present research expects to test the efficacy of a web-based self-help grief intervention for older mourners. Specifically, we expect that the intervention decreases grief symptoms, as well as depression symptoms and perceived loneliness after completing the intervention when compared with the control group. These outcomes are expected are to be stable at follow-up. Moreover, the trial in Switzerland will test the hypothesis that the self-tailored delivery format, by providing participants the opportunity to meet their specific needs at each moment, leads to better outcomes and to higher satisfaction with the intervention than the standardized intervention. In the trial conducted in the Netherlands, the results of this study will also provide insights into the acceptability of web-based self-help interventions directed at older adults who are affected by grief symptoms, psychological distress, or adjustment problems in daily life after the loss of their partner, as well as insights into the prevention of prolonged grief. Finally, in the trial conducted in Portugal, the cost-effective and qualitative analyses of the barriers to using the intervention, will provide insights on how to redirect the resources used to implement it.

The results extend the existing knowledge in several important areas. First, although most web-based grief interventions have focused on coping with prolonged grief or severe grief symptoms, this intervention also aims to support the mourning process after a more recent loss; for example, mourners who lost their partner at least 1 month before accessing the program. Therefore, it has a more inclusive target group than; for example, the LIVIA self-help program. Second, by comparing a standardized with a self-tailored intervention format, the study examines whether the efficacy of web-based grief interventions can be increased by providing a self-tailored version, in which the users can choose the content that seems most relevant to them and that fits their current needs best. This is in line with concurrent developments in face-to-face and web-based interventions [27], which explore the effects of personalizing interventions to the users' specific needs. Third, the study aims to explore mediators of the effects of the intervention on the outcome; that is, the matching of participant's needs and presented content, gains in self-esteem, mastery experiences, insights into one's problems, as well as the working alliance.

Fourth, the study explores the acceptance of this technology among older adults. Technology acceptance among primary end users is crucial for the successful implementation of a web-based intervention in a real-life setting. A caring technology like this intervention should instill trust, should be engaging, and should provide a solid level of usability. To optimize the implementation of the web-based self-help intervention after the project phase, understanding technology acceptance is

essential. Finally, a cost-effectiveness study complements the clinical research goals.

Furthermore, testing the implementation of this intervention in 3 countries will provide higher insights into the efficacy of the intervention in different contexts, enable specific analysis on the acceptability of the proposed technology, and provide further knowledge about the potential generalization of the web-based self-help intervention to a broader audience.

This research will ultimately contribute to meeting the health access needs exacerbated by the COVID-19 pandemic crisis. The development of an evidence-based self-help intervention on the web, dedicated to support older mourners' mental health, will add to the efforts for equality and will contribute to reducing the stigma associated with mental health, death, and grief symptoms.

Limitations and Future Directions

As a limitation, the self-selectivity of the sample may compromise the generalization of the results to a broad population of older adults, as older adults who are willing to take part in a web-based self-help intervention have more cognitive resources and a higher education level. The focus groups focused on technology acceptance will provide important insights into users' skills and difficulties while using the self-help intervention, ultimately contributing to overcoming this potential limitation. Furthermore, we acknowledge that the meditation analysis may require a higher sample size to be informative and meet our research goals, and that, consequently, extending the sample size would be beneficial.

The adaptation of the designs of the trials to different complementary research goals and country-specific conditions, although it brings insightful knowledge, prevents cross-cultural statistical analysis and thus robust cross-cultural comparisons. To overcome this limitation, further research should test an established format of the intervention with the exact same study design. Although the present research brings relevant insights to the field of web-based self-help interventions, it leaves unanswered relevant questions. Despite this research advancing the knowledge on technology acceptance, future research based on this web-based self-help intervention could provide a direct test of the benefits of conversational agents and explicitly identify which of their components potentiate change. Moreover, it could be tested whether information on the grief process as well as the assessment of the personal situation have an impact on the outcomes by not making these modules mandatory in the self-tailored delivery format.

Conclusions

To conclude, the 3 trials of the LEAVES project provide a comprehensive approach for advancing the knowledge on web-based self-help interventions for grief by integrating results on technology acceptance, barriers to and facilitators of using web-based self-help programs, predictors for the clinical efficacy, delivery formats including self-tailoring, as well as cost-effectiveness.

Finally, to foster the impact of this research, study results will be communicated by research peer-reviewed articles, conference talks, newspaper articles, and blog entries. Moreover, participants as well as the involved health care professionals will receive an email with a summary of the results at the end of the study. Importantly, one of the partners of the project will exploit the service, starting with the Dutch population. All the countries will actively contribute to the dissemination of the study protocol and their respective findings to bridge the gap between research and practice.

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Conflicts of Interest

LvV worked at a commercial company that developed the LEAVES service technically. The authors have no further interests to declare.

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Abbreviations

CBT: cognitive behavioral therapy
iCBT: web-based cognitive behavioral therapy interventions
LEAVES: Optimizing the Mental Health and Resilience of Older Adults That Have Lost Their Spouse via Blended, Online Therapy
REDCap: Research Electronic Data Capture
TRIG: Texas Revised Inventory of Grief
WAI: Working Alliance Inventory

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Protocol

A Psychosocial Intervention for Supporting Informal Caregivers of Older People With Alzheimer Disease: Protocol for the InnFamiglia Randomized Controlled Trial

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Abstract

Background: Dementia is a neurodegenerative syndrome characterized by impaired cognitive functions associated with psychological and behavioral disorders. The informal caregiver has a central role in the life of the person with dementia. Committing a large part of the day to caring for the assisted person inevitably has an effect on the caregiver's life.

Objective: The aim of this study is to analyze the impact of a psychosocial intervention dedicated to a group of informal caregivers of patients with Alzheimer disease. The intervention will be guided by a trained psychologist who will facilitate the participants' expression of their emotional states, as compared to a traditional self-help group.

Methods: The intervention described in this paper was designed and developed for the project INNovazione sociale e tecnologica per le FAMIGLIE che assistono malati affetti da Alzheimer (InnFamiglia). The study is designed as a randomized controlled trial (RCT). The RCT includes an experimental group, in which the participants will undertake the psychosocial intervention, and a control group, where participants will receive support according to traditional self-help methodology. Interventions for both groups will last 4 months and will be comprised of 16 sessions.

Results: Participant recruitment, enrollment, and data collection began in 2021. Enrollment continued until September 2022, at which time the last group began the intervention. Data collection will be completed by December 2022, and data analysis will be completed by March 2023. The study findings will be published in peer-reviewed scientific journals and will be presented at scientific meetings. Summaries of the results will also be made available to investigators for dissemination within their clinics.

Conclusions: We hypothesize that the experimental group will be more effective in managing caregiver burden and coping strategies and that this will improve the perception of well-being, anxiety, and depression among caregivers. Our study aims to compare two groups receiving different interventions: a self-help group and a psychosocial group with elements of emotional support. This study may also give us more information about the most appropriate ways to support and help caregivers of people with dementia.

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KEYWORDS

Alzheimer disease; caregiver burden; psychosocial intervention; self-help; emotional support; randomized controlled trial; dementia

Introduction

Dementia is a neurodegenerative syndrome characterized by impaired cognitive functions associated with psychological and behavioral disorders. Dementia causes a significant reduction in the autonomy of daily life, making it one of the main causes of a lack of self-sufficiency among the older adult population. It is not a specific disease but rather a "family of diseases," of which Alzheimer disease is the best known and the most prevalent [1].

According to the Dementia Observatory of the Istituto Superiore della Sanità in Italy, the total number of people with dementia is estimated at over 1 million; about 60% of these people have Alzheimer disease. In addition, an estimated 3 million people are directly or indirectly involved in the informal care of people with dementia [2].

Among the European countries, Italy has one of the highest incidences of dementia among its population. In particular, according to the estimates provided by the United Nation's World Population Prospects from 2018, Italy is second in terms of the number of people with dementia (n=1,279,366); Germany is first, with about 1.5 million people with dementia (n=1,585,166). France follows with an estimated number of people with dementia similar to that of Italy (n=1,227,558). There were estimated to be over 55 million people worldwide living with dementia in 2020. This number will almost double every 20 years, reaching 78 million in 2030 and 139 million in 2050. Much of the increase will be in developing countries. Currently, 60% of people with dementia live in low- and middle-income countries, but by 2050 this number will increase to 71%. The fastest growing older populations live in China and India and in their South Asian and Western Pacific neighboring countries. According to a projection based on these data, in 2050, 4.13% of Italy's population will be suffering from dementia. This significant increase seems to be correlated with the average rate of aging among the Italian population, with the population older than 85 years doubling [3-5].

Informal caregivers have a central role in the lives of people with dementia because they represent both the person responsible for care and the figure who consistently provides emotional support, day after day.

In most cases, the children of people with dementia play the role of caregiver, particularly daughters; 64.2% of caregivers are the patients' children. However, the percentage of partners as caregivers is growing—from 25.2% in 2006 to 37% in 2015—especially if the patient is male. This finding also explains the increase in the proportion of sick people living in their own homes, especially if they live alone with their partner [6].

The caregiver devotes an average of 4.4 hours of direct care and 10.8 hours of supervision to the patient with Alzheimer disease each day. Committing a large part of the day to caring for the assisted person inevitably affects the caregiver's work life. About 59.1% of currently employed caregivers report changes in work life, and the most-cited consequence is repeated absences (37.2%), especially among men (62.5%). Women, compared to men, indicate more frequently that they have requested part-time work schedules (26.9%). In addition, 29.5% of caregivers take time off from work [6]. Among currently unemployed caregivers, 18.7% reported changes in work life that in some cases coincided with the most extreme consequence: job loss [6].

The caregiver's commitment also has consequences on their state of health, especially among women, and shows up as fatigue, reported by 80.3% of women as compared to 68.8% of men; lack of sleep (63.2%); symptoms of depression (45.3%); and frequent diseases (26.1%). In addition, a large percentage of caregivers take medications due to the health consequences caused by the immense commitment involved in the care of the patient [6]. There are also negative effects on the caregiver's relational and social life, from the interruption of activities outside of work (76.0%) to the negative impact on family members (59.7%) and friendships (45.6%) [6].

Caregiver burden is a syndrome that represents the degree to which caregivers negatively perceive their own stress as a result of taking care of their assisted family member. The caregiver can experience problems from a multidimensional perspective, at emotional, social, financial, physical, and spiritual levels [7].

Risk factors for caregiver burden include the following: female sex, low level of education, living with the cared-for person, depression, social isolation, financial strain, high number of hours caring for the sick person, and no other help in caring [8].

Caregivers may suffer from various diseases, such as depression; may have inadequate coping strategies; and may perceive themselves as having a poor quality of life. This may result in physical and psychological symptoms, with which they try to cope by abusing drugs, as compared to noncaregivers [1,9,10]. Support for caregivers is also essential for the well-being of people with dementia. In fact, caregiver characteristics and their perceived burden are factors that are related to the well-being of the person with dementia: high caregiver burden is associated with a higher use of antipsychotic drugs by the patient and a higher risk of institutionalization [11].

Meta-analysis studies revealed that psychosocial interventions had significant effects on caregiver burden, depression, and general health, although the overall effect on quality of life was not statistically significant. The literature also suggests that psychoeducational programs may offer the greatest benefit in relation to reducing the burden of care, while multicomponent and alternative interventions may be better suited to coping with depression [12].

Even cognitive behavioral approaches are promising, especially for the reduction of depressive symptoms, while psychoeducational interventions can instead reduce the subjective load of the caregiver. In particular, the subjective load seems to be the factor that most improves with psychosocial interventions for the caregiver [13]. As seen in the literature, the approaches used to support caregivers focus more on educational support, education, social skills, cognitive behavioral support, information, and psychoeducational support [14].

Among the interventions for caregivers, support groups have been shown to be effective. In this type of group, caregivers

meet each other and freely discuss their practical experiences and their emotional experiences, in particular. These groups can help the person experience the difficult task of caregiving more calmly and consciously.

Caregivers may have the opportunity to discuss common problems, to receive useful information from other people living in similar situations, to increase their coping strategies, and to have emotional support regarding the experience of the disease [6,15,16].

Support groups are one of the most important interventions: people face the same problems and share their experiences through mutual help [15,17-19]. These kinds of groups provide the caregiver with a comfortable environment where they can share their emotions, reduce stress and caregiver burden, alleviate social isolation, and improve quality of life. The World Alzheimer Report 2015 reported that there is a need to strengthen services for caregivers of Alzheimer patients in order to reduce their burden by making health workers aware that caregivers are an essential part of ongoing care for the Alzheimer patient [20,21].

Following these reviews in the literature, it seems important to assess the effectiveness of group interventions in supporting the family caregiver of the person with Alzheimer disease.

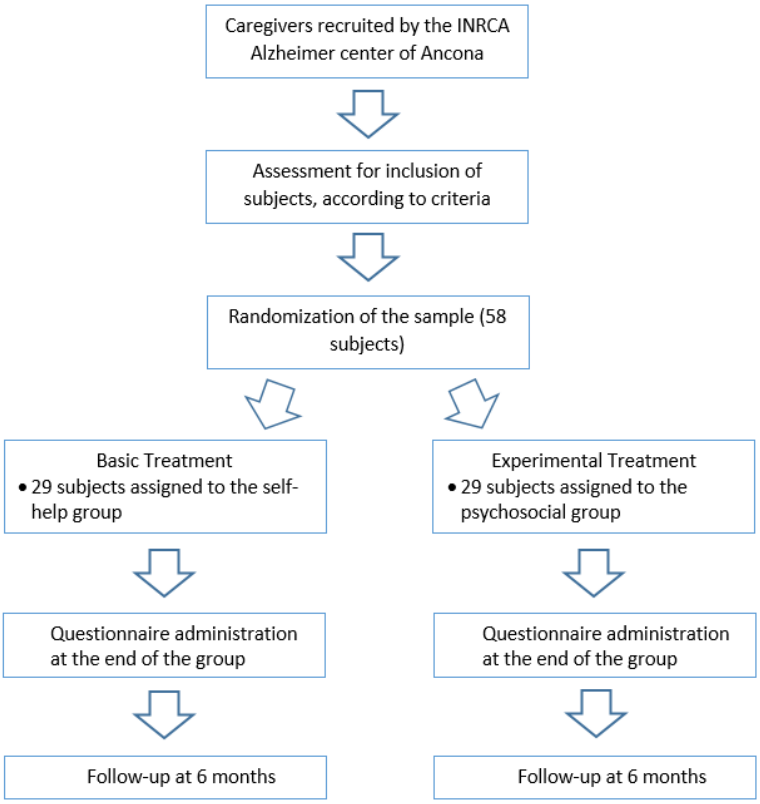
The intervention described in this paper was designed and developed for the project INNovazione sociale e tecnologica per le FAMIGLIE che assistono malati affetti da Alzheimer (InnFamiglia), funded by Fondazione Cariverona. The project aimed to support older people affected by Alzheimer disease and their families throughout the duration of the disease, from initial subjective memory complaints to the severe dementia phase, overcoming the fragmentation of the services available in the local community. The project, in fact, will exploit an ecosystem of innovative services, designed in a participatory approach with the older patients, their families, and local stakeholders. The services will include the following: the development of physical and cognitive interventions, integrated with technological solutions to slow down and prevent disease progression; the availability of a daily care center for patients at the mild to moderate stages; the delivery of specialized training to a multidisciplinary team for home assistance of patients at the severe stage; and the provision of tailored interventions to support and educate informal caregivers, such as the one discussed in this paper. The study presented in this paper aims to analyze the impact of a psychosocial intervention provided to a group of informal caregivers of patients with Alzheimer disease, guided by a trained psychologist for facilitating the expression of emotional states, compared to a traditional self-help group. The factors observed and evaluated in the assessment will be the caregivers' depression and coping strategies, caregiver burden, and their perceived quality of life.

Methods

Study Design

The study is designed as a randomized controlled trial (RCT). The RCT will include an experimental group, in which participants will undertake the psychosocial intervention, and a control group, where participants will receive support according to the traditional self-help methodology. Interventions for both groups will last 4 months and will be comprised of 16 sessions. The following evaluation phases are planned: T0 (baseline), T1 (end of treatment), and T2 (follow-up at 6 months). At each stage, a self-assessment questionnaire will be administered as described in Multimedia Appendix 1. Figure 1 describes the experimental design.

Figure 1. Experimental design of the randomized controlled trial. INRCA: Istituto Nazionale di Ricovero e Cura per Anziani.



Participants, Recruitment, and Sample Size

The sample consists of family caregivers of people with Alzheimer disease who are followed by the Alzheimer Center of the Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Nazionale di Ricovero e Cura per Anziani (INRCA) of Ancona. No limits are set for the ages of both the patient and the caregiver, nor for the type of family relationship between them.

Eligibility criteria for caregivers include the following:

- Signed an informed consent form
- Aged 18 years or older
- Is a caregiver for a person with mild to moderate Alzheimer disease
- The person with Alzheimer disease resides at their home or at the patient's own home.

Exclusion criteria include the following:

- The caregiver failed to meet the inclusion criteria
- The family member with Alzheimer disease has psychiatric disorders that were detected before the diagnosis of Alzheimer disease
- The family members of the patient with Alzheimer disease have psychiatric disorders that were detected before the diagnosis of Alzheimer disease.

The type of intervention hypothesized for this study and the expected efficacy for the case group is comparable to the work of Küçükgüçlü et al [15]. The authors of this work, which included 30 individuals, obtained an average reduction in caregiver burden of 4.61 points, corresponding to an effect size of 0.243.

Assuming the same effect size in our group of cases, setting the statistical power at 90% and a significance level of .05, it was estimated through repeated-measures within-factors analysis of variance (ANOVA)—two groups and two measurement times (ie, baseline and follow-up)—that the total sample size expected must be at least 48 subjects. Considering a dropout rate of about 20%, the sample size increased to 58 subjects: 29 cases and 29 controls.

Recruitment was carried out during daily visits to the Alzheimer Centre of the IRRCS INRCA in Ancona, where the older person was accompanied by a family member. Once the criteria for participation were established and met, a proposal to join a support group was made, the caregiver chose whether or not to participate, and the caregiver was randomly placed in one of the two groups.

Randomization

This study has a single-blind design, as far as the evaluator is concerned, since the characteristics of the treatment do not allow for double- or triple-blind experimental procedures. A randomization technique based on a single sequence of random assignments was used. A list of random numbers generated by the computer was used, and subjects were assigned a number based on their order of inclusion in the study. According to the technique described above, the 58 subjects were randomly assigned to one of the two study groups. Randomized subjects leaving the study will not be replaced, as a dropout percentage has already been considered when estimating the sample size.

Intervention

In this study, we will facilitate two different types of support groups for a sample of caregivers.

Regarding the experimental group, the minimum number of participants will be 3 and the maximum number will be 12. This group includes 16 meetings: 1 to present the study to the participants and for administration of the questionnaire; 14 dedicated to discussions led by the facilitator, who presents topics, as described below; and a final meeting dedicated to the administration of the questionnaire.

The protocol of the psychosocial intervention includes the following topics:

- First meeting—"Presentation of the participants of the group and administration of the questionnaire." The facilitator will present the activity, the participants will introduce themselves, and the questionnaire will be administered.
- Second and third meetings—"Let's get to know Alzheimer disease: what is it? Disease and epidemiology." The facilitator will explain what Alzheimer disease is, providing theoretical information about the disease and its epidemiology. This allows caregivers to get a first complete picture of their family member's disease.
- Fourth and fifth meetings—"Let's get to know Alzheimer disease: what is it? Symptoms and phases." The facilitator will give further theoretical information on Alzheimer disease, focusing in particular on the stages of the disease, descriptions of the stages, and the symptoms of the disease.
- Sixth and seventh meetings—"Our changing family member: how to relate to him/her?" The facilitator will introduce the topic concerning the changes of the ill family member due to the symptoms of dementia. In particular, the facilitator will try to focus on relational changes between the caregiver and family member, providing useful information on how to relate.
- Eighth and ninth meetings—"Parents and children, husband and wife: the changing family." The facilitator will introduce the topic of changes in the family structure as a result of the Alzheimer disease event, expose what are the most common changes, and describe strategies for dealing with them.
- Tenth and eleventh meetings—"Being a caregiver: the changes in our lives." The facilitator will introduce the topic of personal changes in the caregiver's life and what can be useful to improve his or her condition. The facilitator will expose the most common changes in the caregiver's life, focusing on the importance for the caregiver to take care of himself or herself.
- Twelfth and thirteenth meeting—"Let's get to know each other better: emotions and photography." Each participant will bring personal photos that represent his or her life as a caregiver. Through the photos, each participant will talk about his or her own caregiving experience and story.
- Fourteenth and fifteenth meetings—"The emotions and experiences of being a caregiver." The facilitator will give space to the participants' emotions centered on being a caregiver.
- Sixteenth meeting—Administration of the questionnaire and conclusion of the group intervention. The facilitator will collect thoughts and reflections at the end of the group and will administer the questionnaire.

Regarding the control group, the minimum number of participants will be 3 and the maximum number will be 12. This group includes 16 meetings: 1 for the presentation of the study to the participants and for the administration of the questionnaire, 14 for free discussions, and 1 final meeting for the administration of the questionnaire and conclusion of the group intervention. The control group will follow self-help methodology in such a way that the facilitator will have the sole task of facilitating communication between members of the group as the topics are chosen and treated freely by participants.

For both groups, each session will last 1.5 hours. During the first meeting for both groups, the informed consent forms with explanations about the intervention will be completed and the first questionnaires will be completed. In the final meeting, participants from both groups will complete the final questionnaire; after 6 months, they will be contacted by the researchers for the follow-up assessment.

Outcome Measures

Primary Outcome

The primary outcome is caregiver burden, which will be evaluated using the Caregiver Burden Inventory scale [22]. This tool evaluates the care load, analyzing its multidimensional aspect, and was developed for caregivers of patients with Alzheimer disease and related dementias. It consists of 24 questions that are grouped into five sections representing stress-related factors: objective load (questions 1-5), evolutionary load (questions 6-10), physical load (questions 11-14), social load (questions 15-19), and emotional load (questions 20-24). Each statement is assigned a value on a 5-degree scale of increasing activity.

Secondary Outcomes

Secondary outcomes include coping strategy, measured using the Coping Orientation to Problems Experienced (COPE) instrument; depression, measured using the Hospital Anxiety and Depression Scale (HADS); and quality of life, measured using an ad hoc constructed questionnaire.

The COPE instrument is a self-report questionnaire that considers different coping modalities. The questionnaire consists of 60 items. The questionnaire evaluates how often the subject uses particular coping processes in difficult or stressful situations. There are four possible responses, ranging from "I usually don't do it" to "I almost always do it." The 15 different coping mechanisms considered by the questionnaire are as follows: activity, planning, suppression of competitive activities, containment, seeking information, seeking understanding, emotional venting, positive reinterpretation and growth, acceptance, devotion to religion, humor, denial, behavioral detachment, mental detachment, and drug or alcohol use [23].

The HADS is an instrument that measures symptoms of anxiety and depression and consists of 14 items: seven for the anxiety subscale and seven for the depression subscale. With regard to anxiety, we will focus mainly on the symptoms of generalized anxiety disorder; regarding depression, we will focus on anhedonia, the main symptom of depression. Scores range from 0 to 3 for each item. For each of the statements, the subject is

asked which of four possible options best describes their emotional state [24].

The perception of quality of life will be assessed through four ad hoc items that investigate the person's experience with respect to the quality of his or her leisure time, health status, mood, and social relationships. Each item has five possible responses, with scores ranging from 0 to 5.

In addition, a complete checklist on the demographic characteristics of the sample will be collected, with the aim of profiling the participants on the basis of their living arrangements, income, past occupational activity, family composition, age, and gender. Those background variables will be used in descriptive statistics to evaluate their influence on the study outcomes.

Data Analysis

A descriptive analysis of the sample will be carried out through univariate and bivariate statistical analysis. Continuous variables will reported as mean and SD or median and IQR, based on their distribution, and will be evaluated using the Shapiro-Wilk test. The comparison of variables between groups at baseline will be carried out by means of unpaired Student *t* tests or Mann-Whitney *U* tests, based on their distribution. Categorical variables will be expressed as absolute frequencies and percentages, and statistical significance will be evaluated using chi-square tests or Fisher exact tests, in the case of comparisons between small subsamples.

In the second phase, the analysis of follow-up data will be carried out in order to assess the effectiveness of the intervention. This phase of analysis involves the use of multivariate statistical techniques, in particular, repeated-measures ANOVA, in order to compare changes in outcome measures over time between the intervention group and the control group. In the case of different exposure times between subjects, the Cox regression model will be employed in order to identify factors associated with the change in key endpoints. Statistical significance will be set at $P<.05$.

Every effort will be made to collect all data within the specified time frame. In the case of missing and unrecoverable data on the primary endpoints, we will assume that these events are related to chance. Analyses will be performed by applying list-wise deletion to remove cases with missing values from the final database in order to obtain unbiased estimates.

Ethics Approval

The study was approved by the Ethics Committee of the IRCCS INRCA on November 26, 2020 (approval No. CE INRCA 20018). The Ethics Committee will be notified about any protocol modifications. The Ethics Committee is in charge of data monitoring and will periodically assess the progress of the protocol and compliance with what was declared. The study will adhere to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Participants in this study will provide written informed consent.

Results

Participant recruitment, enrollment, and data collection began in 2021. Enrollment continued until September 2022, at which time the last group began the intervention. Data collection will be completed by December 2022, and data analysis will be completed by March 2023. The study findings will be published in peer-reviewed scientific journals and will be presented at scientific meetings. Summaries of the results will also be made available to investigators for dissemination within their clinics.

Discussion

Despite several available studies, there is still moderate evidence on the efficacy of psychosocial interventions for dementia caregivers. In fact, although understanding the needs of caregivers is essential for developing effective interventions, only a few systematically address them.

With this study, we expect to advance the state of the art in the field by evaluating the efficacy of a self-help intervention using an evidence-based approach. We will do this through an RCT study, aimed at improving caregivers' quality of life, reducing their care burden, and easing their anxiety or depressive symptoms, which represent the most felt needs of the population of carers. Moreover, the study will also identify barriers and obstacles that may arise during the organization of group interventions, especially in the COVID-19 era, in which isolation and restriction in mobility may affect participation and relationship-building among the group.

The aim of this study is to analyze the impact of a psychosocial intervention dedicated to a group of informal caregivers of patients with Alzheimer disease; the intervention will be guided by a trained psychologist in order to facilitate the expression of the group members' emotional states and will be compared to a traditional self-help group.

We focused on patients with Alzheimer disease because dementia is becoming one of the main conditions, worldwide, that causes a lack in self-sufficiency [25]. It is estimated that about 3 million people are directly or indirectly involved in the care and support of people with dementia. In particular, informal caregivers (ie, family members) [26,27] play a fundamental role in the lives of people with dementia because they provide both physical and psychological support to ill family members on a daily basis [28]. Therefore, it is important to provide support to the caregiver [29]. Our study compares two groups receiving different interventions: a self-help group and a psychosocial group with elements of emotional support.

The self-help group, based on its typical characteristics, is not a structured group and leaves the content to be decided by the participants. The experimental group is structured around topics defined by the facilitator or psychologist, focused on the experiences and needs of the caregivers, with particular attention paid to their personal emotional experience. We hypothesize that the experimental group will be more effective in managing caregiver burden and coping strategies, which could improve the perception of well-being, anxiety, and depression among caregivers. This is because since the experimental group is more

structured, it provides more skills, advice, and support than the self-help group. This study may also give us more information about the most appropriate ways to support and help caregivers of people with dementia.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Self-assessment questionnaire (in Italian).
[DOCX File , 38 KB - resprot_v11i11e37496_app1.docx]

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Abbreviations

ANOVA: analysis of variance
COPE: Coping Orientation to Problems Experienced
HADS: Hospital Anxiety and Depression Scale
InnFamiglia: INNovazione sociale e tecnologica per le FAMIGLIE che assistono malati affetti da Alzheimer
INRCA: Istituto Nazionale di Ricovero e Cura per Anziani
IRCCS: Istituto di Ricovero e Cura a Carattere Scientifico
RCT: randomized controlled trial

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Protocol

Percutaneous Bioelectric Current Stimulation in the Treatment of Chronic Achilles Tendinopathy: Protocol for a Double-Blind, Placebo-Controlled Randomized Multicenter Trial

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Abstract

Background: The consensus for the optimal treatment strategy for chronic Achilles tendinopathy (AT) is still debated and treatment options are limited. This results in a significant medical need for more effective treatment options.

Objective: The aim of this study is to investigate the therapeutic effects of percutaneous bioelectric current stimulation (PBCS) on AT.

Methods: A multicenter, randomized, double-blind, placebo-controlled clinical trial will be conducted. A total of 72 participants with chronic (ie, >3 months) midpoint AT will be randomized and receive four PBCS sessions—either verum or placebo—over 3 weeks. Both groups will complete daily Achilles tendon loading exercises in addition to the intervention. Evaluation sessions will be completed at baseline and during the intervention (weeks 0-3). Self-reported outcome measures will be completed at follow-up at weeks 4, 12, 26, and 52. The primary outcomes are the Victorian Institute of Sports Assessment–Achilles questionnaire scores and statistical evaluation of intraindividual differences between baseline and 12-week evaluations after initial treatment of verum therapy compared to control. Secondary outcomes will assess Pain Disability Index scores; average pain, using the 11-point Numeric Rating Scale; return to sports; and use of emergency medication.

Results: The study began in May 2021. As of October 2022, we randomized 66 out of 72 participants. We anticipate completing recruitment by the end of 2022 and completing primary data analysis by March 2023.

Conclusions: The study will evaluate the effects of PBCS on pain, physical function, and clinical outcomes.

Trial Registration: German Clinical Trials Register DRKS00017293; https://tinyurl.com/mvz7s98k

International Registered Report Identifier (IRRID): DERR1-10.2196/40894

(JMIR Res Protoc 2022;11(11):e40894) doi:10.2196/40894

KEYWORDS

Achilles tendinopathy; pain; PBCS; conservative treatment

Introduction

Achilles tendinopathy (AT) is a painful overuse injury [1] and is particularly common in athletes. The prevalence of AT among runners is estimated to be between 6.2% and 9.5% [2], with the highest prevalence (83%) among middle-distance runners [3].

AT is caused by increased stress on the Achilles tendon, especially when running long distances in hilly terrain [4]. People older than 35 years are particularly susceptible [4] to AT. Most commonly, the pain and thickening of the Achilles tendon occur in the midportion of the Achilles tendon, especially 2 to 6 cm distal to the insertion of the Achilles tendon to the heel (ie, the calcaneus) [5].

Achilles tendons of patients with AT show advanced degeneration and changes in the arrangement of collagen fibers. Furthermore, there is ventral sprouting of new blood vessels and associated nerve endings [6]. These are considered the main cause of pain, although there are microscopic changes without clinical symptoms as well as clinical symptoms without microscopic changes. In this respect, the cause of the pain is not fully understood. Since these microscopic changes are considered as degenerative rather than inflammatory, the term tendinopathy is used instead of tendinitis [7].

The leading symptom of AT is load-dependent pain in the course of the Achilles tendon, usually associated with swelling. In the acute form, increasing pain occurs at the Achilles tendon a few centimeters above the heel over a period of a few days. The pain can be temporarily relieved by immobilization [8]. Manual examination of the Achilles tendon reveals that it is swollen, reddened, and hardened. Acute AT often progresses to a chronic course [9]. Symptoms may persist for months to years. The pain remains at about the same intensity with any type of exercise or sports activity, but increases when running uphill or climbing stairs. After resting or in the morning, the pain is especially severe because of stiffness and loss of elasticity of the Achilles tendon. Rupture or partial rupture of the tendon is a frequent complication.

AT is a clinical diagnosis based on localized tendon pain and swelling and pain with activities. Imaging, such as sonography or magnetic resonance imaging, can be used to assess tendon morphology and pathologic conditions.

Therapeutic options for AT are limited [1,10]. Current conservative treatment strategies involve the topical or oral application of nonsteroidal anti-inflammatory drugs (NSAIDs), loading exercises (ie, eccentric-concentric loading), cooling, taping, and exercise rehabilitation. Nonsurgical therapies are also used, including acupuncture, focused shock wave treatment, and electrotherapies (ie, different forms of transcutaneous electrical nerve stimulation [TENS]) [11-13]. In cases of long-standing symptoms that cannot be managed conservatively, surgical splitting of the tendon lengthwise and excision of necrotic tissue can be attempted [14]. However, studies show that the long-term results of surgical therapy do not differ from those of conservative therapy and that operative treatments have a higher risk of other complications [15]. The best evidence for treating AT is available for loading exercises (ie, eccentric-concentric loading) [16]; for all other forms of therapy, evidence is contradictory or anecdotal. Overall, it must be concluded that the optimal treatment strategies for chronic AT are still being debated and that treatments are protracted and mostly unsatisfactory. Given the high prevalence of unsatisfactory treatment options, there is a significant medical need for more effective treatment options.

Percutaneous bioelectric current stimulation (PBCS) treatment is a form of microinvasive electrotherapy different from the aforementioned TENS-like approaches. PBCS mimics and increases physiological electric fields to modulate local tissue inflammation and to trigger the regeneration of nerves, muscles, ligaments, and tendons.

In this study, PBCS using the DC Stimulator Mobile (original equipment manufacturer [OEM] version; Axomera-Molsberger), which has already shown promising results in the treatment of ligaments, tendons, and muscle tissue [17], will be compared to a control treatment without electrical output.

Methods

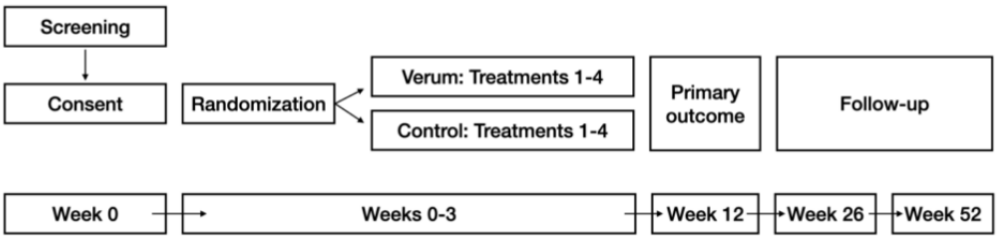
Study Design

This study is a randomized, double-blind, placebo-controlled multicenter trial.

Participants will be randomized to either the verum group or the control group. In addition to the intervention, participants in both randomization groups will receive the same baseline therapy in the form of tendon-loading exercise. Each participant will receive four treatment sessions within 3 weeks of inclusion. Evaluation sessions, where primary outcome data are collected, will be conducted at baseline (ie, inclusion) and at week 4. Self-reported follow-ups will be conducted at weeks 4, 12, 26, and 52 (Figure 1).

In this study, the medical device DC Stimulator Mobile (OEM version; Axomera-Molsberger) developed for PBCS treatment will be tested with regard to its technical and medical performance and safety. The aim is the statistical evaluation of therapeutic effects of PBCS with electrical output (verum) in participants with achillodynia compared to PBCS treatment without electrical output (control) as an additional benefit (ie, “add-on”) to an evidence-based standard therapy. This trial was retrospectively registered at German Clinical Trials Register (DRKS00017293) in February 2022.

Figure 1. Flowchart of the study process. The verum group will receive PBCS treatment with electrical output as described above. The control group will receive PBCS treatment as described above with no electrical output: the current and voltage will be equal to zero. PBCS: percutaneous bioelectric current stimulation.



Recruitment

Study participants will be recruited directly at the trial sites. Recruitment will be supported using posters, mass emails, and direct approach of potential participants at the study centers. Prior to inclusion in the study, each participant will be informed by the investigator about the nature, significance, risks, and scope of the clinical trial, as well as about the right to terminate participation in the study at any time without incurring any negative effects. Generally understandable information documents will be handed out.

Participants must be given a reflection period of at least 24 hours to decide whether to participate in the study. In addition, they must be given the opportunity to clarify any unanswered questions beforehand. Study-specific investigations to verify the inclusion and exclusion criteria will be performed after the participant has given legally effective consent to the study. Only participants who meet all inclusion criteria will be included and randomized into the SMART-TRIAL electronic data capture (EDC) platform. Participants who do not meet the eligibility criteria will be excluded.

The inclusion criteria will be as follows: achillodynia diagnosis confirmed by a consulting doctor, pain in the Achilles tendon approximately 2 to 7 cm from calcaneus insertion, pain intensity of at least 4 on the 11-point Numeric Rating Scale (NRS) on at least one day in the last 7 days before the start of treatment, aged 18 to 65 years, Achilles tendon pain for 3 or more months, adequate communication skills, and participant must be able to recognize the nature, significance, and scope of the clinical trial and to direct his or her will accordingly.

The exclusion criteria will be as follows: needle phobia; previous PBCS treatment or eccentric training, as specified in this study, of the affected Achilles tendon; Achilles tendon pain for more than 2 years; BMI greater than 30 (obesity grade I); in women, pregnancy; pain intensity of 9 points or higher on the 11-point NRS on any day in the last 7 days before the start of treatment; inability to technically perform the Victorian Institute of Sports Assessment (VISA); pending disability pension application; pacemaker; history of surgery on the Achilles tendon; cortisone injection to the Achilles tendon in the last 3 months; chronic pain of other etiology with ongoing pain management; anticoagulant therapy within 7 days before start of treatment—taking acetylsalicylic acid up to 100 mg/day is not an exclusion criterion; taking opiates within the last 4 weeks before start of treatment; history of taking fluoroquinolone, antibiotics, or statins within the past 6 months; analgesic, drug, or opiate dependence; alcoholism; local infection; type 2 diabetes; renal disease requiring dialysis; autoimmune disease; vascular disease; peripheral neuropathy; other nerve compression syndromes of the lower extremities; radiculitis; rheumatoid arthritis; Reiter syndrome; and other medical reasons as determined by the study physician.

Randomization

Structural equality of both study arms will be achieved by randomization. Randomization will be performed using the randomization module of the SMART-TRIAL EDC platform. Allocation to the two study arms will be in the form of permuted blocks of variable length, stratified by study site in an allocation ratio of 1 to 1.

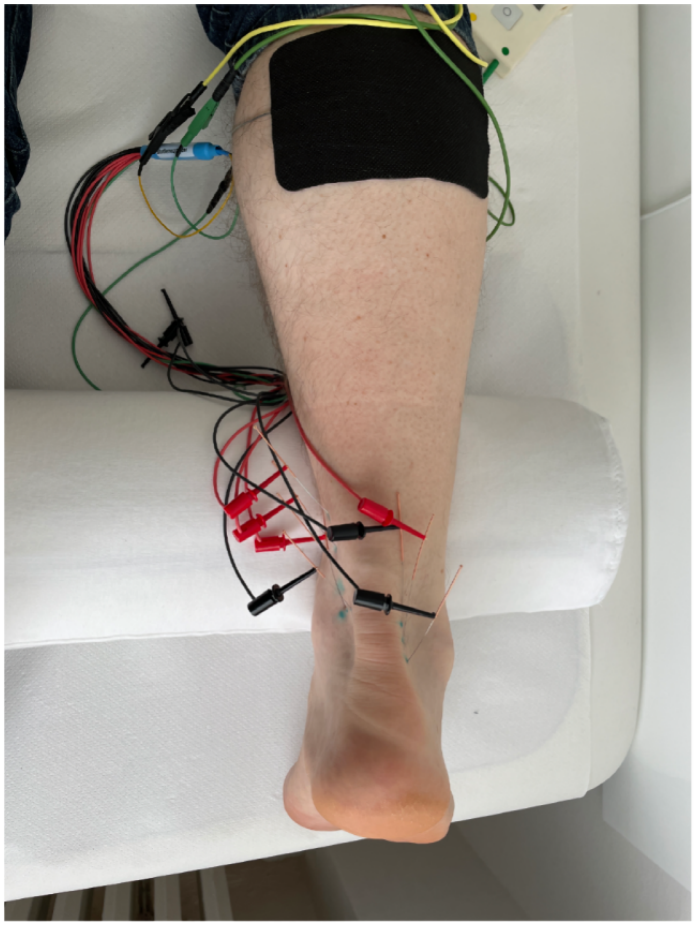
Interventions and Blinding

Four mandatory PBCS treatments will be performed within 3 weeks after inclusion. There must be at least 2 days between treatments.

Depending on the extent of the painful area, 2 to 8 stainless steel needles (0.20-0.3 mm) will be used. Each needle will be inserted into the affected (ie, paratendinous) tissue until the participant feels the tip of the needle exactly at the painful area. The needle will then be withdrawn a few millimeters so that the tip of the needle is as close as possible to the painful area. The needle probes will be individually connected to the PBCS stimulator via clips and flexible cables. PBCS direct current stimulations will then be performed over 30 minutes according to the indication-specific stimulation protocol; electrical signals will be of the order of 140 mV/ mm, and the drive current will be approximately 20 to 50 µA/cm (Figure 2).

Double-blinding is ensured by the identical design of the treatment hardware. One of the connection cables, however, is technically modified in such a way that no current will be conducted, thus generating no electrical stimulation. The difference in the connection cables will not be detectable by either investigator or participant. The success of blinding will be additionally measured using a blinding question after the first treatment: the participant will be asked whether he or she thinks that he or she has been treated with or without electrical stimulation.

Figure 2. Intervention with PBCS therapy. PBCS: percutaneous bioelectric current stimulation.



Outcome Measures

Primary Outcome

The VISA–Achilles questionnaire (VISA-A) score [18] will be used as the primary outcome measure. Intraindividual differences between values at baseline and values 12 weeks after initial treatment with verum therapy compared to control will be evaluated. The VISA-A questionnaire is an index of the severity of a clinically diagnosed condition (ie, AT). It contains eight questions on three domains of pain, function, and activity. Scores are summed to a total with a maximum of 100. In this study, the German adaptation (VISA-A-G) will be used. The VISA-A-G questionnaire was tested for reliability, validity, and internal consistency [19].

Secondary Outcomes

Secondary outcome measures will be as follows:

1. Statistical evaluation of intraindividual differences in the VISA-A score and the Pain Disability Index (PDI), including all subscales, between values at baseline and weeks 4, 12, 26, and 52 after verum therapy compared to control.
2. Pain on exertion after standing on one leg for 30 seconds, using the 11-point NRS: statistical evaluation of intraindividual differences between values at the beginning of treatment and before each therapy session and at weeks 4, 12, 26, and 52 after verum therapy compared to control.
3. Average pain on average exertion in the last week, using the 11-point NRS: statistical evaluation of intraindividual differences between values at therapy start and before each therapy session and at weeks 4, 12, 26, and 52 after verum therapy compared to control.
4. Return to exercise: statistical evaluation of intraindividual differences between values at baseline and at weeks 4, 12, 26, and 52 after verum therapy compared to control.
5. Treatment response: statistical evaluation of verum therapy compared to control.
6. Use of emergency medication (eg, the NSAID acetaminophen) within 1 week: statistical evaluation of intraindividual differences between values at baseline and at weeks 4, 12, 26, and 52 after verum therapy compared to control.

Safety Evaluation Criteria

Safety evaluation criteria will be as follows:

1. Listing by month of treatment of adverse events (AEs), adverse reactions (ARs), serious AEs (SAEs), and serious ARs (SARs) stratified by organ classes and events: total sum, total AEs and ARs, total SAEs and SARs, total AEs and SAEs, and total ARs and SARs will be formed.
2. Total listing of AEs, ARs, SAEs, and SARs, including suspected unexpected SARs, stratified by participant and organ classes and events: formed as the total sum, sum of AEs and ARs, sum of SAEs and SARs, sum of AEs and SAEs, and sum of ARs and SARs.

3. Total listing of AEs, ARs, SAEs, and SARs stratified by organ class and severity (ie, intensity): formed as the total, total AEs and ARs, total SAEs and SARs, total AEs and SAEs, and total ARs and SARs.
4. Listing of reasons for study exclusion (ie, violation of inclusion and exclusion criteria) with the duration of study participation to date.
5. Calculation of the probability of occurrence of the respective number of AEs that occurred.

Sample Size

The sample size is calculated on the basis of the primary outcome, taking into account a clinically relevant effect size between verum and control.

In this study, the treatment effect is considered clinically relevant if the effect size between study arms is at least $\Delta/\sigma = 0.75$.

To demonstrate a significant treatment effect in the primary statistical analysis with 80% power using a 2-sided Wilcoxon-Mann-Whitney test at the $\alpha=.05$ level, a sample size of 62 participants in total is needed, with 31 participants per intervention group.

The allocation ratio is 1 (verum) to 1 (control). Assuming a dropout rate of 15%, a total of 72 participants should be included in the study.

Statistical Analysis

Statistical evaluation will generally be carried out using descriptive methods in the form of frequency tables and statistical parameters, such as means, SDs, and quantiles. As graphical procedures, bar charts will be created for qualitative data, and box-and-whisker plots will be created for quantitative data. In addition, inferential statistical analyses will be performed using appropriate significance tests and CIs. Missing values will not be replaced.

The primary statistical evaluation will be performed with a 2-sided Wilcoxon-Mann-Whitney test at the global significance level of $\alpha=.05$; the results will be interpreted in a confirmatory sense.

The evaluation of the secondary evaluation criteria of efficacy will be performed with adequate 2-sided tests. Here, local levels (local level $\alpha=.05$) will be controlled instead of the global significance level, and no adjustment will be made for multiple testing. *P* values of the secondary evaluation criteria will be interpreted descriptively only.

The safety evaluation criteria will be evaluated exploratively. In the exploratory evaluation of the safety criteria, adjustment for multiple testing would be counterproductive and will, therefore, not be performed.

For the primary target criterion, the following 2-sided test problem will be set up:

H_0: $d=0$ versus H_1: $d\neq0$

where d indicates the effect size between intervention groups.

The null hypothesis is as follows: in the statistical evaluation of intraindividual differences between scores at start of treatment and at week 12, there will be no difference in the VISA-A score for symptom assessment between verum and control.

The research hypothesis is as follows: in the statistical evaluation of intraindividual differences between values at start of treatment and at week 12, there will be a difference in the VISA-A score for the assessment of symptomatology between verum and control.

For the secondary outcome of efficacy, corresponding 2-sided test problems will be set up and solved.

The evaluation of the primary and secondary outcomes will be performed according to the intention-to-treat (ITT) principle. The respective collective includes all participants included in the study, regardless of possible protocol violations (eg, study discontinuations or premature discontinuation of intervention). In addition to the ITT analyses, sensitivity analyses will be performed according to the per-protocol principle. Relevant protocol violations leading to exclusion from the per-protocol collective will be defined in the statistical analysis plan. The statistical analysis plan will be prepared in a blinded review without knowledge of the target criteria.

The safety evaluation criteria will be evaluated using the as-treated principle. That is, all participants who participated in the study and received at least one dose of the study intervention (ie, safety collective) will be included.

Subgroup analysis will only be done exploratively, as previous studies have shown that, for example, gender appears not to be a risk factor for AT [20].

Ethics Approval

The first positive ethics vote was issued on March 27, 2020, by the North Rhine Medical Association (reference No. U1111-1233-2760). Based on this, further positive ethics votes were subsequently issued for the other federal states in Germany where patients are recruited. Informed consent will be given before enrollment. This trial will be conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

Results

Onboarding of trial sites started at the end of 2020. Enrollment of the first participant occurred on May 28, 2021. As of October 2022, we randomized 66 out of 72 participants. We anticipate completing recruitment by the end of 2022 and completing primary data analysis by March 2023.

Discussion

Overview

Evidence-based therapies for AT are rare, leaving practitioners and patients with limited treatment options [21]. Against this background, PBCS has the potential to become one of the few effective therapies available. Therefore, this clinical trial will compare the therapeutic effects of verum versus control PBCS on AT. We aim to show that PBCS could improve function, pain, and other clinical outcomes by measuring differences

between VISA-A, NRS, and PDI scores. Although many cases of AT can heal spontaneously, chronic courses, where the symptoms persist for months or years, are frequent. There is no clear evidence on whether AT that includes partial tendon rupture needs to be treated surgically [15]. Surgical treatment of acute Achilles tendon ruptures has been shown to reduce the risk of rerupture compared with nonoperative treatment. However, rerupture rates were low, and differences between treatment groups were small [15,22]. Surgery and injections are associated with various risks, mostly attributable to increased risk of infection [23,24]. Limited therapeutic options for treating AT result in a significant medical need for research and development of effective conservative treatments. With the PBCS treatment, we aim to advance nonsurgical treatment options for practitioners. Up to now, there have been no other comparable randomized controlled trial studies available on microinvasive direct current stimulation for the treatment of AT.

Unlike electroacupuncture or TENS therapy, the PBCS stimulation current is so low—in the range of a few microamperes instead of milliamperes—that it cannot be perceived by the patient. Consequently, the patient cannot reliably distinguish between a verum and a placebo stimulation. This makes it possible, unlike with TENS and electroacupuncture, to actually blind the verum and placebo electrostimulation to the patient and the therapist. In addition, the success of the blinding is checked by a blinding question within the study.

Limitations

Insertion of needle electrodes is mandatory for the application of PBCS. Prior studies have shown that no placebo control for needle insertion is available and that needling itself can have clinical effects [25]. For this reason, therapeutic effects of needling may influence the results independently of the study intervention. In the verum and placebo groups, needle electrodes are positioned and inserted in an identical manner. The practitioner locates the particularly pain-sensitive points in the area of the Achilles tendon and advances the needle to the painful point. This procedure corresponds to dry needling or professional acupuncture at locus dolendi points; it has been shown that this kind of needling can produce therapeutic effects in pain disorders [26,27]. Therefore, the mere insertion of the needle probes, independent of electrical stimulation, may raise the success rate in both verum and control groups. In light of this consideration, we will additionally examine whether the therapeutic effect of electrical PBCS exceeds that of pure needle insertion. We are convinced that this will further strengthen the clinical relevance of the study.

Conclusion

This study will evaluate the effects of PBCS on pain, physical function, and clinical outcomes in AT patients. Given the refractory nature and limited therapeutic options for AT, we aim to advance evidence-based nonsurgical care for patients and practitioners.

Acknowledgments

This trial is sponsored by Columbus Health Products GmbH, Düsseldorf, Germany.

Data Availability

All data sets supporting the conclusions of the study (ie, all raw data) will be made available in publicly available repositories by the first author upon publication of the final results for analysis and reanalysis.

Authors' Contributions

All authors made substantial contributions to the study design. PS and AM wrote the first draft of the manuscript, with AD, HM, and MK revising and approving the submitted version.

Conflicts of Interest

PS is shareholder of the medical device company Columbus Health Products GmbH, Germany. AM is CEO and shareholder of the medical device company Columbus Health Products GmbH, Germany.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 388 KB - resprot_v11i11e40894_app1.pdf]

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Abbreviations

AE: adverse event
AR: adverse reaction
AT: Achilles tendinopathy
EDC: electronic data capture
ITT: intention-to-treat
NRS: Numeric Rating Scale
NSAID: nonsteroidal anti-inflammatory drug
OEM: original equipment manufacturer
PBCS: percutaneous bioelectric current stimulation
PDI: Pain Disability Index
SAE: serious adverse event
SAR: serious adverse reaction
TENS: transcutaneous electrical nerve stimulation
VISA: Victorian Institute of Sports Assessment
VISA-A: Victorian Institute of Sports Assessment–Achilles questionnaire
VISA-A-G: German adaptation of the Victorian Institute of Sports Assessment–Achilles questionnaire

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Protocol

Physical Activity Program for the Survival of Elderly Patients With Lymphoma: Study Protocol for Randomized Phase 3 Trial

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Abstract

Background: The practice of regular physical activity can reduce the incidence of certain cancers (colon, breast, and prostate) and improve overall survival after treatment by reducing fatigue and the risk of relapse. This impact on survival has only been demonstrated in active patients with lymphoma before and after treatment. As poor general health status reduces the chances of survival and these patients are most likely to also have sarcopenia, it is important to be able to improve their physical function through adapted physical activity (APA) as part of supportive care management. Unfortunately, APA is often saved for patients with advanced blood cancer. As a result, there is a lack of data regarding the impact of standardized regular practice of APA and concomitant chemotherapy as first-line treatment on lymphoma survival.

Objective: This study aimed to assess the impact of a new and open rehabilitation program suitable for a frail population of patients treated for diffuse large B-cell lymphoma (DLBCL).

Methods: PHARAOM (Physical Activity Program for the Survival of Elderly Patients with Lymphoma) is a phase 3 randomized (1:1) study focusing on a frail population of patients treated for DLBCL. The study will include 186 older adult patients with DLBCL (aged >65 years) receiving rituximab and chemotherapy. Overall, 50% (93/186) of patients (investigational group) will receive APA along with chemotherapy, and they will be supervised by a dedicated qualified kinesiologist. The APA program will include endurance and resistance training at moderate intensity 3 times a week during the 6 months of chemotherapy. The primary end point of this study will be event-free survival of the patients. The secondary end points will include the overall survival, progression-free survival, prevalence of sarcopenia and undernutrition, and patients' quality of life. This study will be conducted in accordance with the principles of the Declaration of Helsinki.

Results: Recruitment, enrollment, and data collection began in February 2021, and 4 participants have been enrolled in the study as of July 2022. Data analysis will begin after the completion of data collection. Future outcomes will be published in peer-reviewed health-related research journals and presented at national congress, and state professional meetings. This publication is based on protocol version 1.1, August 3, 2020.

Conclusions: The PHARAOM study focuses on highlighting the benefits of APA intervention on survival during the period of first-line treatment of patients with DLBCL. This study could also contribute to our understanding of how an APA program can

reduce complications such as sarcopenia in patients with lymphoma and improve their quality of life. By documenting the prevalence and relationship between sarcopenia and exercise load, we might be able to help physicians plan better interventions in the care of patients with DLBCL.

Trial Registration: ClinicalTrials.gov NCT04670029; https://clinicaltrials.gov/ct2/show/NCT04670029

International Registered Report Identifier (IRRID): DERR1-10.2196/40969

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KEYWORDS

diffuse large B-cell lymphoma; adapted physical activity; survival; sarcopenia

Introduction

Background

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin malignant lymphoma (representing 31% of lymphomas), with an incidence of 15 to 20 new cases per year per 100,000 inhabitants in France [1]. The median age of DLBCL diagnosis is 65 years, and one-third of the patients are aged >75 years [2]. Since the 2000s, the standard first-line treatment consists of 6 to 8 cycles of rituximab plus cyclophosphamide, hydroxydaunorubicin (doxorubicin), vincristine, and prednisone (R-CHOP) administration, and to date, no additional molecule has managed to demonstrate its superiority over the R-CHOP scheme in terms of the overall survival or event-free survival (EFS) [3,4]. The risk of relapse within 3 years after the first-line treatment in patients with DLBCL is 40%, and >50% of patients develop complications during the treatment [5]. Poor prognostic factors include age >60 years, high lactate dehydrogenase levels, an advanced stage of the disease, and an impaired general condition (as indicated by the National Comprehensive Cancer Network Prognostic Index) [6].

Several phase 3 trials have attempted to improve the survival of these patients by either offering maintenance treatment after an R-CHOP scheme with the use of an innovative molecule (such as enzastaurin in the Prevention of Relapse in Lymphoma Using Daily Enzastaurin trial [7]), everolimus in the Adjuvant everolimus in high-risk diffuse large B-cell lymphoma trial [8], and lenalidomide in the Study of Lenalidomide Maintenance Versus Placebo in Responding Elderly Patients With Diffuse Large B-Cell Lymphoma and Treated With Rituximab Plus Cyclophosphamide, Hydroxydaunorubicin (Doxorubicin), Vincristine, and Prednisone trial [3] or by combining an R-CHOP scheme with an experimental treatment, such as ibrutinib in the Randomized Phase III Trial of Ibrutinib and Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Non–Germinal Center B-Cell Diffuse Large B-Cell Lymphoma trial [4] and venetoclax in the A Study Evaluating the Safety, Efficacy and Pharmacokinetics of Venetoclax Combined With Chemotherapy in Participants With B-Cell Non-Hodgkin's Lymphoma and Diffuse Large B-Cell Lymphoma trial [9]. To date, only polatuzumab has demonstrated a significant improvement of progression-free survival (PFS) but not of overall survival in the Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma trial [10].

One should not oversee the fact that other risk factors might be associated with relapse. Some of these factors are related to the lymphoma itself (coexpression of BCL2 or BCL6 and C-MYC markers, ABC profile, high metabolic tumor volume, etc) and others to the patient (comorbidities, vitamin D deficiency, hypoalbuminemia, etc) [6,11-16]. Nutritional disorders (obesity and undernutrition) and sarcopenia can also affect PFS and overall survival [17]. Sarcopenia is defined by a reduction in skeletal muscle mass and physical performance, that is, a decrease in muscular strength, overall physical activity, and walking, as well as the onset of balance disorders and falls [18-21], leading to (1) loss of muscle mass, (2) decreased strength, and (3) reduced physical performance [18]. Sarcopenia is diagnosed when at least criteria, (1) + (2) or (1) + (3) can be confirmed. The causes of sarcopenia are often multiple [19]: chronic diseases (including cancer), inflammatory diseases, endocrine dysfunctions, insulin resistance, undernutrition, sedentary lifestyle, aging, and certain anticancer treatments (chemotherapy, radiotherapy, targeted therapy, and corticosteroid administration) can lead to loss of muscle mass, muscle deconditioning, and even development of neuropathies and chronic fatigue [22].

The assessment of the severity of sarcopenia is based on anthropometric measurements (weight; height; skin folds; and waist, arm, and calf sizes in cm), quantification of muscular strength (handshake test and breathing test by peak flow meter or peak flow), and measurement of physical performance. Measurement of skeletal muscle mass by assessing the muscular surface at the L3 level of the spinal column through computed tomography (CT) is recommended [23,24]. Several studies have confirmed the negative effects of sarcopenia in patients with DLBCL. In a recent study of a cohort of patients (n=522) who received first-line treatment with R-CHOP, 47% of these patients were found to be sarcopenic and sarcopenia was significantly correlated with more hospitalizations owing to febrile neutropenia, higher treatment-related mortality, and a reduction in the dose intensity of chemotherapy [25]. Sarcopenia was also significantly associated with age >60 years and high comorbidity score [26]. Adverse effects and early discontinuation of R-CHOP treatment are known to have a negative impact on the overall survival and PFS of patients with DLBCL [26,27].

Treatment for sarcopenia can involve physical exercise and adequate protein intake [18]. Two studies have shown reduction in the risk of death when patients undertake physical activity with sufficient volume or intensity before starting their first-line treatment [28,29]. Interestingly, the benefit is maintained if the physical exercise is continued during and after chemotherapy

[28]. A single study evaluated the impact of adapted and supervised physical activity on survival and response to treatment in patients with lymphoma (where several histological types were considered); the study revealed a significant increase in PFS of patients with lymphoma [30]. However, for the 42 patients with DLBCL in the same study, the results were inconclusive [30].

Objectives

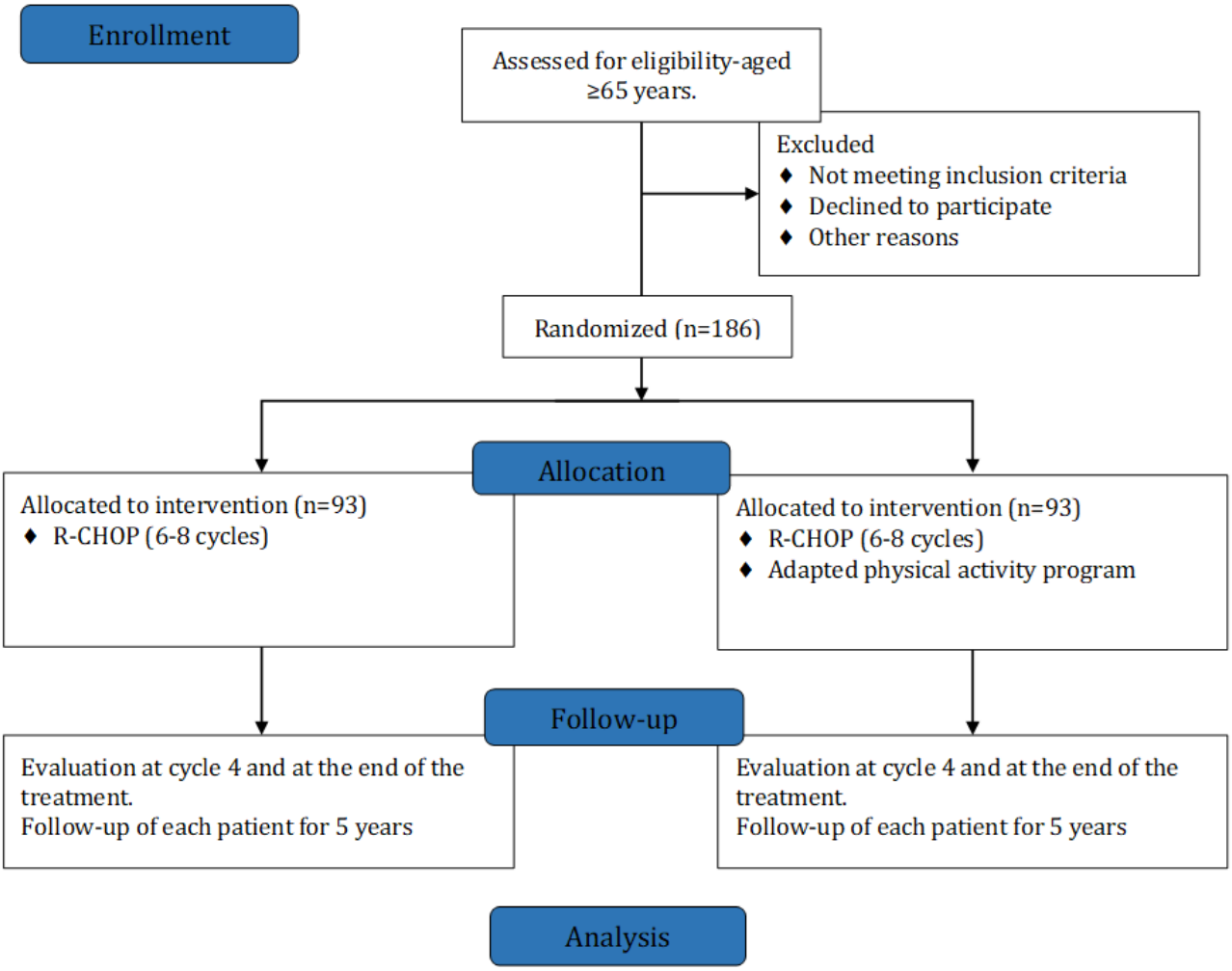
PHARAOM (Physical Activity Program for the Survival of Elderly Patients with Lymphoma) is the first randomized trial to evaluate the impact of a physical activity program on EFS of patients aged >65 years with previously untreated DLBCL. Sarcopenia will be screened in each group, and its impact on survival will also be assessed.

Methods

Study Design and Recruitment

This is a phase 3, open-label, randomized, multicenter, and prospective study. A total of 186 patients with DLBCL will be included: 93 (50%) will be randomized in the R-CHOP-alone arm and 93 (50%) will be included in the experimental arm (R-CHOP + physical activity program). A flowchart of the study is shown in Figure 1. We expected to detect an absolute difference of 15% in the EFS between the 2 groups. The final analysis will be performed at the end of the last patient's follow-up, that is, at the 60th month after the last inclusion. Inclusions are planned for 36 months, and the follow-up period for each patient will have a duration of 60 months.

Figure 1. Flowchart of the PHARAOM (Physical Activity Program for the Survival of Elderly Patients With Lymphoma) study according to the usual CONSORT (Consolidated Standards of Reporting Trials) flowchart type. R-CHOP: rituximab plus cyclophosphamide, hydroxydaunorubicin (doxorubicin), vincristine, and prednisone.



Participants and Inclusion and Exclusion Criteria

The PHARAOM study will include patients who fulfill all the following criteria: patients with DLBCL regardless of their 2016 World Health Organization subtype classification [31] or a low-grade B lymphoma that has quickly transformed into a high-grade B lymphoma (follicular lymphoma of the marginal zone, mucosa-associated lymphoid tissue, and lymphocytic or lympho-plasma cells); patients aged >65 years; patients eligible for treatment with R-CHOP (left ventricular ejection fraction [LVEF] of >50%) regardless of the age-adjusted International Prognostic Index; patients with a performance status of <2 for treatment-naive patients or 2 cycles of chemotherapy (prephase or reduction phase treatment [Cyclophosphamide, Vincristine sulfate, Prednisone] and cycle #1 of R-CHOP) received owing to the development of a hemopathy; patients affiliated with a

social security scheme; and patients providing written informed consent.

By contrast, patients with the following criteria will not be included in the study: patients with any other type of lymphoma (T lymphoma, Burkitt's lymphoma, nontransformed low-grade B lymphoma, etc); patients with cerebral or meningeal damage related to hemopathy; deficit—acquired, congenital, motor, or sensory—that does not allow the implementation of adapted physical activity (APA) sessions; patients with uncontrolled arterial hypertension; patients with an LVEF of <50%; patients with a disabling heart or respiratory failure not allowing the completion of the APA sessions; patients with a disabling osteo-articular or muscular pathology; patients having received ≥3 cycles of the first-line chemotherapy; patients who are pregnant or breastfeeding; patients with an active infection of HIV, hepatitis C virus, or hepatitis B virus; patients lacking liberty (under guardianship or guardianship); patients with dementia, mental alteration, or a psychiatric pathology that may compromise the their ability to provide an informed consent, their compliance with the protocol, and the monitoring related to the trial; patients unable to perform the protocol follow-up for psychological, social, family, or geographic reasons.

Sample Size

Given the experience gained by previous studies (particularly according to that of Feugier et al [32]), the sample size was calculated on the basis of the primary end point (EFS) to detect a difference of 15% at 24 months. Enrollment will take place for 36 months and follow-up for 60 months; thus, a significance level of 5% (2-sided) and power of 80% are required. Using the function plansurvct.func from the gsDesign (GNU General Public License) package of the R software and by planning an interim analysis at 50% of the event using DeMets–Lan and O'Brien–Fleming boundaries, we found it will be necessary to include 170 patients (85 per group) to obtain 114 events for the final analysis [33]. Moreover, considering that 10% of the patients could be lost during follow-up, we will need to enroll 93 patients per group (ie, 186 patients in total).

To be able to determine as quickly as possible whether the incorporation of APA into the follow-up of older adult patients with DLBCL improves EFS, we plan to perform an interim analysis that is scheduled to take place according to the DeMets–Lan limit at 50% of events [34]. To determine the number of patients needed to verify our hypothesis, we will ensure conforming to the following:

where λ_E and λ_c are the hazard ratios for the APA (investigational) and usual care (control) groups, respectively. By setting the risk for wrongly rejecting the "null hypothesis" at 5% during the final analysis and the power at 80% (ie, 20% of risk for wrongly concluding that there is "no difference"), inclusions will be considered over 36 months. If H_0 is not retained (P<.003), then we will conclude that APA produces a significant benefit for patients with DLBCL. In contrast, if H_0 is not rejected (P>.003), then the study will be continued to provide us with all the required events necessary to obtain a definitive conclusion. The 1:1 randomization will be carried out following minimization with stratification on the center, age, sex, and comorbidities. The randomization will be performed by the investigator directly via the e-Case Report Form developed by the Ennov Clinical software.

Primary and Secondary End Points

The primary objective of this study is to evaluate the effect of R-CHOP treatment combined with APA on EFS. EFS is defined as the time between the inclusion of patients and the date of the first event, such as relapse, infection, thrombosis, progression, or death, reported. The secondary objectives are to evaluate the compliance of the patients with the APA sessions and to quantify the overall physical activity load (in terms of volume and intensity) per patient and per session, overall survival, PFS, prevalence of complications (febrile neutropenia, anemia or thrombocytopenia requiring transfusion, infections, and venous or arterial thrombosis), prevalence of sarcopenia and nutritional disorders, patients' quality of life, and cost of the required hospitalization.

Survival

When the patient is censored, EFS is calculated as the time between the inclusion date and the date of the latest visit. The overall survival is defined as the time between the date of inclusion and the date of death (regardless of the reason for death) or the time between the date of inclusion and the date of the latest visit (if the patient is still alive). PFS is defined as the time between the date of inclusion and date of the first relapse, progression, or date of death (if no progression is seen before death), or date of the latest visit when the patient is censored.

Evaluation Parameters

After inclusion, data will be collected from the medical records in the form of an e-Case Report Form (Ennov Clinical).

Nutritional Disorders

Screening for nutritional status disorders (overweight, obesity, undernutrition, and severe undernutrition) has been defined by the Haute Autorité de Santé [35,36]. Being overweight is defined as a BMI of >25 kg/m^2 and obesity is defined as a BMI of >30 kg/m^2. In contrast, malnutrition is defined according to the criteria presented in Textbox 1.

Textbox 1. Criteria for defining undernutrition and severe undernutrition in patients.

Undernutrition

- Weight loss of >5% in 1 month or >10% in 6 months
- Albuminemia, albumin <35 g/L
- Mini Nutritional Assessment questionnaire global score <17

Severe undernutrition

- Weight loss of >10% in 1 month or >15% in 6 months
- BMI <18 kg/m^2
- Albuminemia, albumin <30 g/L

The nutritional status (weight, height, BMI, albuminemia, and Mini Nutritional Assessment questionnaire) will be evaluated at the time of diagnosis, after 4 cycles of R-CHOP, and at the end of the treatment [37]. Moreover, the assessment of food intake (ingesta) using the visual analog scale is a good reflection of the average consumption of the patient. A threshold of <7 reflects a significant decrease in food intake that justifies a specialized treatment [37], and it will be offered during each cycle. This evaluation will be performed by the registered dietitian of each center or the investigating physician.

Sarcopenia

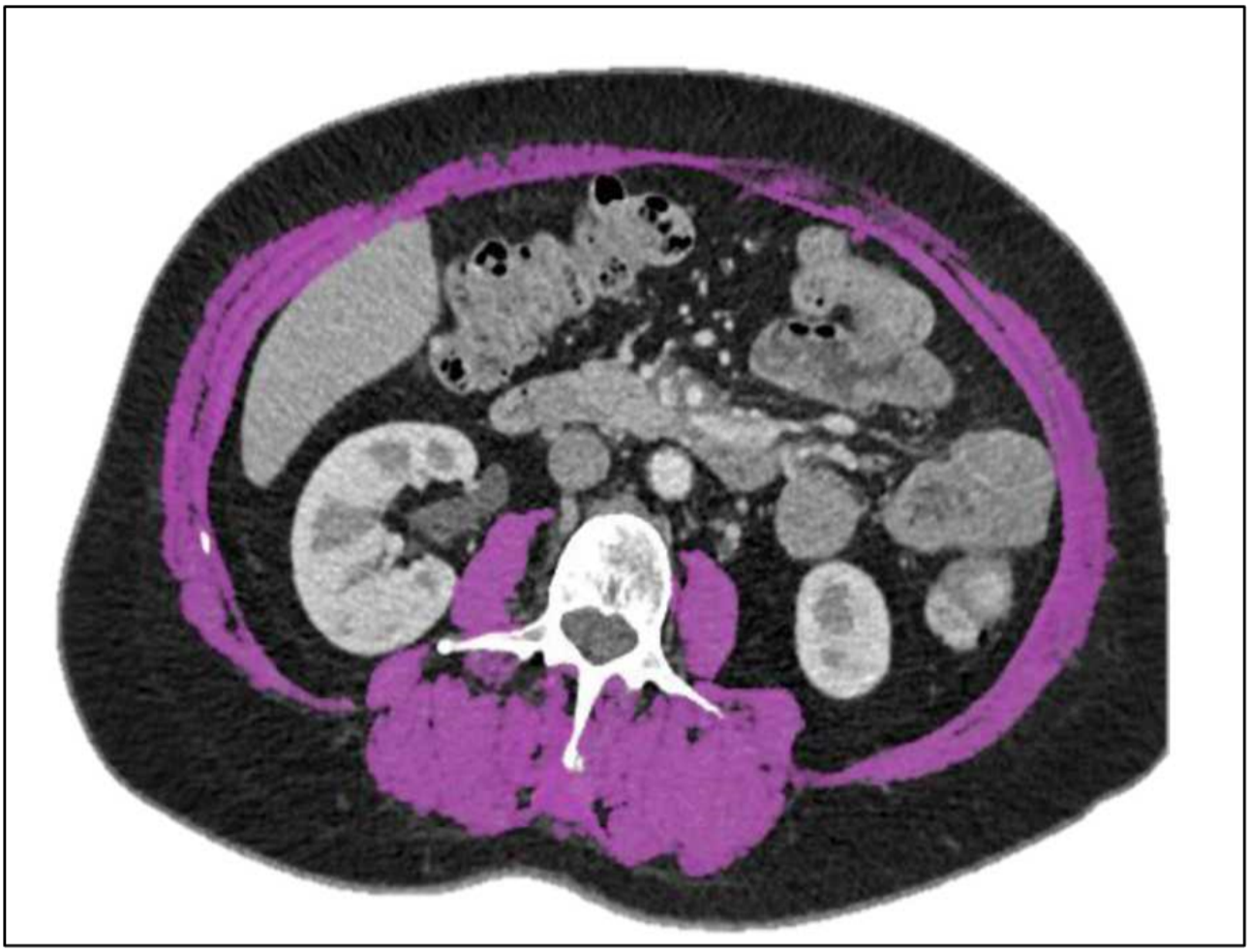
The European Working Group on Sarcopenia in Older People and the Asian Working Group for Sarcopenia guidelines require the assessment of muscular strength, physical performance, and skeletal muscle mass for the diagnosis of sarcopenia. The third lumbar vertebra (L3) has been selected as the standard marker for the quantification of skeletal muscles using CT scans. The L3 muscle area is strongly associated with whole-body skeletal muscle mass (psoas, paravertebral, and abdominal wall muscles) [17]. The muscle area is measured on CT images [38] using the first automatic segmentation process of the Synapse 3D software (Fujifilm Medical Systems) followed by a manual inspection by a trained analyst. After inspection, minor manual measurements will be performed as required. The already used, validated, and free ImageJ software has been chosen for the final measurement and validation of the muscle surfaces [39] (Figure 2) on a digital imaging and communications in medicine format file as described in detail by Gomez-Perez et al [40].

The lumbar skeletal muscle index (LSMI) quantifies the overall muscle mass of the patient and is a recognized marker for sarcopenia [41]. It corresponds to the cross-sectional muscle area (cm^2) at the L3 level that is used for the quantification of muscle mass, which is normalized by the squared height (m^2) of the patient [33]. Thus, the LSMI is expressed in cm^2/m^2 and is positively correlated to the BMI. A second marker, skeletal muscle density, which quantifies the fat content, is based on the mean radio attenuation expressed in Hounsfield units (HUs) from a cross-sectional area at the L3 vertebral level, whose values are within the range of −29 to +150 HU [42,43]. These 2 markers are complementary, and it has been proposed to use their product to obtain the skeletal muscle gauge, which is expressed in HU cm^2/m^2 [44]. The skeletal muscle gauge correlates better with the outcomes in patients with some types of cancer [44-46].

The finger flexor muscle force is measured using a handgrip dynamometer (MAP 80K1; Instramed). During the testing procedure, the participants are seated with their tested elbow flexed to a right angle by their side, while the wrist is at a neutral position to minimize the involvement of peripheral muscles. Measurements of sarcopenia and muscle parameters will be conducted every 3 months during chemotherapy and every 6 months until 5 years during the follow-up.

In our study, sarcopenia will be diagnosed if patients present 2 of the 3 criteria as follows [26,47-49]: (1) an LSMI of <55.8 cm^2/m^2 for men or <38.9 cm^2/m^2 for women, (2) a maximum voluntary contraction of <32 kg for men or <22 kg for women, and (3) a short physical performances battery score of <8.

Figure 2. Illustration of the skeletal muscle segmentation (purple) at the third lumbar vertebra level (L3) using the ImageJ software in a 65-year-old female patient with diffuse large B-cell lymphoma.



Cardiovascular and Respiratory Abnormalities

Clinical examinations will be conducted to identify signs of heart failure (dyspnea, edema of the lower limbs, crackles on pulmonary auscultation, weight gain, arterial hypertension, etc). Two additional tests will be performed: (1) LVEF which is the ratio (%) between the volume of ejected blood and the end diastolic volume of the left ventricle; this evaluation highlights the functioning of the left ventricle, which plays the role of maintaining an ejection volume adapted to peripheral blood requirements, and (2) pulmonary function tests, which measure respiratory volumes and flows by spirometry, flowmetry, plethysmography, and free diffusion of carbon monoxide; they can detect early abnormalities in lung capacity. Both evaluations will be conducted at the time point of inclusion, after 4 cycles of R-CHOP, and at the end of the treatment.

Frailty and Comorbidities

Frailty will be assessed by (1) the detection of comorbidities with the calculation of the Charlson score [48], (2) dependency using the G8 geriatric questionnaire [50], (3) cognitive disorders by calculating the mini mental status [51], and (4) autonomy through the Activities of Daily Living and the Instrumental Activities of Daily Living questionnaires [52,53]. These questionnaires will be offered only at the time point of inclusion.

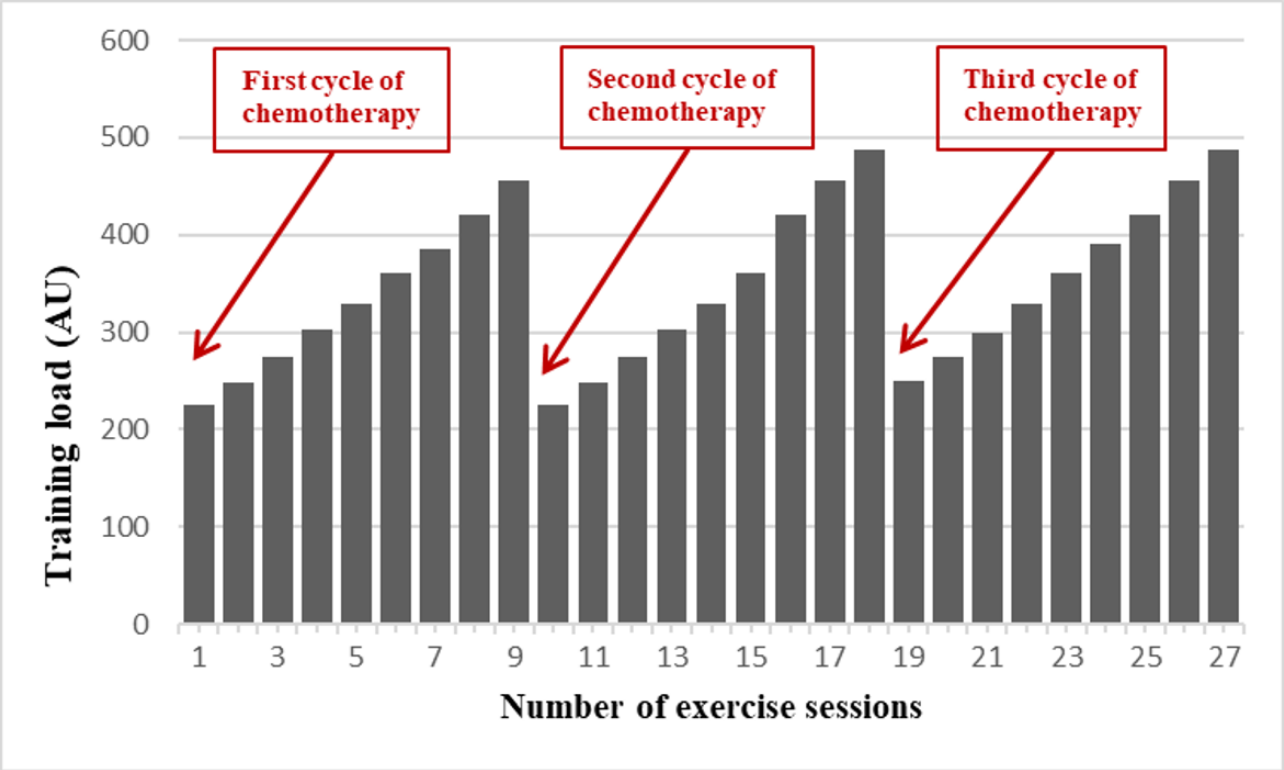
Fatigue and Quality of Life

The overall quality of life will be assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire [54]. Depression will be assessed using the Geriatric Depression Scale questionnaire [55]. Fatigue will be assessed using the Multidimensional Fatigue Inventory questionnaire [56]. These questionnaires will be offered at the time of inclusion, after 4 cycles, at the end of the treatment, and then every 6 months until the end of the study.

Physical Activity Program

The physical activity program is based on international recommendations in terms of its intensity and duration while also considering the side effects induced by chemotherapy [57]. A qualified physical activity teacher (eg, a kinesiologist or physical therapist) will be in charge of carrying out the sessions. To trigger the phenomenon of supercompensation [58-60], the workload of the exercise program will be modulated during the protocol. Thus, the exercise program will be characterized by a periodic and regular increase in workload during each cycle of chemotherapy planned by the physician (Figure 3).

Figure 3. Representative sketch of the periodization to be followed for the exercise interventions (training load). AU: arbitrary unit.



The APA program can be described using the frequency, intensity, time, and type principle [61]. *Frequency*: participants will have to exercise 3 times a week. *Intensity*: to match the World Health Organization recommendations [62], the objective is to maintain an intensity of ≥6/10 (on Borg scale) as often as possible. *Time*: the APA program will last approximately 6 months, that is, the total duration of chemotherapy administration. *Type*: exercise should include resistance training (indoor with elastic bands, weight machines, and free weights) and endurance training, such as Nordic walking. According to the COVID-19 context, an amendment has been added to the protocol to offer the patient the possibility of following the same program through video calls with the supervision and direction of the APA teacher.

The training load (in arbitrary units) will be designed according to the Foster method, which is well known in the world of sports training and has the advantage of being able to quantify the training load in a simple way [63,64]. The principle is based on multiplying a patient's feeling of the intensity of the effort (rating of perceived exertion; graded 0-10) by the duration of the session in minutes, thereby leading to the marker:

Training load AU = rating of perceived exertion 10 × duration min **(1)**

This approach to measure training load also provides a means to educate the patients to better assess their training load and to improve their independent practice. Another advantage of using this easy-to-use parameter of follow-up is that we can ensure an opportunity to design and perform the exercise program freely. Professionals and patients may choose the type of physical exercise and activity according to their preferences, equipment, and possibilities and still evaluate the training load as a parameter that can be used for interpatient comparisons.

Statistical Analysis

A general description of the study population (demographics, disease history, and previous treatments) will be presented by group (experimental and control) and in total. For categorical variables, we will present the number of patients (n) and the percentage for each group in the study cohort. The significance of the statistical differences will be assessed using the chi-square test or Fisher exact test. For quantitative variables, we will report the median value or the mean value with the SD depending on the normality of the variable; the minima and maxima will also be indicated. Comparisons will be made by using the Fisher exact test, or Student test for small groups, or nonparametric Wilcoxon test, depending on the normality of the variables.

Survival curves will be plotted according to Kaplan-Meier estimates; median survival will be reported with their 95% CIs. The curves will be compared using the log rank test. The Cox model will be used to calculate the hazard ratios that will be reported with their 95% CIs. The completion rates of different Quality of Life Questionnaires (European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, Geriatric Depression Scale, Male Sexual Health questionnaire, and Brief Index of Sexual Functioning for Women) will be defined for each questionnaire and at each measurement point. The quality of life will be described for each evaluation (median value, mean value and SD, minima and maxima, and the frequency of the floor and ceiling effects) compared with the values obtained at the time of inclusion and then studied longitudinally using mixed-design analysis of variance for repeated measures. The degradation time will also be analyzed. The definitions that will be used are those proposed by Bonnetain et al [65]. Absolute prevalence—that is, the number of cases with an event—will be reported in addition to

the prevalence (number of cases existing at the time of the assessment or number of patients observed at the same time). The incidence rate, which is the number of patients with a new event divided by the time spent by the patient during the follow-up period, will also be reported. Adherence, defined as the fraction of APA sessions that have been actually completed, will be reported. The cost analysis will be conducted over a 36-month period. The duration of our clinical follow-up is sufficient to allow us to assess the impact of APA on the care and quality of life of patients with DLBCL. Only the cost of hospitalization (medicines, surgery, or postcure rehabilitation) will be assessed. Data related to hospital stays will be made available through medical information departments of the participating centers. The cost will be estimated according to the rates provided by the Homogeneous Groups of Stays and will be considered as a daily supplement. The analyses will be performed using the SAS software (version 9.3, SAS Institute Inc), with a degree of significance set at 5%.

Ethical Considerations

The study has been approved by the national research ethics committee (AU1636) and was registered as a clinical trial (NCT04670029) on December 16, 2020. This study will be conducted in accordance with the principles of the Declaration of Helsinki.

After the medical consultation, a research team member will provide patients with the study brochure and verbal description of the study and give them an opportunity to ask questions about the study. If the participant agrees, screening for eligibility to participate in the study is performed and signed informed consent will be obtained. The protocol complies with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist. No compensation is included for participants within the framework of the study. All the care proposed is provided by the national social security. Travel to the study site is not financially covered for the participant.

Results

We expect that APA will reduce relapse and complications in the short and medium term (infections, secondary cancers, and cardiovascular diseases induced by the treatments). This program is associated with nutritional and training-load monitoring and has the benefit of being reproducible from one center to another.

Recruitment, enrollment, and data collection began in February 2021, and 4 participants have been enrolled in the study as of July 2022. Data analysis will begin after the completion of data collection. Future outcomes will be published in peer-reviewed health-related research journals and presented at regional, national, congress, and state professional meetings. This publication is based on protocol version 1.1, August 3, 2020.

Discussion

Anticipated Principal Findings

The primary purpose of the PHARAOM study is to evaluate the effect of a standardized APA program applied concomitantly with R-CHOP chemotherapy on the survival of patients receiving first-line treatment for DLBCL.

The relationship between physical exercise and survival is poorly understood, especially in patients with DLBCL [27]. To the best of our knowledge, the PHARAOM study is the first randomized trial to propose a complete and repeated APA intervention in a population of patients receiving first-line treatment for DLBCL. The study findings should promote the growing body of evidence concerning the role of specific interventions such as APA in patients with cancers; for example, lymphoma.

Indeed, we expect an increase in the survival of patients who undertake an APA program initiated at diagnosis as reported in a previous study, where patients obtained benefit in survival only when completing physical activity before or after the first-line treatment [28,29]. We expect to obtain the benefit of APA in survival by implementing it at the beginning and during the first-line treatment period. The hitherto poorly studied and delicate character of the first-line treatment period explain why we experimented with an adjustable training-load process in our study. Our objective is to show that an APA program is conclusive for our population of patients with DLBCL, contrary to what is observed in the study conducted by Courneya et al [30] with this type of hematologic cancer.

Regarding the expected results of the evaluation, we anticipate that the results involved in the implementation of the intervention may be somewhat different, as the treatment period of the fragile population that will be assessed in this study may involve more complications previously cited, such as sarcopenia. Consequently, a lower survival rate in the sarcopenic group should be expected based on the studies reporting the outcomes in sarcopenic patients with solid tumors [66,67]. Similar results were obtained in patients with hematologic malignancies [20,27,68].

Strengths and Limitations

We expect a major difficulty in adhering to the study owing to its innovative nature and the voluntary basis of the trial's participation. In France, especially in the context of the COVID-19 pandemic, physicians are not yet involved in providing physical exercise–related care to their patients, mostly owing to a lack of information regarding this type of care. The same applies to patients themselves, where their spontaneous involvement in physical therapy during the treatment of their cancer is not common. Therefore, our study is faced with the challenge of helping to modify the management of a chronic illness (such as DLBCL) and at the same time, providing the tools to materialize national recommendations [69,70]. The COVID-19 pandemic has also disturbed the study development and has delayed the enrollment of patients owing to their immune frailty. Hematological conditions and human physical interactions through face-to-face exercise sessions are not compatible with the COVID-19 pandemic context; therefore, we propose the adoption of videoconference in the training sessions. The strength of this study is that it will be, to our knowledge, the first study to assess the prevalence of sarcopenia in both survival and clinical outcomes in this specific patient

population. This is the first randomized trial to propose a complete and repetitive APA program for this frail population.

Conclusions

Our study should provide new objective data that are needed for a deeper understanding of the effect of exercise on muscle mass and sarcopenia, which act as prognostic markers for patients with DLBCL. The frailty of the older adult population with DLBCL demands specific attention to the APA methodology used; therefore, we use a malleable training load in this study in an attempt to reduce (as far as possible) the chances of causing fatigue while inducing sufficient physical input in this fragile population.

The long-term objective of our research team is to develop and test APA interventions that improve survival and quality of life management in all cancer populations and can be implemented in various clinical settings. Findings from the PHARAOM study will consolidate refinement of APA interventions and trial design concerning physical activity in hematological cancer. Later inclusion of health economic modeling could shed further light on the long-term effects of intervention participation on the cost-effectiveness of this approach for APA promotion and integration in the national health system.

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Data Availability

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

Authors' Contributions

JD, MB, ALS, and KLD designed the research protocol; JD, MB, and KLD defined the inclusion and exclusion criteria for the patients; MB submitted the protocol to the ethics committee; JD and KLD obtained the funding; MB and KLD were responsible for the description and organization of the study; JD, FD, SL, CL, and KLD wrote the first draft of this protocol, and the final version was reviewed and approved by all authors.

Conflicts of Interest

FD reports conflicts of interests with Chugai, Astra-Zeneca, Merck, Sivan, Takeda, Ipsen, Bristol Meyer Squibb, Viatris, Kelindi, and Hyperion where he is an invited speaker, and also serves on the advisory board at Sivan and Roche.

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Abbreviations

APA: adapted physical activity
CT: computed tomography
DLBCL: diffuse large B-cell lymphoma
EFS: event-free survival
HU: Hounsfield unit
LSMI: lumbar skeletal muscle index
LVEF: left ventricular ejection fraction
PFS: progression-free survival
PHARAOM: Physical Activity Program for the Survival of Elderly Patients with Lymphoma
R-CHOP: rituximab plus cyclophosphamide, hydroxydaunorubicin (doxorubicin), vincristine, and prednisone
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Effectiveness of a Web-Based Intervention to Prevent Anxiety in the Children of Parents With Anxiety: Protocol for a Randomized Controlled Trial

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Abstract

Background: Anxiety is the most common childhood mental health condition and is associated with impaired child outcomes, including increased risk of mental health difficulties in adulthood. Anxiety runs in families: when a parent has anxiety, their child has a 50% higher chance of developing it themselves. Environmental factors are predominant in the intergenerational transmission of anxiety and, of these, parenting processes play a major role. Interventions that target parents to support them to limit the impact of any anxiogenic parenting behaviors are associated with reduced anxiety in their children. A brief UK-based group intervention delivered to parents within the UK National Health Service led to a 16% reduction in children meeting the criteria for an anxiety disorder. However, this intervention is not widely accessible. To widen access, a 9-module web-based version of this intervention has been developed. This course comprises psychoeducation and home practice delivered through text, video, animations, and practice tasks.

Objective: This study seeks to evaluate the feasibility of delivering this web-based intervention and assess its effectiveness in reducing child anxiety symptoms.

Methods: This is the protocol for a randomized controlled trial (RCT) of a community sample of 1754 parents with self-identified high levels of anxiety with a child aged 2-11 years. Parents in the intervention arm will receive access to the web-based course, which they undertake at a self-determined rate. The control arm receives no intervention. Follow-up data collection is at months 6 and months 9-21. Intention-to-treat analysis will be conducted on outcomes including child anxiety, child mental health symptoms, and well-being; parental anxiety and well-being; and parenting behaviors.

Results: Funding was received in April 2020, and recruitment started in February 2021 and is projected to end in October 2022. A total of 1350 participants have been recruited as of May 2022.

Conclusions: The results of this RCT will provide evidence on the utility of a web-based course in preventing intergenerational transmission of anxiety and increase the understanding of familial anxiety.

Trial Registration: ClinicalTrials.gov NCT04755933; https://clinicaltrials.gov/ct2/show/NCT04755933

International Registered Report Identifier (IRRID): DERR1-10.2196/40707

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KEYWORDS

anxiety; parenting; online; RCT; child; parent; randomized controlled trial; youth; pediatric; mental health; mental well-being; online intervention; digital intervention

Introduction

According to a systematic review of the prevalence of mental health conditions in childhood, anxiety disorders are more common than any other mental health disorder, including depression and behavior disorders [1]. However, this vulnerability is not randomly distributed; it is clear that anxiety disorders run in families and that children of parents with anxiety are at an increased risk of developing anxiety disorders themselves. A recent meta-analysis reported that the children of parents with anxiety were approximately twice as likely to have anxiety problems than those of parents without anxiety [2].

Moreover, it is clear that this intergenerational transmission of anxiety is not solely (or even largely) attributable to genetic processes; environmental factors have also been shown to contribute substantially to the transmission of anxiety within families [3]. The focus of the research that has sought to understand these environmental processes has been largely on parenting, and it seems likely that a number of parental processes are at play. For example, it has been reported that parents who experience significant anxiety show attentional biases to child-threat stimuli [4] and are more likely to show biased processing of ambiguous information about their children (for review, see [5]). In addition to these anxiety-based cognitive biases, there is evidence that the behavior of parents with anxiety is also altered in some situations. For example, parents with anxiety have been shown to encourage more avoidance and less approach in situations when their child is fearful [6]. Similarly, parents who experience high anxiety levels are more likely to report employing anxiogenic child behavior management techniques such as harsher discipline styles and inconsistency in following through on commands and on consequences for unacceptable behavior [7,8].

Children who develop anxiety disorders, regardless of their cause, are likely to face a number of challenges: they experience lower quality of life than other children [9], and although some will become less anxious as they grow older, a large proportion will experience anxiety-related difficulties into adulthood [10]. Many will also experience educational difficulties [11] and difficulties with relationships [12]. Children with anxiety disorders are also at an increased risk of developing other ailments, particularly mood disorders [13] and substance use disorders [14]. Moreover, childhood anxiety disorders are costly to society: a Netherlands-based study found that the societal costs associated with anxiety disorders in children were 21 times higher than those for children without anxiety disorders [15].

Despite evidence that children of parents with anxiety are at an increased risk of anxiety disorders and the problems that anxiety disorders bring, little has been done to prevent this intergenerational transmission. Ginsburg et al [16] sought to address this gap, devising the US-based “Coping and Promoting Strength” program for parents who experience high levels of anxiety and their children. The intervention comprised a 60-minute session each week for 8 weeks, followed by 3 optional booster sessions each month, and employed a range of psychoeducational, cognitive restructuring and problem-solving approaches to cover both child- and parenting-related factors. Although the program produced encouraging results, it is unlikely to be viable in the financial and operational context of the National Health Service (NHS) in the United Kingdom (and other similar systems). Furthermore, it is onerous for families; if their children are currently doing well, it may seem particularly burdensome.

In an attempt to address these constraints, Cartwright-Hatton et al [17] developed a very brief, clinic-based group intervention aimed at parents who were seeking treatment for their own difficulties with anxiety. The aim of this 1-day intervention was to help parents develop a calm, consistent behavior management style, while learning skills to discourage children’s avoidance and encourage confident behaviors. During the sessions, parents were also supported to identify areas where anxiety might affect their parenting and to make plans to minimize this. A UK NHS–based randomized controlled trial of this intervention reported 16.5% fewer children meeting the criteria for an anxiety disorder 1 year later, compared to those whose parents did not receive the intervention [17].

It is clear that there are ways in which the intergenerational transmission of anxiety can be reduced. However, the two aforementioned currently available evidence-based interventions have the capacity to reach only a tiny fraction of the families that might benefit. For example, in the United Kingdom, primary care mental health services (where such interventions would likely be based) aim to reach only 25% of people with clinically diagnosed anxiety, of whom only 50% are expected to meet the criteria for recovery after treatment (NHS England, 2022 [18]). The children of the estimated 75% who do not access support for their anxiety are likely to be as vulnerable (if not more so) as those whose parents do receive some support. Moreover, even the 25% of adults who do access assistance for their anxiety may not have the resources to attend an additional in-person

intervention aimed at the needs of their children. In the randomized controlled trial conducted by Cartwright-Hatton et al [17], and in their clinic offering the intervention since, approximately half of interested parents fail to attend as a result of childcare or work commitments or because a group-based intervention was unacceptable. Therefore, this paper describes the protocol for a randomized controlled trial of a self-guided, web-based version of Cartwright-Hatton's [17] intervention. If effective, this digital intervention has the potential to increase access to a substantially larger group of parents with anxiety, including those who do not or cannot access mental health services, and those who cannot attend a workshop in person.

Fathers are particularly disadvantaged by these barriers to accessing mental health services and clinics. This may be attributable in part to the traditional family model of the mother as the primary caregiver and father as the main earner; that is, it is assumed that attending to children's health and emotional needs is part of the mother's role and not part of the father's domain. This is supported by the fact that parenting interventions are overwhelmingly focused on mothers: interventions tend to concentrate on the recruitment of mothers and consider what would be most convenient to them. Panter-Brick et al's [19] systematic review of fathers' inclusion in parenting interventions found that the vast majority of studies included few or no fathers, with very little data disaggregated by parent gender. However, focusing mainly on mothers in psychological interventions is problematic. There is clear evidence that fathers have a key role to play in children's emotional development, and greater involvement from fathers in parenting has been shown to have positive outcomes for children [20]. Moreover, in terms of the transmission of anxiety, it is possible that fathers who experience significant anxiety might have different and potentially more deleterious impacts on child outcomes than do mothers with anxiety [21,22]. It is hoped that in providing this intervention in a self-guided, digital format, more fathers will be reached.

We believe that there is value in increasing confidence and reducing anxiety in both a child who is only at risk of subthreshold anxiety and in reducing the severity of symptoms in a child with an ongoing anxiety disorder. The study, therefore, takes a "public health" approach; that is, the intervention is intended not only to reduce the risk of clinically diagnosable anxiety disorders but also to reduce the likelihood of symptoms across the anxiety spectrum.

Similarly, we do not believe that the intervention might be of benefit only to children whose parents have clinically diagnosable anxiety disorders; hence, we will invite any parent who identifies as experiencing high levels of anxiety to participate in the study without requiring a formal diagnosis of anxiety. By sampling into the subclinical range of parental anxiety, we will maximize preventative opportunities. This may be of particular relevance given the heightened level of anxiety experienced by many parents during the course of the COVID-19 pandemic [23].

Research into preventing anxiety disorders is in its infancy, and this is particularly the case for efforts that are targeted among parents with anxiety. While there are reasonable models of the processes involved in the intergenerational transmission of anxiety, little is known about what changes in parenting behavior are necessary and sufficient for preventative interventions to be effective. To maximize efficiency for parents (and services), we need to understand which intervention components are most effective, and for whom, particularly in a web-based format and for the wider, more inclusive group that is likely to access this. This study aims to recruit a very large sample of parents, which will allow us to conduct an analysis of intervention components. In doing so, we will not only optimize the intervention but also gain a better theoretical understanding of the mechanisms underpinning intergenerational transmission of anxiety.

Methods

Study Aims and Objectives

This study aims to evaluate the effectiveness of a web-based intervention designed to prevent anxiety in the children of parents with anxiety and provide information for the optimization of this intervention. The study has 3 core objectives:

1. To investigate the effectiveness of a web-based, parent-focused intervention for the prevention of anxiety in children of parents with anxiety.
2. To determine which components of the intervention have the most or least impact on outcomes and test whether the effect of each component is moderated by participant characteristics (type or severity of parent or child anxiety symptoms, socioeconomic status, and child age).
3. To explore the impact of coparent anxiety and parenting behaviors on child outcomes—we hypothesize that child outcomes will be worse when the coparent is also anxious or engages in frequent anxiogenic parenting behaviors.

Study Setting

The study will be completed entirely in a digital setting, with UK-based, self-referred participants.

Sample Size

The sample size was calculated to provide adequate power for our first objective (to detect a difference between trial arms in child anxiety). Based on existing research carried out by the trial team, a small effect size is anticipated (Cohen d=0.2) [17]. With 90% power for 5% significance, this requires 526 participants in each of 2 arms of the trial. Allowing 40% attrition, which is likely to be substantial in a web-based study, we need to randomize 877 participants to each arm, or 1754 in total.

Eligibility Criteria

The eligibility criteria are designed to resemble those that would be employed in any eventual rollout of a web-based intervention. As such, they are minimal. To be eligible, a participant must be a parent (any gender; adoptive, biological, step, foster, or grandparent) residing in the United Kingdom, aged over 16 years and with a child aged 2 to 11 years (inclusive). The participant must have at least 50 days' contact with the index child per year and confirm that they see enough of the child to report on the child's current anxiety level. The participant must

self-report subjectively substantial levels of current or lifetime anxiety (it is not necessary to have a diagnosis) and be able to commit to completion of measures at (up to) 3 time points, even if allocated to the control arm.

Participants will not be excluded on the basis of current or previous psychiatric treatment (parent or child) or on any psychological, neuropsychological, or physical condition.

Recruitment, Randomization, and Allocation

This study is intended to reach parents with anxiety, the majority of whom never receive treatment for anxiety (although those who have will not be excluded). As such, recruitment activities will focus outside of health services, and will involve the dissemination of study materials by mental health charities, schools, parent groups, parenting magazines, social media, and through the Genetic Links to Anxiety and Depression (GLAD) study [24] within the National Institute for Health and Care Research (NIHR) Mental Health Bioresource.

To reach potential participants directly, we will utilize social media platforms, including contracting a public relations agency to run a paid-for social media campaign. We will also commission advertisements in parent-orientated publications. To maximize the recruitment of fathers, we will partner with male mental health organizations and organizations supporting fathers including charities and social media influencers.

Participants will be randomized in large blocks using block randomization to 1 of 2 arms (intervention or control [no Intervention]) in a ratio of 1:1. This will be carried out using predefined lists generated by the Brighton and Sussex Clinical Trials Unit, with study IDs all prerandomized and concealed until the participant completes baseline questionnaires. Those assigned to the intervention group will be further randomized to one of 8 conditions to allow analysis of the intervention components (see *Interventions* below). If a parent has more than one child within the target age range (2-11 years), the web-based system will allocate one child at random on which the parent will report when responding to outcome measures.

Given the digital nature of the intervention and use of self-report measures, no assessor or clinician blinding is required.

Interventions

Eligible participants will be randomized in equal proportions between the intervention arm, which comprises a web-based parenting course, and the control arm, which receives no provision over and above what the parent might be accessing outside of the study.

The parenting course is delivered fully digitally and follows the format of the evidence-based in-person version [17]. It has one "Starter" module and 8 "further" modules and is completed by parents (children do not participate). The Starter module is completed by all parents. Subsequently, parents complete 7 of 8 further modules (one is disabled at random), which are displayed to parents in random order. The modules cover the following subject areas: the Seven Confident Thoughts, avoidance, play, emotion coaching, positive behavior management, basic needs, hotspots and overprotection, and modeling and compensation. Each module takes between 20 and 30 minutes to compete and has accompanying home practice tasks, which the participant is encouraged to try out before progressing to the next module. An overview of the course module content and example intervention images can be found in Multimedia Appendix 1 and Multimedia Appendix 2.

Participants can share a "mirrored" version of the course with a supporter to facilitate shared learning and support. To promote adherence, participants will be automatically "nudged" with a limited number of email and SMS text messages should they disengage from the intervention for a period in excess of 73 hours if they have partially completed a module, and 1 week if they are between modules.

The intervention may be modified during the study, only on the grounds of external activities (eg, an amendment to mobile operating systems) or should disproportionate attrition be identified in one or more modules.

Participant Timeline

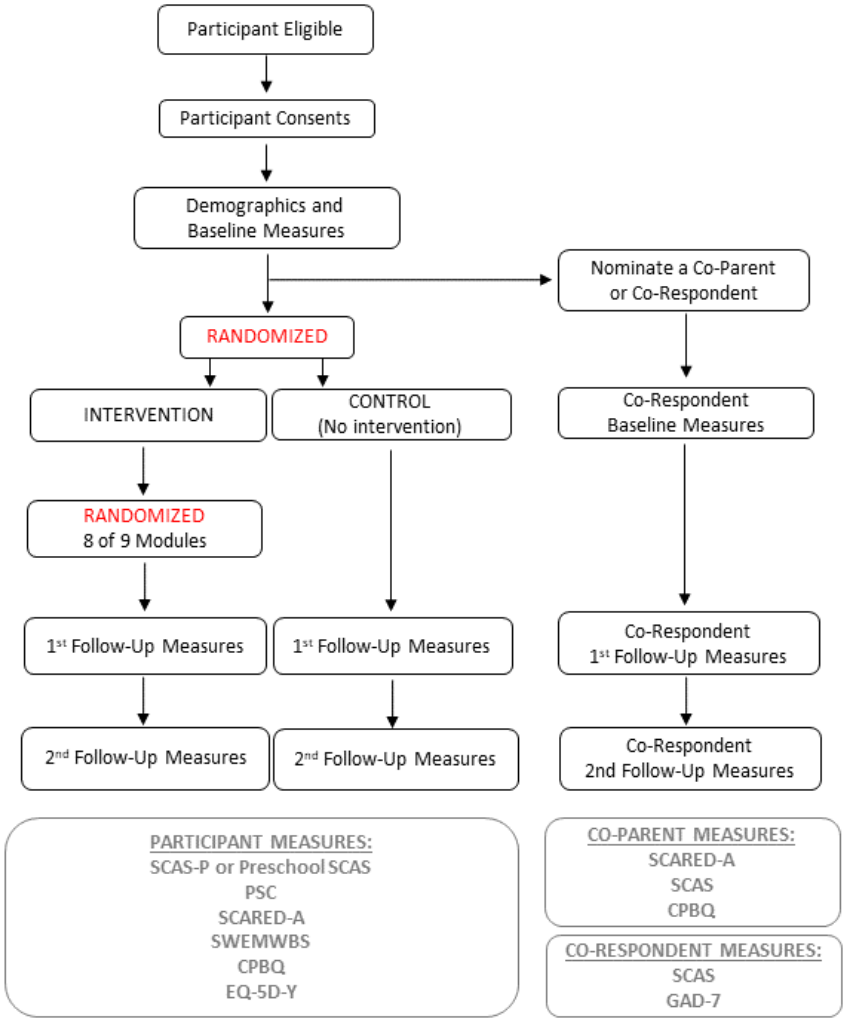
The entire study will be completed digitally. Participants will flow through the study as follows:

1. Receive summary information.
2. Be screened for inclusion and exclusion criteria (see Eligibility Criteria above). Those meeting the criteria will proceed to step 3.
3. Receive detailed information about the study and give consent digitally.
4. Invited to provide details of a corespondent who will be asked to complete a measure of child anxiety. This person, who can be a coparent, friend, or family member who has good knowledge of the index child, will be emailed from within the study platform 48 hours after the participant has completed measures (allowing parents time to explain the study to their chosen corespondent). Participants can also choose not to refer or to make a referral later.
5. Participants (and corespondents, if applicable) complete baseline measures.
6. Participants will be informed of the arm of the trial they have been randomized to.
7. Undertake intervention or control group tasks.
8. Participants (and corespondents, if applicable) complete outcome measures at 6 months (same outcomes as the baseline assessment).
9. Participants (and corespondents, if applicable) recruited prior to the final 6 months of recruitment will complete outcome measures again, once, 4 months prior to the study end to allow exploration of longer-term outcomes. This follow-up is contingent on the participant submitting their 6-month follow-up questionnaire a minimum of 2 months prior to this point.

Participants have the option of inviting a corespondent to also complete a measure of child anxiety, allowing us to access a different perspective on the child. Where the corespondent is a coparent, they will additionally be asked to complete a measure of their own anxiety and of parenting behavior, which will be used in support of objective 3: to explore the impact of coparent anxiety and parenting behaviors on child outcomes. Corespondents will be invited to complete follow-up measures

at 6 months post consent and 4 months prior to the end of the trial. Participant flow through the study is shown in Figure 1.

Figure 1. Participant flow through the project. CPBQ: Comprehensive Parenting Behavior Questionnaire; PSC: Pediatric Symptom Checklist; SCARED-A: adult version of the Screen for Child Anxiety Related Disorders; SCAS: Spence Children's Anxiety Scale; SCAS-P: parent-report version of the Spence Children's Anxiety Scale; SWEMWBS: Short Warwick Edinburgh Mental Well-being Scale.



Outcomes

Unless otherwise indicated, "outcomes" are those reported by the index parent, in both arms, at baseline, at 6 months, and in the final follow-up.

To determine the effectiveness of the web-based parenting-focused intervention, the primary outcome will be child anxiety symptoms. The secondary outcomes will be parental anxiety and parental well-being. We hypothesize that children and parents in the intervention arm will show fewer anxiety symptoms (and greater parental well-being) at 6-month follow-up than those in the control arms.

Intervention feasibility and acceptability will be examined on the basis of the following parameters: study attrition rate, which is the proportion of participants that complete 6-month follow-up measures; study completion rate, which is the proportion of participants in the intervention arm who complete 3 modules; and participants' self-reported satisfaction with the intervention modules.

Data Collection, Management, and Analysis

Primary Outcome

Child anxiety symptoms will be assessed using the Spence Children's Anxiety Scale (SCAS-P [parent-report version of the SCAS] and Preschool SCAS) [25,26]. These parallel instruments are acceptable to parents and have good validity or reliability.

Secondary Outcomes

Parent and Coparent Anxiety Symptoms

The adult version of the Screen for Child Anxiety Related Disorders (SCARED) [27] will be used to assess each of the Diagnostic and Statistical Manual of Mental Disorders (DSM) anxiety disorders, consisting of 71 items. It has good internal consistency and is positively correlated with results from the diagnostic anxiety disorders interview schedule of the Anxiety Disorders Interview Schedule for DSM-IV: Lifetime version.

Parent Well-being

The Short Warwick Edinburgh Mental Well-being Scale [28], a 7-item self-report measure (rated 1 to 5) of features of positive mental health (positive affect, interpersonal relationships, and positive functioning), will be used. It is positively correlated with the original 14-item Warwick-Edinburgh Mental Well-being Scale [29] and has high internal consistency and good validity.

Child Emotional and Behavioral Symptoms

The Pediatric Symptom Checklist, a 17-item general mental health screening tool for children, will be used. The parent reports how often their child demonstrates internalizing, externalizing, or attentional symptoms using 3 levels of frequency. The scale has good validity and sensitivity with comparable case detection to semistructured clinical interviews and is widely used as a screen in primary care [30].

Child Health

We will use the EQ-5D-Y Proxy Report [31], a 5-item plus visual analogue scale proxy report measure of health-related quality of life, developed for use with children. The parent reports how they would measure the child's health (on that day) across 5 dimensions—mobility; looking after themselves; doing usual activities; having pain or discomfort; and feeling worried, sad, or unhappy—using 3 levels of severity, and further marks "health today" on a scale of 0 to 100. This is a version of the EQ-5D-3L, which is widely used in cost-effectiveness analyses and has good validity and internal consistency.

Demographics

Parents' age, gender, socioeconomic status, ethnicity, coparenting status, child age, developmental disability, and previous parent or child treatment for anxiety will be assessed.

Adverse Events

A short instrument has been designed for the study; it is based on the number of children and parents whose anxiety deteriorates.

Mediators

We will measure parenting behavior by asking parents (in both arms) to complete measures of parenting behaviors that are addressed by each module. For most modules, items are taken from a 104-item shortened version of the Comprehensive Parenting Behavior Questionnaire (CPBQ) [32,33], a psychometrically strong, self-report instrument measuring parenting behaviors associated with the risk of child anxiety. For the few areas in our intervention not covered by the CPBQ (eg, sleep, exercise, and diet), items have been constructed for the purposes of this study.

Moderators

We will assess the following baseline parameters and changes in them, where appropriate: severity or type of parent and child anxiety (SCAS and adult version of the SCARED), socioeconomic status, previous parent or child treatment for anxiety, parent and child gender, child age, and child developmental disabilities.

Maximizing response rate and retention of participants is a priority, so participants and corespondents will be offered shopping vouchers for completion of measures. Participants will be provided with a £15 (US $17.39) voucher on completion of follow-up measures; corespondents will be provided a £10 (US $11.59) voucher on completion of all measures.

Data Management

Data will be entered directly by participants via Moodle, a secure web-based learning platform and via an embedded survey hosted by Qualtrics. Upon randomization, the participants will each be given a unique identifier by which they will be referred for the duration of the study. This entire database is encrypted. In order to collect special category data (eg, mental health data and ethnicity), we have in place a Secure Sockets Layer setup, which will establish an encrypted link between a web server and a browser. All investigators will comply with the requirements of the Data Protection Act of 1998 [34]. A specific data management plan and a monitoring plan have been developed for the study (available from Brighton and Sussex Clinical Trials Unit).

Data Analysis

Overview

We will report participant flow through the trial and results in line with the 2010 Consolidated Standards of Reporting Trials statement [35]. All analyses will be carried out following intention-to-treat principles, incorporating data from all participants in their allocated arm, including those who do not complete the intervention.

Primary and Secondary Outcome Analysis

Objective 1

Descriptive statistics will be presented by randomization arm. At baseline and 6 months, these will include counts and percentages for binary and categorical variables and means and SDs or medians with lower and upper quartiles for continuous variables and counts of missing values. Number of adverse events will be presented as the number of events and number of individuals with events by randomization arm and in accordance with the treatment received. We will also report the number of parents in each arm whose anxiety worsens.

For primary and secondary outcomes, we will analyze using multiple linear regression and include a fixed effect for intervention versus control groups, adjusting for baseline child anxiety severity. Other covariates considered—a priori, to be prognostic of outcome at 6 months (particularly parent gender)—may be included in the linear models and written into the analysis plan prior to sign off. Treatment effects (between-group differences) will be reported as the adjusted mean difference with 95% CIs. Cohen *d* effect sizes at 6 months will be calculated as the adjusted mean difference of outcomes divided by the sample SD of the outcome at baseline. Potential moderators will be assessed by including the randomized arm by moderator interactions as fixed effects.

Objective 2

To examine the contribution of each component of the intervention, we will compare those randomized to the intervention containing a given module (eg, module E), to those randomized to the intervention but not containing that component, and to those randomized to the control arm (ie, no intervention). Using the measure of parent behavior congruent with each module as a dependent variable, we will test whether there are differences between these groups each for modules A to H separately (parent behavior measures are shown in Multimedia Appendix 3). For all modules, we will perform a mediation analysis with the primary outcome as the dependent variable and the measure of parenting behavior congruent with that module as a mediator.

Objective 3

The analysis conducted to explore the impact of coparent anxiety and parenting behaviors on child outcomes will be restricted to participants where the coparent agrees to provide data. We will include baseline covariates (their anxiety type and severity and parenting variables) in a linear regression model with randomization as a fixed effect and child anxiety severity along with other variables to be agreed prior to database lock at 6 months as the outcome variable [36]. For scaling data with actively unanswered items, we will either prorate or perform item-level multiple imputation [37].We will perform multiple imputation if we can identify predictors of missingness upon fitting logistic regression models that include variables not present in the analysis models, which may be variables collected post randomization.

Where outcome data are missing (assumed to be missing at random), we will perform multiple imputation using chained equations to create (eg, 10) completed data sets, the analyses of which will be pooled using Rubin's Rules.

A detailed statistical analysis plan will be agreed on prior to final analysis. Analyses will be conducted in Stata (version 17.0 or later; StataCorp) [38].

Ethics Approval

The study has been approved by the University of Sussex Cross Schools Research Ethics Committee (ER/SC430/1) and is registered on ClinicalTrials.gov (NCT04755933) [39]. Peer reviews of the study issued as part of the grant application process can be accessed in Multimedia Appendix 4.

Results

The study was funded in April 2020. Recruitment started in February 2021 and is projected to end in October 2022. A total of 1350 participants have been recruited as of May 2022.

Discussion

This paper describes the protocol for a randomized controlled trial to test the effectiveness of a web-based intervention for parents with anxiety. We hypothesize that children and parents in the intervention arm will show significantly fewer anxiety symptoms (and greater parental well-being) at 6-month follow-up than those in the control arm. Given the extensive data set generated in the study, it is anticipated that the final results will offer valuable evidence on the utility of a web-based course in preventing intergenerational transmission of anxiety, as well as broader evidence regarding familial anxiety, anxiogenic parenting behaviors, and intergenerational transmission.

The findings from this study will be disseminated as follows. Outcomes will be delivered to academic audiences via fully open access journals and conferences (including user conferences). Anonymized data will be entered into a data repository at the end of the study (in liaison with steering and ethics committees). The results will be communicated to the participants and the wider public via a short video. A Plain English summary of the results will be disseminated to all stakeholders and participants and will be published on the study website.

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Data Availability

At the end of the study, anonymized data will be entered into a Figshare data repository [40].

Conflicts of Interest

SC-H designed the digital intervention and funded its development.

Multimedia Appendix 1
Digital intervention content.
[DOCX File , 50 KB - resprot_v11i11e40707_app1.docx]

Multimedia Appendix 2
Intervention images.
[PDF File (Adobe PDF File), 360 KB - resprot_v11i11e40707_app2.pdf]

Multimedia Appendix 3
Intervention measures.
[DOCX File , 46 KB - resprot_v11i11e40707_app3.docx]

Multimedia Appendix 4
Peer review report by The Kavli Trust Programme on Health Research (Bergen, Norway).
[PDF File (Adobe PDF File), 232 KB - resprot_v11i11e40707_app4.pdf]

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Abbreviations

CPBQ: Comprehensive Parenting Behavior Questionnaire
DSM: Diagnostic and Statistical Manual of Mental Disorders
GLAD: Genetic Links to Anxiety and Depression
NHS: National Health Service

NIHR: National Institute for Health and Care Research
SCARED: Screen for Child Anxiety Related Disorders
SCAS: Spence Children's Anxiety Scale

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Proposal

Automatic Detection of Adverse Drug Events in Geriatric Care: Study Proposal

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Abstract

Background: One-third of older inpatients experience adverse drug events (ADEs), which increase their mortality, morbidity, and health care use and costs. In particular, antithrombotic drugs are among the most at-risk medications for this population. Reporting systems have been implemented at the national, regional, and provider levels to monitor ADEs and design prevention strategies. Owing to their well-known limitations, automated detection technologies based on electronic medical records (EMRs) are being developed to routinely detect or predict ADEs.

Objective: This study aims to develop and validate an automated detection tool for monitoring antithrombotic-related ADEs using EMRs from 4 large Swiss hospitals. We aim to assess cumulative incidences of hemorrhages and thromboses in older inpatients associated with the prescription of antithrombotic drugs, identify triggering factors, and propose improvements for clinical practice.

Methods: This project is a multicenter, cross-sectional study based on 2015 to 2016 EMR data from 4 large hospitals in Switzerland: Lausanne, Geneva, and Zürich university hospitals, and Baden Cantonal Hospital. We have included inpatients aged ≥65 years who stayed at 1 of the 4 hospitals during 2015 or 2016, received at least one antithrombotic drug during their stay, and signed or were not opposed to a general consent for participation in research. First, clinical experts selected a list of relevant antithrombotic drugs along with their side effects, risks, and confounding factors. Second, administrative, clinical, prescription, and laboratory data available in the form of free text and structured data were extracted from study participants' EMRs. Third,

several automated rule-based and machine learning–based algorithms are being developed, allowing for the identification of hemorrhage and thromboembolic events and their triggering factors from the extracted information. Finally, we plan to validate the developed detection tools (one per ADE type) through manual medical record review. Performance metrics for assessing internal validity will comprise the area under the receiver operating characteristic curve, F_1-score, sensitivity, specificity, and positive and negative predictive values.

Results: After accounting for the inclusion and exclusion criteria, we will include 34,522 residents aged ≥65 years. The data will be analyzed in 2022, and the research project will run until the end of 2022 to mid-2023.

Conclusions: This project will allow for the introduction of measures to improve safety in prescribing antithrombotic drugs, which today remain among the drugs most involved in ADEs. The findings will be implemented in clinical practice using indicators of adverse events for risk management and training for health care professionals; the tools and methodologies developed will be disseminated for new research in this field. The increased performance of natural language processing as an important complement to structured data will bring existing tools to another level of efficiency in the detection of ADEs. Currently, such systems are unavailable in Switzerland.

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KEYWORDS

adverse drug events; adverse drug reactions; older inpatients; aged 65 and older; multimorbidity; polypharmacy; patient safety; inappropriate prescribing; medication errors; natural language processing; clinical decision support system; automated adverse drug event reporting system; electronic medical record; hospitals; multicenter study; interdisciplinary research; quality of hospital care; machine learning; antithrombotics; venous thromboembolism; hemorrhage

Introduction

Adverse Drug Events in Older Inpatients: A Significant Health Issue

Patient injury resulting from medication use [1,2], also known as adverse drug events (ADEs), is the second most frequent complication experienced by hospitalized patients, accounting for approximately one-third (10%-40%) of all inpatient care-related adverse events [3,4]. ADEs include nonpreventable ADEs subsequent to appropriate care and preventable ADEs (pADEs) resulting from suboptimal care [5]. Between 0.2% and 65% of hospitalized patients experience at least one ADE during their stay [5-9]. This prevalence depends on the selected definition of ADEs, the methods used for their detection, the study size, various risk factors related to the clinical setting (eg, medical or surgical), patient characteristics (eg, age of ≥65 years and polypharmacy), and prescribed drugs [6,8,10,11]. Apart from increasing morbidity and mortality, ADEs have a significant impact on hospital use (ie, increased length of stay and readmissions) and associated costs [2,4,12-15]. Moreover, pADEs, which account for 20% to 50% of all ADEs, are often more serious and associated with increased lengths of stay and costs compared with non-pADEs [2,4,8,13,15].

Older inpatients (aged ≥65 years) and, in particular, oldest-old inpatients (aged ≥80 years) are especially at risk of ADEs and pADEs. Over 30% of these patients experience at least one ADE during their hospital stay, and up to 70% of these events are deemed preventable [8,16-18]. In addition, ADEs have more severe consequences in this population, such as inducing or worsening frailty; causing functional and cognitive disability; and leading to loss of autonomy, more frequent and prolonged hospitalizations, nursing home admissions, and even death [16,17,19]. Finally, ADEs affect patients' hospital care experience and quality of life [19,20]. Given that older patients are hospitals' most frequent users [21,22], ADEs represent an important clinical and economic burden to this population and to health systems [23,24]. Thus, limiting ADEs has become a major patient safety and public health concern worldwide [23].

Antithrombotic Therapy

Cardiovascular drugs, in particular antithrombotic and antihypertensive drugs, are frequently associated with ADEs in older patients. Although recommended and widely used in older patients who are at increased risk of cardiovascular events, antiplatelet and anticoagulant treatments are highly associated with bleeding complications in this population and are a major cause of emergency department admissions and death [25-27]. Thus, antithrombotic therapy is similar to the sword of Damocles, conferring protection against thrombosis while exposing patients to bleeding, with severe consequences in both cases [27]. A recent study indicated that bleeding events were the most common ADE (36%) in patients aged >65 years [28]. The drugs most frequently involved in serious ADEs were antithrombotic agents (31%). Disregarding drug interactions, contraindications, and precautions caused 20% of ADEs, and drug overdoses were present in 17% [28]. In addition, combinations of factors and inefficacy raise particular concerns from an individual and public health point of view [28].

Epidemiology and Risk Management of ADEs in Swiss Inpatients

The Swiss health system is taking an increasing interest in medication safety issues. Few studies have been conducted in Switzerland to assess the incidence of ADEs during hospital stays and ADEs as the cause of hospital admissions [29-32]. A cohort study (Stiftung für Arzneimittelsicherheit or Comprehensive Hospital Drug Monitoring) conducted in the internal medicine departments of Zürich and St. Gallen university hospitals found incidences of ADEs and pADEs of 11.2% and 0.4%, respectively [30,31]. The causative drugs were

antithrombotic and cardiovascular drugs, antibiotics, hypnotics, and nonsteroidal anti-inflammatory drugs. The observed pADE-related mortality was 3 deaths per 100,000 persons annually [30,31]. Another study conducted in 10 hospitals in the canton of Vaud estimated that between 10% and 17% of hospitalized patients were exposed annually to ADEs [32]. In this study, a patient safety improvement program was deployed over 18 months with the aim of reducing ADEs by 20%. After implementing the patient safety program, which entailed patient identification, high-alert medication, and medication preparation in the ward, the annual rate of harmed patients decreased to 7% within 2 years [32]. Another study conducted at Lausanne University Hospital (LUH) found that 7% of all emergency department admissions were caused by ADEs, of which 32% were classified as avoidable. The most frequent ADEs were gastrointestinal bleeding (22.3%) and febrile neutropenia (14.4%) [29]. Similar results were reported in a prospective analysis of reasons for hospital admission in the internal medicine department of the Bellinzona Regional Hospital. The authors estimated that 6.4% of patients admitted over 1 year presented with ADEs at admission and that most of them were potentially preventable. Cardiovascular and cerebrovascular drugs accounted for 65% of ADEs, and the risks of occurrence increased with age, polypharmacy, multimorbidity, and length of stay. The authors finally estimated that, in Switzerland, 12,000 to 16,000 admissions per year were caused by inappropriate or unnecessary treatment, with additional direct annual costs of CHF 70 to CHF 100 million (US $70.8-101.1 million) [33].

ADE Detection Tools

Worldwide, numerous optimization strategies have been adopted to improve the quality and safety of medications prescribed to older patients [4,23,34-37]. Among these are evidence-based specific guidelines [38]; lists of potentially inappropriate medication criteria [37,39]; pharmacist-based interventions, including patient counseling [35]; medication reconciliation; clinical pharmacist rounding; and team-based interventions such as multidisciplinary geriatric teams [35,36,40,41].

The availability of clinical decision support systems within computer provider order entry systems has raised hopes and expectations to improve the safety and efficiency of care [42]. Clinical decision support systems comprise a wide range of functionalities, including medication dosing support, point-of-care alerts or reminders (eg, for drug-drug interactions), or workflow support for medication reconciliation [43-45]. Many studies have reported the positive impacts of such systems on patient outcomes, such as fewer duplicate orders, dosage errors, drug interactions, or delayed actions using reminders [41].

Clinical event monitors are a type of clinical information system with considerable potential to contribute to the detection and monitoring of medication-related problems, in particular ADEs [44]. Such systems provide feedback to clinicians through alerts and reminders when certain signals regarding pharmacy orders (eg, sudden stop orders, antidote ordering, and dose correction orders), laboratory test results, or patient characteristics are triggered [42]. Classen et al [43] developed a computerized method for detecting ADEs that uses signals identified from several types of patient medical record data. This computerized monitor increased >60-fold the detection and reporting of ADEs in hospitalized patients. Owing to growing evidence regarding the benefits of such clinical event monitors, several prominent national organizations have recommended their use to detect ADEs. Compared with voluntary reporting or manual methods of chart reviews, electronic clinical event monitors are faster, less expensive, and often identify ADEs that are not normally detected during the course of routine hospital care [6,44]. However, current clinical event monitors generate many false-positive alerts, target rather inappropriate prescriptions instead of clinically relevant ADEs, and do not consider the type of hospital or unit (eg, medical or surgical) or the patients' characteristics [42,46,47]. In Switzerland, health care facilities have progressively introduced clinical decision support. However, current systems are mostly decision support tools targeting drug dosage or drug-drug interaction or incompatibilities or supporting information from the hospital drug formulary [40,46].

Owing to the poor specificity and overalerting of existing ADE detection tools and the availability of large amounts of structured and unstructured information contained in computer-based patient records, new ADE detection and monitoring systems are currently being developed [47-51]. They are based on multiple sources of data and rely on new methodologies for data processing combining structured data mining (SDM) and natural language processing (NLP). SDM is defined as the process of finding and extracting useful information from semistructured data, whereas NLP is a domain at the crossroads of computer science and linguistics that aims at modeling language to extract meaningful information from free text. Typically, structured data include drug names, doses, treatment durations, administration routes, laboratory results, and diagnostic or procedure codes, whereas reasons for admission, patient histories and conditions, nursing and medical progress notes, inpatient reports, and discharge summaries are essentially available in the form of free text. The use of NLP improves the ability to detect ADEs because the available data sources are often in free text. As a result, structured data analytics have the advantage of being language-independent, though limited by poor specificity and overalerting, whereas free-text analytics have strong power to support ADE detection while strongly depending on language [51]. Tools have already been developed for the English language but are not directly applicable to other languages such as French, German, or Italian, which are 3 of the 4 official languages in Switzerland. As a result, no ADE detection and monitoring system based on electronic medical record (EMR) SDM and NLP is currently available in Switzerland.

Aim and Research Questions

This Swiss national initiative aims to develop and validate a multimodal, multisource, and multicentric approach for the automated detection of antithrombotic-related ADEs and their risk management in older inpatients. Our hypothesis is that the automated detection of ADEs from EMRs using SDM and NLP could significantly improve risk management and patient safety in hospitalized older inpatients with multimorbidity, frailty, and

polypharmacy. This will provide reliable data regarding the incidence of ADEs for health care professionals, patient safety organizations, and policy makers. Thus, the project will comprise complementary steps aimed at (1) quantifying the cumulative incidence of ADEs associated with and caused by antithrombotic drugs; (2) assessing the causality, severity, and preventability of detected ADEs induced by antithrombotic drugs; and (3) developing strategies for the implementation of the project results to improve the risk management of antithrombotic drugs in the hospital setting.

Methods

Overall Design

We will conduct a multicenter cross-sectional study using retrospective medical data (years 2015 and 2016) from the EMRs of 4 large Swiss hospitals. Our project will include 2 hospitals in the French-speaking part of Switzerland (Lausanne and Geneva; LUH and Geneva University Hospital [GUH]) and 2 hospitals in the German-speaking part (Zürich and Baden; Zürich University Hospital [USZ] and Baden Cantonal Hospital [KSB]). Three are large university hospitals (GUH, LUH, and USZ), and one is a smaller cantonal hospital (KSB).

Study Participants

Study participants will consist of all Swiss residents aged ≥65 years who were admitted for >24 hours to 1 of the 4 hospitals between 2015 and 2016 (ie, the inclusion period) and received at least one antithrombotic drug during their stay. We will exclude any patients for whom an explicit refusal to be involved in research projects or give access to their personal health data is documented.

Source Data

This project will use health-related information that is routinely collected during daily practice. Relevant health-related data, as defined in this section, will be extracted by each participating hospital for all patient stays fulfilling the inclusion criteria.

Health-related data include the following: (1) structured data, which encompass each included stay; patient administrative data (eg, age, gender, place of residence, and admission and discharge mode and date); admission unit, diagnosis, and procedure codes (International Classification of Diseases, 10th Revision [ICD-10], and Swiss classification of surgical interventions [CHOP] codes); drug administration orders (eg, drug names, administration dates and times, drug dosages, frequencies, durations, administration routes, and Anatomical Therapeutic Chemical codes); laboratory test orders (ie, test names, time stamps, and samples); laboratory test results (ie, test names, typical ranges, units, results, and time stamps); and imaging and endoscopic test orders (ie, test names and time stamps); and (2) free-text data, including discharge letters, medical and nursing progress notes, pharmacological consultation notes, ADE reports, and all existing local metadata. The extracted variables are presented in Table 1 for structured data. The documents that will be extracted as free text are presented in Textbox 1. Details of the extracted items are presented in Tables S1-S4 in Multimedia Appendix 1.

Table 1. Structured data extracted for the project.

Data type, extracted data, and subcategory	Unit
General administrative data	
Patient identification number (coded)	Category
Case identification number (admission ID, hospitalization ID, or stay ID)	Category
Insurance type	Category
Region of residence (MedStat[a] region)	Category
Admission mode (eg, admission via emergency department, planned admission, or transfer)	Category
Nationality	Category
Date of birth (coded)	Date
Gender	Category
Date of death (if applicable)	Date
Clinical measurements	
Blood pressure	Value
Weight	Value
Height	Value
Sum of alcohol withdrawal syndrome score	Value
Patient location or locations and transfers	
Unit of hospitalization	Category
Transfers (medicine, surgery, intermediate care, and intensive care)	Category
Date and time of admission	Date and time
Date and time of discharge	Date and time
Diagnoses and procedures	
DRG[b] codes	Category
CHOP[c] codes	Category
ICD-10[d] codes	Category
Readmissions and reasons for readmissions (first, second, third, fourth, and subsequent readmissions)	Category
Drugs coded for reimbursement	Category
Intensive care unit length of stay (in hours)	Category
Duration of mechanical ventilation (in hours)	Category
Disease severity and scores	Category
NEMS[e]	Category
Laboratory values[f]	
Electrolytes and ions	
Blood ionogram (sodium and potassium)	mmol/L
Serum lactate and bicarbonate levels	mmol/L
Serum uric acid level	mmol/L
Serum urea level	mmol/L
Serum iron, transferrin saturation, and serum ferritin level	mmol/L and µg/L
Enzymes	
Serum levels of aminotransferases	AST[g] and ALT[h] (UI[i]/L)
Serum levels of 5′-nucleotidase	UI/L

Data type, extracted data, and subcategory	Unit
Serum level of CK[j]	UI/L
Serum level of GGT[k]	UI/L
Serum level of ALP[l]	UI/L
CBC[m]	
Red blood cell count	Absolute value/mm^3
Hemoglobin	mmol/L
Hematocrit	Percentage of total blood volume
Mean corpuscular volume	μ^3
White blood cell count	Absolute value/mm^3
Platelet count	Absolute value/mm^3
Reticulocyte count	Absolute value/mm^3
Hemostasis	
PT[n]	Time
APTT[o]	Time
TT[p]	Time
INR[q]	N/A[r]
Plasma fibrinogen	g/L
Procoagulant balance	Antithrombin (g/L), protein C and S (nmol/L), anticardiolipin antibody (GPL[s] unit), and anti-beta-2-glycoprotein 1 antibody (GPL unit)
Individual coagulation factors	Percentage relative to a reference pool
Fibrinolysis	D-dimer (µg/L)
Anticoagulation monitoring	Anti-Xa (percentage relative to a reference value) and anti-IIa (percentage relative to a reference value)
Markers of coagulation	TAT[t] (ng/mL) and fragment 1 and 2 of prothrombin (percentage relative to a reference value)
Other	
Serum albumin	g/dL
Serum total protein	g/dL
Oxygen saturation in arterial blood	Percentage
CRP[u]	mg/L
Serum myoglobin	µg/L
Serum troponin	µg/L
Serum creatinine and creatinine clearance	mg/L and mL/minute
Serum total bilirubin and direct and indirect bilirubin	mg/L
Serum glycated hemoglobin	Percentage
Serum tumor markers available	N/A
Prescription or medication[v]	
ATC[w] code (and product ID)	Category

Data type, extracted data, and subcategory	Unit
Information on dose and planned administration frequency, including unit (eg, milligrams)	Value and category
Information on administration route (eg, intravenous administration vs oral)	Category
PRN[x] orders (“as needed”: drugs available at patient’s request; eg, analgesics)	Category
Administrations performed (signed by nurses)	Category

[a]MedStat: MedStat regions are geographic areas with a sufficiently large population to anonymously assign a residence to each person hospitalized in Switzerland.

[b]DRG: Swiss Diagnosis Related Groups.

[c]CHOP: Swiss classification of surgical interventions.

[d]ICD-10: International Classification of Diseases, 10th Revision.

[e]NEMS: Nine Equivalents of Nursing Manpower Use Score.

[f]Laboratory results that were ordered or received within the time frame of any of the recorded or extracted stays (if available).

[g]AST: Aspartate aminotransferase.

[h]ALT: Alanine transaminase.

[i]UI: international unit.

[j]CK: creatine kinase.

[k]GGT: gamma-glutamyltransferase.

[l]ALP: alkaline phosphatase.

[m]CBC: complete blood count.

[n]PT: prothrombin time.

[o]APTT: activated partial thromboplastin time.

[p]TT: thrombin time.

[q]INR: international normalized ratio.

[r]N/A: not applicable.

[s]GPL: immunoglobulin G [IgG] phospholipid unit.

[t]TAT: thrombin-antithrombin III complex.

[u]CRP: C-reactive protein.

[v]All medication orders that have (1) a planned start date ≤discharge date AND (2) a planned discontinuation date ≥admission date.

[w]ATC: Anatomical Therapeutic Chemical.

[x]PRN: Pro re nata.

Textbox 1. Free texts and narratives extracted for the project.

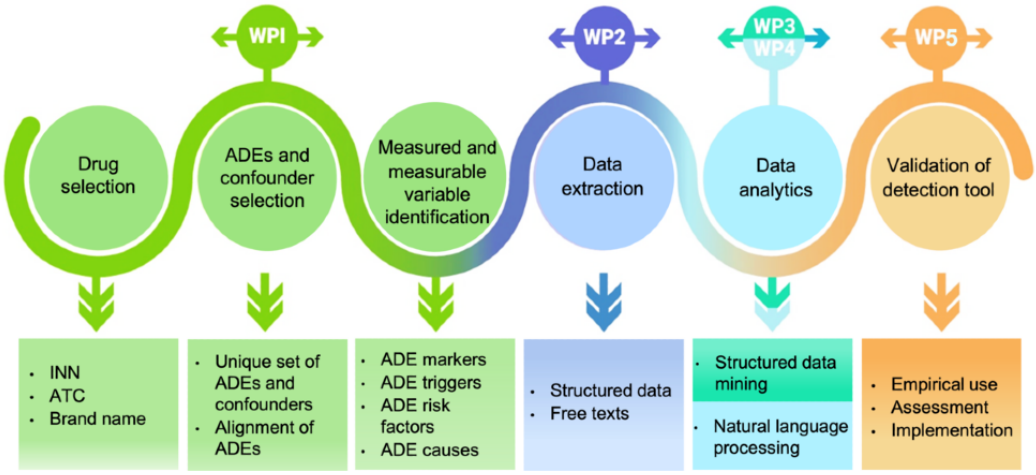
Extracted free-text data

- Patient identification number (metadata)
- Case identification number (admission ID, hospitalization ID, or stay ID, metadata)
- Notes taken at admission
- Discharge summaries and letters
- Nurses’ progress notes
- Imaging and radiology reports
- Specialists’ (eg, hematologist, cardiologist, angiologist, and particularly endoscopy reports) consultation notes
- Clinical pharmacology or pharmacy service consultation notes
- Adverse drug event or pharmacovigilance reports
- Critical incidence reporting system reports

Data Analysis

The overall strategy includes the development of automated detection tools that will provide quantitative measures and triggers of ADEs associated with antithrombotic drugs and the elaboration of measures for implementation, replication, and prevention (Figure 1). A total of 5 work packages (WPs) will provide answers to these objectives.

Figure 1. Schematic framework of the SwissMADE project. ATC: Anatomical Therapeutic Chemical; INN: international nonproprietary name; work package (WP) 1: drug selection and adverse drug event (ADE) marker and trigger definition and selection; WP 2: data extraction and management; WP 3: algorithm generation based on structured data; WP 4: resource and algorithm generation for free-text data; WP 5: ADE detection tool assessment.



Drug Selection and ADE Marker or Trigger Definition and Selection From the Literature (WP 1)

Five different classes of antithrombotic drugs (approved and licensed in Switzerland) will be considered: heparins (eg, unfractionated heparins and low–molecular-weight heparins), vitamin K antagonists (eg, coumarin derivatives), directly acting oral anticoagulants and fondaparinux (eg, direct thrombin and factor Xa inhibitors), and antiplatelet drugs. The list of selected drugs is provided in Table S4 in Multimedia Appendix 1. For each administration of an antithrombotic drug during each inpatient stay, we will retrieve the following information from the corresponding EMR: international drug name; active pharmaceutical ingredient; Anatomical Therapeutic Chemical code; approved therapeutic regimen (eg, dose, range, frequency, and duration); pharmacokinetics (eg, absorption, primary metabolism pathways, and elimination); and potential drug-drug or drug-disease interactions, indications, and contraindications.

To identify thromboembolic and hemorrhagic ADEs caused by antithrombotics, we will first develop direct and indirect indicators of ADEs (Textbox 2). Potential clinical and biological antithrombotic-related ADEs will be assembled from clinical guidelines and standard pharmacological references, including Swiss medic product information, Lexicomp, Martindale, and Meyler's Side Effects of Drugs encyclopedia [52]. We will focus on 3 types of ADEs in particular: hemorrhages and venous and arterial thromboembolisms, which will be defined according to international references [53-55].

Similarly, potential confounding factors in the causal relationship between antithrombotic drugs and related ADEs will be identified from scientific literature. They will include concomitant drugs (eg, drugs that modulate up or down the coagulation process or affect the metabolism or elimination of anticoagulants), patient characteristics (eg, congenital deficit in coagulation factors), and concomitant health conditions (eg, cirrhosis and kidney failure).

Finally, relevant ADEs and confounding factors will be selected using a modified Delphi method, which combines the summarized evidence with the collective judgment of an expert panel [56-58]. The panel will comprise geriatricians, pharmacologists, pharmacists, and internists from the research team. These experts will assess several statements on ADE characteristics during a 2-round process. These characteristics will comprise clinical significance, association with quality of care, and relevant confounding factors. The first round will consist of an individual remote rating with no interaction among the panelists. During the second round, the experts will meet and reach a consensus on ADE selection and relevant confounding factors. In each round, each panelist will receive an individualized document showing the distribution of all the experts' ratings together with the panelist's specific ratings.

Textbox 2. Direct and indirect adverse drug event (ADE) indicators.

ADE indicators

- ADE markers: clinical signs or symptoms, diagnostic or treatment procedures, prescription and imaging orders, and biological test results indicating that an antithrombotic-related ADE occurred (ie, event)
- ADE triggers: diagnostic procedures, prescription and imaging orders, and biological test results that indicate that an antithrombotic-related ADE should have occurred but did not (ie, near miss)
- ADE confounding conditions and risk factors: conditions or factors that increase the risk of antithrombotic-related ADEs or the occurrence of a spontaneous bleeding or thrombotic event; risk factors include patient characteristics, specific concomitant health conditions that may interact with antithrombotic drugs, and concurrent use of more than one antithrombotic drug

Data Extraction and Management (WP 2)

Overview

Structured data and free texts will be extracted from EMRs by the IT department of each hospital. Before being processed, structured data will be standardized in a unique common format (see the common data model in Tables S1-S4 in Multimedia Appendix 1), and unstructured data will be transformed into a machine-readable format when necessary.

Owing to the multisite and bilingual (ie, French and German) nature of the project, we will use a centralized and decentralized data governance strategy. A 2-step approach will be undertaken for data processing.

Step 1 (Decentralized Data Processing)

Raw data from the study participants' EMRs will be managed and processed by the IT team of each hospital according to established protocols. Nominative identifiers of the structured data will be coded, and a table of correspondence between the original and coded identifiers will be stored on a protected server of each IT team. There are 18 identifiers to delete as described in the Health Insurance Portability and Accountability Act Privacy Rule, Code of Federal Regulations [59] Title 45: Public Welfare, Subtitle A §164.514. Free-text data of the learning set will be deidentified and coded locally by an encryption software before being transferred to secured servers dedicated to the project within each hospital.

Step 2 (Centralized Data Processing)

Locally extracted coded data of the learning set from the German-speaking part of Switzerland (USZ and KSB) and the French-speaking part (LUH and GUH) will be transferred to a centralized common SwissMADE database (DB). After proof of deidentification, structured items from free texts and narratives will be transferred to the SwissMADE DB. One authorized person per site will be allowed access to personal data and will decide who can access which data linked to which analysis. Remote access to the local working DBs within each hospital and the SwissMADE DB to authorized investigators will be made possible through a virtual private network.

Data Analysis (WP 3 and 4)

Part of the structured and unstructured data will be used to develop ADE detection algorithms (working set), and another part will be used for validation (validation set). To test the algorithms' accuracy, we will randomly select a validation data set to verify in the corresponding EMRs (gold standard) whether an ADE has truly occurred. As a result, the algorithms will be improved according to the results of the validation (ie, maximization of sensitivity and specificity as well as of positive predictive values [PPVs] and negative predictive values [NPVs]). Finally, validated algorithms will serve to identify ADEs accurately (ie, validated outcomes). For each 2015 and 2016 hospital stay of patients aged ≥65 years treated with antithrombotics, we will obtain a Case ID of positive ADE detected from the developed algorithms based on structured data (SDM), free-text data (NLP), and both types of data (SDM+NLP).

Elaboration of Algorithms Based on Structured Data (WP 3)

Computational algorithms based on logical rules applied to structured data will be developed to identify ADE markers, triggers, confounding conditions or risk factors, and causes. Detection algorithms for clinical markers of ADEs (ie, hemorrhagic events or thromboembolism) and confounding clinical conditions (eg, chronic liver or kidney disease, hypertension, diabetes, cancer, and multimorbidity) will target ICD-10-German Modification diagnostic codes in hospital discharge data [60-62]. Regarding ADE triggers, clinical conditions (eg, hypotension, shock, and acute kidney failure) and procedures (eg, postoperative control of hemorrhage, drainage of hematoma, or surgical treatment of venous or arterial thromboembolism) will be identified from hospital discharge data using algorithms based on ICD-10-German Modification diagnostic codes and CHOP codes, respectively. Biological triggers of ADEs (ie, abnormal laboratory values) will be detected by algorithms applied to laboratory test results. Similarly, some algorithms based on prescription orders will search for pharmacological triggers of ADEs, including sudden medication stop orders, antidote ordering, dose correction orders, underdosing and overdosing, misprescribing, insufficient monitoring, and drug-drug or drug-disease associations.

In addition to the rule-based algorithms, data-driven algorithms will be created from the same data. Thus, we will perform predictive modeling of ADEs using penalized and nonpenalized logistic regression models with backward selection of predictors based on the Akaike information criterion and supervised and unsupervised machine learning approaches (eg, random forest, cluster analysis, and neural networks).

Elaboration of Resources and Algorithms for Free-Text Data Processing (NLP; WP 4)

Overview

To develop models for classifying free-text discharge summaries as containing or not containing an ADE, multiple approaches will be considered. We divide these approaches into 2 categories: *pure NLP* approaches that require little to no medical or pharmaceutical expertise and hybrid approaches that are performed in close collaboration with medical and pharmaceutical experts. Both types of approaches require that we have access to a data set of discharge summaries that have been classified as containing or not containing an ADE. Pure NLP approaches include but are not limited to word and document embeddings, Bidirectional Encoder Representations from Transformers (BERT) for document classification, and other modern NLP methodologies. For hybrid approaches, we wish to build a named-entity recognition (NER) model that automatically annotates discharge summaries with various entities related to and relationships with ADEs. NER is a well-studied task in NLP in which a model learns to detect and label the mention of any predefined entity (ie, symptom, disease, and drug) in a span of unstructured text. Such a model will provide us with structured information from the free text that we could then exploit by designing rule-based algorithms or machine learning classification models using the entities as derived features. We note that more methods may be used to

develop better classification models depending on the classification scores obtained using the aforementioned methods.

Pure NLP Approaches

These approaches require only a set of discharge summaries classified as containing or not containing an ADE. We can then, upon some preprocessing of the summaries, apply various NLP methods for classification. Popular methods include word and document embedding, BERT for document classification, and other modern approaches.

Word embeddings (respectively document embeddings) are a class of functions that transform a high-dimensionality space of words (respectively documents) into information-rich vectors in a lower-dimension embedding space, which can be used for evaluating the word-to-word (respectively document-to-document) similarity or used as a feature for more complex models. Recently, there have been promising results for several document classification tasks such as patient classification [63] or legal document classifications [64]. BERT [65] is a language model published in 2019 that can be used for a variety of tasks such as translation [66], question answering [67], and document classification. Although the original BERT model is based on the English language, French and German variants have since been published [68-70].

Hybrid Approaches

In this approach, we wish to leverage medical and pharmaceutical expertise to complement NLP methods. This hybrid approach can be seen as approximating the behavior of an expert classifying a discharge summary as “containing” or “not containing” an ADE. As a first step, we build an NER model to highlight various entities and connections that are highly related to ADEs in the discharge summaries. We focus on the following entities: antithrombotic drugs, other drugs, dosages, risk factors, hemorrhagic events, and thrombotic events. We also identify the relationships between a drug and its corresponding dosage as well as hemorrhagic and thrombotic events that happened in the past and not during the hospital stay. Already, domain expertise is required to build dictionaries of drugs and risk factors for the events we wish to detect. These sets of concepts will be organized in a coherent and pertinent taxonomy validated by pharmacologists, pharmacists, and geriatricians from the research team. To build an NER model, we rely on data annotated with the various entities that we want to predict. To work with gold-standard annotated data, we follow a robust annotation protocol inspired by Gurulingappa et al [71], which guarantees consistency between different annotators. Indeed, highly technical annotations such as those we are performing in our context can lead to disagreements between annotators. We mitigate this risk through several rounds of protocol harmonization as well as annotation review—each letter is independently annotated by 2 annotators and then reviewed by a third annotator. To build the NER model, we can rely, for instance, on the 2018 National NLP Clinical Challenges shared task [72]. This shared task focused on the detection of ADEs and related entities from clinical records. It led to breakthrough results (best overall F_1-score of 0.94 on similar entities), and we intend to replicate some of the methods on our French and German corpora. We will also leverage new language models that have arisen since, such as BERT (and, more specifically, its French and German counterparts). With a data set of discharge summaries that have been classified as “containing” or “not containing” an ADE, we can then use features extracted with our NER model to train a machine learning classification model. We can also design rule-based algorithms based on domain expertise.

Eventually, NLP models for text annotation and ADE detection will be deployed as part of a pipeline that takes raw clinical text as input and outputs annotated text files with a list of detected ADEs, confounding conditions, and their probability scores.

ADE Detection Tool Assessment (WP 5)

To assess the performance (eg, sensitivity, specificity, PPVs, and NPVs) of the ADE detection tool, a validation will be performed on a random sample of 600 hospital stays. ADE occurrence, type, causality, severity, and preventability will be assessed by means of a patient medical record review and analyzed by a team of pharmacologists, pharmacists, and geriatricians from the research team.

To ensure that the ADE assessment and data abstraction are structured and reliable, pharmacologists and pharmacists from the research team will develop a common ADE assessment form both in French and German based on existing good pharmacovigilance practice rules that will be disseminated in its original languages and English after study completion. Pairs of trained clinicians (eg, pharmacists, pharmacologists, and geriatricians) will then assess all selected medical records using this form. The causality between taking a drug and the advent of an ADE will be assessed using existing causality assessment scales [73,74]. The severity of the ADEs will be scored according to the Common Terminology Criteria for Adverse Events. Finally, an ADE will be deemed preventable if it was caused by a medication error that occurred during prescribing, transcribing, dispensing, administering, and monitoring or if it was due to a lack of medication adherence [75].

To test the reliability of the ADE assessment by pharmacists and pharmacologists, we will calculate intra- and interrater agreements for overall ADE occurrence, causality, severity, and preventability. For each pair of trained pharmacists and pharmacologists, the interrater agreement will be tested by comparing the results of the ADE assessment between members of the pair. To test for intrarater agreement in each participating hospital, a random sample including 100 ADEs detected by SDM and NLP will be reassessed by the assigned pair 3 months after their first assessment. For both intra- and interrater agreements, the measure of agreement will be the Cohen or uniform κ statistic [76]. After excluding false-positive ADEs, we will measure the cumulative incidence of true positive pADEs and nonpreventable ADEs for each hospital and medical unit as well as overall.

Ethics Approval

The research project was approved by all cantonal ethics commissions involved in the project: Commission cantonale d'Ethique de la Recherche sur l'être humain Vaud" (CER-VD), Ethikkommission Nordwest- un Zentralscheiz (EKNZ), Commission cantonale d'éthique de la recherche Genève (CCER)

and Kantonale Ethikkommission Zürich, under approval CER 2018-00272. Obtaining ethical permission is necessary for every study involving human participants. A method in which study participants can be satisfied that potential hazards have been evaluated, minimized, and declared acceptable is through the ethical review process.

Results

Health Data and Study Populations

After accounting for the inclusion and exclusion criteria, we will include 34,522 residents aged ≥65 years in our study (n=5888, 17.06% from LUH; n=11,581, 33.55% from GUH; n=8986, 26.03% from KSB; and n=8067, 23.37% from USZ).

Sample Size Calculation for Geriatric Patient Safety Indicators Criterion Validity Assessment

The sample size was estimated to assess the performance of the SDM+NLP tool in detecting hemorrhagic adverse events. Indeed, the SDM+NLP tool is considered the critical outcome determining project feasibility, and hemorrhage is considered the most important adverse event related to antithrombotic drugs. We used a test result–based sampling method to minimize the number of medical records to be abstracted [77]. Given that CI is the cumulative incidence of ADEs detected from both structured and unstructured data, N is the number of 2016 hospital stays of patients at risk (ie, patients aged ≥65 years treated with antithrombotic drugs), p(ADE+) is the proportion of hospital stays with an ADE detected by the SDM+NLP tool among all at-risk hospital stays (calculated as the number of true positive and false-positive ADEs detected divided by N), Se is the expected sensitivity of the SDM+NLP tool, Sp is the expected specificity of the SDM+NLP tool, PPV, and NPV. We calculated the sample sizes for CI ranging from 3% to 24%, a desired Se of 80%, a 20% width for the 95% CI of Se, volumes of at-risk hospital stays ranging from N=2000 to N=20,000, and a balanced sample of ADE+ and ADE−hospital stays (ie, hospital stays with and without ADEs, respectively; Textbox 2). CI values were obtained from the literature (ie, a range of 30%-40% for ADE cumulative incidence and a range of 10%-40% for proportion of hemorrhagic ADEs among ADEs). The values of N were estimated from annual numbers of at-risk stays in the 4 participating hospitals. In particular, we considered selecting hospital units with a high prevalence of antithrombotic prescriptions (ie, acute geriatric unit, internal medicine, cardiology, angiology, orthopedic surgery, thoracic surgery, and cardiovascular surgery), which would increase the number of at-risk stays. The frequencies of 2015 at-risk stays in these selected units were 4711, 5130, 5564, and 5016 for LUH, GUH, USZ, and KSB, respectively (N=20,421). Therefore, we made the assumption that the number of at-risk stays for the 2015 to 2016 period would approximate 40,000. The sample size calculation was performed using Stata IC (version 14; StataCorp LLC). Thus, assuming CI equals 10% and p(ADE+) equals 12%, with 40,000 at-risk hospital stays and an expected Se equal to 80% with a 20% width for its 95% CI, a random sample of at least 523 medical records (51 ADE+ medical records and 472 ADE–medical records) will be necessary to assess the SDM+NLP tool. Considering that some medical records might not be available (perhaps 1%), the validation will finally require 530 medical records. Thus, we will abstract 15 medical records flagged as ADE+ and 120 medical records flagged as ADE–by the SDM+NLP tool during the 2015 to 2016 period in each of the 4 participating hospitals (135 medical records per hospital). Under these assumptions, the expected values and CIs for Se, Sp, PPV, and NPV should be as follows: Se=80% (95% CI 68%-88%), Sp=96% (95% CI 94%-97%), PPV=67% (95% CI 52%-79%), and NPV=98% (95% CI 96%-99%).

Regarding the external validation of predictive models, we will compare predicted outcomes with true outcomes based on medical record screenings for a small sample of 20 to 30 hospital stays for which predicted and validated outcomes diverge.

Project Timetable

All structured and free-text data are now available to all research teams. However, the planned time frame for data extraction and the start of analyses was delayed by almost 1 year because of difficulties in obtaining approval from the 4 ethics committees. We also underestimated the challenges and time required to extract data from the 4 participating hospitals. Hospital information systems are not interoperable, so we had to provide additional resources to meet this challenge during 2021 and 2022. In addition, the barriers to data transfer or sharing from these hospitals despite ethics approval were highly unexpected. The data are being analyzed in 2022. We have completed ADE identification rules based on coded data (ICD-10 and CHOP codes) for all ADEs. Similar procedures will be applied to quantify the frequency of other ADEs related to antithrombotics and evaluate whether additional sources of information (laboratory values, drug prescriptions, and free text) will improve the detection algorithms. Tools for automatic annotation of free text (eg, exit letters) were developed in late 2021 and mid-2022 for the automated annotation of free texts (ie, discharge letters). They focus on drugs and symptoms for the German-language–based pipeline and on drugs, events, and risk factors for the French-language–based pipeline. These tools are in the validation phase in mid-2022, consisting of the “manual” revision and annotation of 600 (ZH) and 300 (CHUV) documents. Several machine learning models were trained and tested on a data set of 334 documents. Dictionaries specific to the medical languages encountered in these documents have been developed to explore the texts using both rule-based and machine learning algorithms. The research project will run until the end of 2022 to mid-2023.

Discussion

Overview

This interdisciplinary and integrative project involves 4 hospitals and experts with a background in different disciplines. Apart from the core competencies in clinical research and pharmacology, extracting meaningful information from electronic health records requires competencies in data analysis and NLP. First, we ensured data availability at each participating hospital. Moreover, summary statistics provided by each hospital show a good representativeness of the target population and of the medical or surgical units. The choice of antithrombotic drugs in the geriatric population should guarantee sufficient data to

build the SDM and NLP tools. Although some feasibility risk exists with the NLP part of the project (ie, suboptimal specificity and sensitivity), the information gathered during the NLP process and all other project components (pharmacology and SDM) will provide new and relevant data on the safety of antithrombotics in the geriatric population.

This is the first study aiming at developing and validating a reliable automated tool to detect ADEs in older hospitalized patients using different data sources in Switzerland. Currently, only structured data are considered of value for the computerized patient record. However, the use of natural interfaces such as language analytics, which is being developed for the English language, has yet to expand to the German and French landscapes of health care systems. Assessing the quality and safety of antithrombotic therapy in older inpatients based on such data is innovative. This project will be able to leverage the importance of expressiveness in clinical free text and narratives by demonstrating that an analytical approach is applicable to such sources, thus fostering the possibility of using them for numerous other purposes such as within the Swiss Personalized Health Initiative.

The greater understanding of the development of ADEs as a result of antithrombotic therapies, including the identification of important contributing factors, the early recognition of repeating events, and the setting up of preventative measures for sustained risk reduction, will have a major impact on the increasing population of older patients in hospitals and at particular risk of toxicity. Although antithrombotic therapy is highly recommended and commonly prescribed in the older adult population [27], antiplatelet and anticoagulant treatments have been shown to be highly associated with bleeding complications [25-27], which are a major cause of emergency department admissions and mortality in this population [27,78]. Vulnerable older inpatients experience more ADEs compared with younger adults. These adverse events result in considerable morbidity and mortality and frequent institutionalization. They also considerably affect patients' quality of life and their confidence in the health care system and health care professionals. Some ADEs cannot be prevented, but most are associated with poor patient safety and quality of care [2,16,23,79,80]. Moreover, older patients are underrepresented in trials, and accurate information regarding the benefit-risk balance of most drugs in this population is limited [22,23,27,29,35,36]. Classen et al [6] wrote that "identification and measurement of adverse medical events is central to patient safety, forming a foundation for accountability, prioritizing problems to work on, generating ideas for safer care, and testing which interventions work." We also claim that detecting and monitoring ADEs in older inpatients, in particular pADEs, is the most important step to reducing age-related disparities in patient safety and, therefore, health inequities.

The technical and methodological aspects of the project (with multimodal, multisource, and multicentric data management) are the third strong point of the study. Owing to the multicomponent and multisite nature of the project, all organizational aspects to ensure effective scientific interactions between disciplines and hospitals throughout the research process will be disseminated for the Swiss research community. The algorithms used for SDM and NLP with all key information on data extraction and data mining will be made available (as open source) for further developments of medical NLP tools. Logical rules developed for SDM and the text-mining pipeline are electronic applications that can be directly implemented in hospital information systems. However, adapting automated detection tools to various hospital information systems and ADEs has proven to be difficult, but our ambitious and stepwise project will benefit from an interdisciplinary and experienced research team. We will focus on the 5 most clinically significant antithrombotic drug classes and plan to extend this project to other drug classes in the future. This tool could be implemented within EMRs and completed by e-alerts and reminders notifying providers of probable ADEs. It may also feature an automated causality assessment facilitating pharmacovigilance reports. This automated version of the Global Trigger Tool may help improve adverse drug effects and reaction reporting to local pharmacovigilance centers—and, therefore, to the Swiss authority for therapeutic products—while consuming fewer resources and being faster than the manual version currently in use.

Finally, our project is consistent with the Swiss Federal Council "Health 2030" agenda that advocates for "better data" to inform health policy and patients' choice and improve quality [81], safety, and efficiency in vulnerable patients, particularly in older inpatients at high risk of developing ADEs. Although ADE reporting by health care professionals has regularly improved between 2002 and 2019, Swissmedic suspects considerable underreporting. Frequent and common adverse drug reactions (ADRs), even severe ones, are less subject to professionals' focus than rare and new events [82]. Therefore, ADRs only partially reflect the real ADE prevalence. Presuming that the nationwide pharmacovigilance DB collects ADRs that are subject to selection and underreporting and given the lack of systematic ADE reporting and monitoring in Swiss hospitals, new strategies encompassing more comprehensive and systematic detection of ADEs are needed.

Conclusions and Perspectives

This innovative study aiming to develop and validate an electronic application for the automated detection of ADEs related to antithrombotics will allow for the introduction of measures aimed at improving safety when prescribing antithrombotic medication. The increased performance of NLP as an important complement to structured data will bring existing tools to another level of efficiency in the detection of ADEs. Currently, such systems are not available in Switzerland, nor can "ready-made" systems from other countries be adapted as they are language-dependent. We hope that, in the near future, with these new types of tools developed for the French and German languages, the specificity of alerts will be improved, notifications will be prioritized, and clinical decision support will become more patient-centered.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary tables.
[DOCX File , 118 KB - resprot_v11i11e40456_app1.docx]

Multimedia Appendix 2
Evaluation of the protocol by the Swiss National Science Foundation.
[PDF File (Adobe PDF File), 92 KB - resprot_v11i11e40456_app2.pdf]

Multimedia Appendix 3
Decision on the protocol submitted to the Swiss National Research Fund.
[PDF File (Adobe PDF File), 125 KB - resprot_v11i11e40456_app3.pdf]

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Abbreviations

ADE: adverse drug event
ADR: adverse drug reaction
BERT: Bidirectional Encoder Representations from Transformers
CHOP: Swiss classification of surgical interventions
DB: database
EMR: electronic medical record
GUH: Geneva University Hospital
ICD-10: International Classification of Diseases, 10th Revision
KSB: Baden Cantonal Hospital
LUH: Lausanne University Hospital
NER: named-entity recognition
NLP: natural language processing
NPV: negative predictive value
pADE: preventable adverse drug event
PPV: positive predictive value
SDM: structured data mining
USZ: Zürich University Hospital
WP: work package

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Protocol

Characterization of the Viral Reservoirs Among HIV-1 Non-B Vertically Infected Adolescents Receiving Antiretroviral Therapy: Protocol for an Observational and Comparative Study in Cameroon

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Abstract

Background: Antiretroviral therapy (ART) can bring HIV-1 levels in blood plasma to the undetectable level and allow a near-normal life expectancy for HIV-infected individuals. Unfortunately, ART is not curative and must be taken for life, because within a few weeks of treatment cessation, HIV viremia rebounds in most patients except for rare elite or posttreatment controllers of viremia. The primary source of this rebound is the highly stable reservoir of latent yet replication-competent HIV-1 proviruses integrated into the genomic DNA of the resting memory cluster of differentiation 4 (CD4+) T cells. To achieve a cure for HIV, understanding the cell reservoir environment is of paramount importance. The size and nature of the viral reservoir might vary according to the timing of therapy, therapeutic response, ART duration, and immune response. The mechanisms of reservoir maintenance generally depend on the levels/type of immune recognition; in addition, the dynamics of viral persistence are different between pediatric and adult populations. This difference could become more evident as children grow toward adolescence.

Objective: We aim to characterize the HIV reservoirs and their variability as per the virological and immunological profiles of HIV-1 non-B vertically infected adolescents receiving ART in Cameroon during the Adolescents' Viral Reservoirs study to provide accurate and reliable data for HIV cure research.

Methods: This study will involve HIV-1 non-B vertically infected adolescents selected from an existing cohort in our institution. Blood samples will be collected for analyzing immunological/virological profiles, including CD4/CD8 count, plasma viral load, immune activation/inflammatory markers, genotyping, and quantification of HIV-1 viral reservoirs. We will equally recruit an age-matched group of HIV-negative adolescents as control for immunological profiling.

Results: This study received funding in November 2021 and was approved by the national institutional review board in December 2021. Sample collection will start in November 2022, and the study will last for 18 months. The HIV-1 sequences generated will

provide information on the circulating HIV-1 subtypes to guide the selection of the most appropriate ART for the participants. The levels of immune biomarkers will help determine the immune profile and help identify factors driving persistent immune activation/inflammation in HIV-infected adolescents compared to those in HIV-uninfected adolescents. Analysis of the virological and immunological parameters in addition to the HIV-1 reservoir size will shed light on the characteristics of the viral reservoir in adolescents with HIV-1 non-B infection.

Conclusions: Our findings will help in advancing the knowledge on HIV reservoirs, in terms of size and genetic variability in adolescents living with HIV. Such evidence will also help in understanding the effects of ART timing and duration on the size of the reservoirs among adolescents living with HIV—a unique population from whom the findings generated will largely contribute to designing functional cure strategies.

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KEYWORDS

HIV; viral reservoirs; adolescents; vertical infection; Cameroon

Introduction

Importance and Relevance

Sub-Saharan Africa is disproportionally affected with HIV/AIDS, with close to 70% of the global epidemic and the highest burden of pediatric HIV infections; about 9 out of every 10 children living with HIV is found in the Sub-Saharan African region [1,2]. Due to combination antiretroviral therapy (ART) benefits, adolescents and young people represent a growing share of people living with HIV worldwide. In 2019, about 1.7 million adolescents between the ages of 10 and 19 years were living with HIV worldwide, representing about 5% of all people living with HIV; about 1.5 million or 88% of HIV-infected adolescents live in Sub-Saharan Africa. In 2019 alone, 460,000 young people between the ages of 10 and 24 years were newly infected with HIV, of whom 170,000 were adolescents. Of the estimated 690,000 people who died of AIDS-related illnesses in 2019, 110,000 (or approximately 16%) of them were children younger than 20 years, including 32,000 aged 10-19 years [2,3].

With the advent and scalability of ART, there is a global decrease in AIDS-related deaths. As of June 2021, 28.2 million [3] people were accessing ART, representing 73% of all people living with HIV. However, only 54% of the children living with HIV were receiving ART. Interestingly, about 94% of all the children receiving ART are from Sub-Saharan Africa [4]. In this context of continuous new HIV pediatric infections and increasing coverage in pediatric ART, the number of children living with HIV will increase, suggesting a higher likelihood of reaching adolescent age and even adulthood if treatment regimens remain fully effective in controlling HIV infections [3,4]. Adolescents living with HIV (ADLHIV) therefore constitute an HIV population with growing health concerns and with very limited findings for generalizable best practices specific to this target population, especially in Sub-Saharan Africa.

Cameroon still faces a generalized HIV epidemiology (2.7% prevalence) [5], with higher prevalence among pregnant women (5.7%) and HIV-exposed infants/children (5.8% positivity at first polymerase chain reaction [PCR] and 15% at the end of the prevention of mother-to-child HIV transmission cascade) [6]. As of December 2020, the national coverage of ART was 74% (or 367,871 HIV positive), which includes 12,017 children (35% coverage) younger than 15 years [6]. Regarding response to ART in Cameroon, an overall rate of 79.4% viral suppression was reported, with significant disparities across age ranges: 81.1% in adults, 75.6% in children, and only 53.3% in adolescents aged 10-19 years [7]. Similar to that reported by the Joint United Nations Programme on HIV/AIDS, ADLHIV represent the most vulnerable and underserved population in response to the epidemic [1,5]. For a safer growth toward adulthood, there is need to prioritize this population for the quest of innovative treatment strategies that ensure their well-being and their contribution to the development of Sub-Saharan Africa.

Despite the unquestioned benefits of ART, there are limitations with current treatment strategies. Of note, the lifelong nature of current ART goes with challenge-related adherence for most patients, ART-attributed toxicities and persisting immune dysfunction in patients lead to significant health impairments, and HIV drug resistance is increasing, mostly in Sub-Saharan African countries where most ART-experienced patients are living [8]. There is a threat of an emerging new HIV epidemic, driven by HIV drug resistance to existing antiretrovirals. These challenges are particularly true for pediatric populations due to limited ART options, poor drug formulations, and increasing events of nonadherence as they grow toward adolescence. These challenges call for approaches toward HIV (functional) cure or remission, especially for the most vulnerable populations (ie, ADLHIV) [7,9].

Concepts Underpinning the Project Including Ideas and Models or Assumptions

HIV-1 remission or eradication strategies aim to achieve durable control of the virus in the absence of ART. The development of an HIV-1 cure remains challenging due to latent reservoirs. The latter can be defined as the fraction of cells harboring transcriptionally silent proviral DNA that can produce infectious virions following activation [10]. Resting memory cluster of differentiation 4 (CD4) T cells are the primary host of the latent reservoir, but HIV-1 infection in these cells is inefficient due their low coreceptor expression and inherent restrictions to reverse transcription [11,12]. The provirus is maintained in a latent state in these cells via host factors due to integration into

the expressed genes [13]. Viral rebound from the latent reservoir following ART cessation is rapid, leading to detectable viremia within weeks of therapy interruption [14]. Initiating ART early during infection is not sufficient to stop the formation of the latent reservoir, suggesting that the latent reservoir is established and disseminated early [15], even in vertically infected children who started ART soon after birth [16]. Despite years of suppressive ART, the latent reservoir is stable and is the source of rebound viremia following therapy interruption. Latently infected cells therefore represent a critical barrier to HIV-1 cure. The progress toward the development of a functional or sterilizing cure (virus remission/eradication) for HIV-1 has been significantly hindered by the presence of the latent reservoir. Therefore, understanding of where and how HIV persists in individuals on ART has transformed substantially with evidence that the virus persists in multiple cell types and tissue sites. Thus, in the frame of virological success during ART, accurate estimates of the viral reservoir would help in better mastering of viral persistence, which in turn might overcome existing barriers for achieving a complete cure [17].

Total HIV DNA is a reference biomarker that includes both integrated and unintegrated HIV DNA and reflects the global level of the viral reservoir. Buzon et al [18] reported a statistical correlation between the time from the start of the HIV infection to treatment initiation and the total HIV DNA level after 10 years of continuous treatment in a cohort of adults first treated with early infection [19]. In children, the HIV DNA level was markedly lower when viral control was achieved before the age of 1 year [18]. By comparison with other markers, total HIV DNA has the advantage of easy quantification by standardized, sensitive, real-time PCR, including digital droplet PCR [20].

Generalized immune activation is typically related to HIV-1 infection. A variety of immune cells show an increase in the expression of activation and production of proinflammatory cytokines [21,22]. Immune activation is associated with HIV-1 disease progression; suppression of viral replication with effective ART reduces immune activation, but even effective ART regimens are unable to bring it to levels seen in healthy individuals [21]. HIV-infected children, even if successfully treated with ART regimens, face a lifetime of elevated immune activation; evaluating the potential impact of this chronic immune activation and inflammation on their immune system and on disease outcome is very important [23]. Recent studies showed that immune activation and exhaustion markers are strongly associated with the reservoir size in ART-treated adults; thus, it might be anticipated that minimizing the viral reservoir with early ART might equally minimize the level of immune activation [23,24].

There is limited evidence in characterizing HIV reservoirs in the western and central African region—a geographical setting having the highest variability in circulating HIV-1 and HIV-2 strains [25,26]. For example, Cameroon, a zoonotic epicenter of HIV-1, is host to an extensively diverse landscape of HIV driven by the CRF02_AG recombinant, including most group M (sub-) subtypes, a vast array of unique recombinant forms, circulating recombinant forms, group N, group O, group P, and HIV-2 viruses [27-29]. Thus, generating baseline data on the genotypic and quantitative profile of the viral reservoir across several HIV clades in settings like Cameroon would inform the design of optimal strategies for HIV cure. Considering the aforementioned vulnerability of adolescents with vertical infection and the limited knowledge on viral reservoirs and immune activation/inflammatory reaction in this population, evidence generated from this target will be highly complementary to current global efforts. Such evidence, generated in a context of high burden of coinfections [30,31], might depict differential mechanisms of HIV persistence far from those reported in other parts of the world.

Preliminary Work

Within the frame of the European and Developing Countries Clinical Trial Partnership-Resistance Evolution among Adolescents in Yaoundé and its surroundings (EDCTP-READY) study (Multimedia Appendix 1), we have set up a cohort of 292 vertically infected adolescents (10-19 years) receiving ART in Cameroon. In this cohort, we reported a rate of 40% undetectable viral load (<40 copies/mL) after a median of 8 years of ART, about 20% immunological failure (CD4<250 cells/mm^3) rate, and less than 10% clinical failure (ie, World Health Organization stages III/IV) [32]. This population offers a unique opportunity for understanding the size and nature of the reservoir; the variability of immune response/cytokine profiling; and the effect of the viral subtype, treatment history of ART (regimen and duration), gender disparities, and adherence level on the control of the viral reservoir. To date, most HIV cure research has been restricted to high-income countries with relatively low HIV burden and has most often engaged men who have sex with men. HIV strains are genetically and biologically diverse, and host mechanisms of antiviral immunity required for durable control may differ by age, sex, geography, and ethnicity. Basic discovery research and clinical trials in resource-limited settings must be strengthened to contribute to the global cure strategy [33]. Our study aims to characterize the HIV reservoirs and their variability according to the virological and immunological profiles of vertically infected adolescents receiving ART in Cameroon and therefore improve the understanding of the viral reservoirs and provide accurate and reliable data for HIV cure research in settings harboring broad genetic diversity. In this study, we shall (1) determine HIV-1 genetic variability and drug resistance in cellular reservoirs, (2) determine the immune profile of ADLHIV, (3) quantify their HIV viral reservoir, and (4) evaluate the effect of ART and immune response on the viral reservoir profile.

Methods

Study Design

We plan to conduct a cross-sectional, observational, and comparative study among vertically infected ADLHIV receiving ART in Cameroon. Participants will be selected and enrolled from an existing cohort of close to 300 vertically infected adolescents recruited for the EDCTP-READY study [7]. They will provide written assent and legal guardians will provide written proxy consent. HIV positive adolescents with incomplete ART history and hepatitis B virus/hepatitis C virus and malaria coinfections will not be considered for this study.

Sample Size

The minimum sample size was estimated at 90 participants, assuming an HIV prevalence of 2% in adolescents in Cameroon, a 95% confidence, and 80% statistical power. The sample size was further stratified into 3 arms of 30 participants each: arm A, HIV viral load<40 copies/mL; arm B, HIV viral load=40-999 copies/mL; and arm C, HIV viral load≥1000 copies/mL. A group of 30 HIV-negative adolescents will serve as control for immunological profiling.

Study Procedures and Variables

Procedures and Timelines

This study requires 18 months to be completed: 3 months (month 1-3) for administrative and ethics approvals; 12 months (month 4 to 15) for enrolment of participants, sampling, and laboratory analyses; and 3 months (month 16 to 18) for data curing, processing, and reporting.

Sampling Strategy

Based on inclusion criteria, HIV positive adolescents case report forms will be selected from the EDCTP-READY study and their legal guardians will be contacted and invited to the clinic. Study clinicians will obtain new assent and informed consent from adolescents and legal guardians, respectively. Sociodemographic data, clinical data, and complete ART history will be collected, and eligible participants will be enrolled. Intravenous blood (5 mL × 2) will be collected by a trained phlebotomist for analyses in the central laboratory (Chantal Biya International Reference Center for Research on Prevention and Management of HIV/AIDS [34]).

Laboratory Procedures

Samples will be collected only once at enrolment along with all the relevant sociodemographic and clinical data. Samples will be transported to the central laboratory on the same day within 6 hours to be processed. Samples will be used for CD4/CD8 measurements (absolute counts and percentages), immune activation/inflammatory markers assessment by flow cytometry (FACSCanto II, BD BioSciences), and plasmatic viral load by real-time PCR (Abbott m2000rt). Peripheral blood mononuclear cells will be isolated by density-gradient centrifugation. HIV DNA will be subsequently extracted from peripheral blood mononuclear cells by using the QIAamp DNA Mini Kit (Qiagen), stored at –80 ^{o}C, and shipped every 3 months to the Department of Experimental Medicine, University of Rome Tor Vergata for HIV viral reservoir quantification using a homemade droplet digital PCR [35]. Proviral DNA will be extracted from the buffy coat by using the DNeasy blood and tissue extraction kit (Qiagen), and HIV viral RNA will be extracted from participants with virological failure (viral load>1000 copies/mL) using the QIAamp viral RNA Mini Kit (Qiagen); HIV proviral DNA and HIV viral RNA will be subsequently genotyped following a homemade protocol [36] on a 3500 genetic analyzer (Applied Biosystems). DNA sequences will be analyzed for drug resistance mutations by using the Stanford University database genotypic resistance interpretation algorithm [37]. For phylogenetic analysis, neighbor joining phylogenetic trees will be created using the Molecular Evolutionary Genetics Analysis software (Kimura 2-parameter model, 200 bootstrap replications) and FigTree [38,39].

Data Collection and Analysis

Data analysis will be performed under the responsibility of the project's biostatistician and the supervision of the principal investigator. Data will include sociodemographic data, clinical data, and laboratory data. Standardized case report forms will be generated for onsite data collection and laboratory results. Case report forms will be completed by the authorized clinic and laboratory personnel under the supervision of the principal investigator and the co–principal investigators. All data will be entered onsite through a double entry system in a password-protected computer, and case report forms will be kept in a locked office only accessible to authorized project personnel. Each participant will be assigned a unique identifier. Data will be analyzed using SPSS software (IBM Corp). Associated factors will be evaluated using multivariate logistic regression, with an estimate approach for the unbiased effect of different parameters. The data will be reported as medians. Nonparametric tests will be used for data not normally distributed. Comparisons of medians among different groups (virological success vs virological failure) will be performed using the Mann-Whitney *U* test. Correlations will be made with Spearman test, and *P* values less than .05 will be considered statistically significant.

Ethics Approval and Consent to Participate

This study will be conducted per the declaration of Helsinki on ethical principles for medical research involving human subjects. A written proxy-informed assent from legal guardians and a written assent from the participating HIV positive adolescent will be obtained without any coercion. Privacy and confidentiality will be ensured through the use of unique identifiers and a password-protected database accessible only by authorized staff. Participants will be free to deliberately leave the study at any time, without any effect on their routine monitoring at the study clinic. Phlebotomy will be noninvasive (venipuncture) and will be performed by a trained nurse. Ethical clearance has been obtained from the Cameroon National Ethics committee for research on human health (No2021/12/1426/CE/CNERSH/SP).

Management of Potential Risks

The risks to the participants are minimal since the only procedure the volunteer is subjected to, is venipuncture by a phlebotomist or physician. The venipuncture may be slightly painful, but it is practically without any risk of complication. The potential risks to subjects, none of which are likely to occur, may include momentary pain and bruising at the site or possible (but extremely unlikely) infection. If such complications arise, participants will be provided with emergency medical care.

Quality Assurance

Our study team will include a quality assurance officer who will be responsible for all the standard operating procedures for the study protocol and who will manage proficiency testing and data validation during the entire study. Quality assurance will

be assessed by external proficiency testing for plasmatic viral load, CD4/CD8 count, and genotyping.

Discussion

Despite the current success of ART (66% viral control globally) [3], lifelong treatment is required because there is no cure. On the basis that not everyone can access and adhere indefinitely to ART, a global consensus emerged several years ago that a curative intervention was a high priority to bring an end to the HIV pandemic [33]. Within a few weeks of treatment cessation in individuals with undetectable plasmatic viral load, HIV viremia rebounds in most patients, except for rare elite or posttreatment controllers of viremia; the primary source of this rebound is the highly stable reservoir of latent yet replication-competent HIV-1 proviruses integrated into the genomic DNA of resting memory CD4+ T cells [17,40]. To achieve a cure for HIV, understanding the cell reservoir environment is one of the key topics to address as prerequisite for the development of successful cure strategies and interventions [33].

The first specific objective of this study, that is, to determine HIV-1 genetic variability and drug resistance in cellular reservoirs, will help inform if the development of HIV drug resistance mutations in circulating viruses correlates with mutations found in latent reservoirs for possible eradication considerations and therefore, guides the selection of the most active ART with potential impact on latent reservoirs.

The second specific objective, that is, to determine the immune profile (activation/inflammation status) of the study participants, will help identify factors driving persistent immune activation, particularly during immunological/virological success/failure in vertically infected adolescents. Additional research is needed to conclusively state whether there are clear differences in the effects of specific ART history or HIV-1 subtypes on inflammation and immune activation in ADLHIV.

The third and fourth specific objectives, which are to quantify HIV reservoirs and evaluate the effect of ART and immune response on the reservoir profile, will inform if the characteristics of the latent reservoirs are associated with immune activation/inflammation, HIV-1 subtypes, and treatment outcome (virological success vs virological failure), especially in adolescents and therefore call for specific management of this sensitive population.

Overall, our findings will help in advancing knowledge on the HIV reservoir, in terms of size, genetic variability, and immune profile in ADLHIV. Such evidence will also help in understanding the effects of ART timing and duration on the size of reservoirs among ADLHIV—a unique and vulnerable population from whom the findings generated will largely contribute to designing functional cure strategies.

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Data Availability

The data sets used and analyzed during this study will be available from the corresponding author on reasonable request. HIV gene sequences generated during this study will be publicly available in the GenBank database [42].

Authors' Contributions

AJN, GEAN, JF, ACK, CFP, VC, and AN initiated the study protocol. NS, BS, EE, GB, LK, and MT revised the study protocol. All the authors approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by European & Developing Countries Clinical Trials Partnership (EDCTP2) - Horizon 2020 (European Union).
[PDF File (Adobe PDF File), 195 KB - resprot_v11i11e41473_app1.pdf]

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Abbreviations

ADLHIV: adolescents living with HIV
ART: antiretroviral therapy
CD: cluster of differentiation
EDCTP-READY: European and Developing Countries Clinical Trial Partnership-Resistance Evolution among Adolescents in Yaoundé and its surroundings
PCR: polymerase chain reaction

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Protocol

Effects of High and Low-To-Moderate Intensity Exercise During (Neo-) Adjuvant Chemotherapy on Muscle Cells, Cardiorespiratory Fitness, and Muscle Function in Women With Breast Cancer: Protocol for a Randomized Controlled Trial

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Abstract

Background: (Neo-)adjuvant chemotherapy for breast cancer is effective but has deleterious side effects on muscle tissue, resulting in reduced skeletal muscle mass, muscle function, and cardiorespiratory fitness. Various exercise regimens during cancer treatment have been shown to counteract some of these side effects. However, no study has compared the effect of high-intensity training versus low-to-moderate intensity training on muscle tissue cellular outcomes and physical function in patients with breast cancer during chemotherapy.

Objective: The aim of this substudy within the Physical Training in Cancer (Phys-Can) consortium is to evaluate and compare the effects of high and low-to-moderate intensity exercise on muscle cellular outcomes, muscle function, and cardiorespiratory fitness in women with breast cancer undergoing (neo-)adjuvant chemotherapy. We further aim to investigate if the effects of chemotherapy including taxanes on muscles will be different from those of taxane-free chemotherapy.

Methods: Eighty women recently diagnosed with breast cancer scheduled to start (neo-)adjuvant chemotherapy will be randomized to a combination of strength and endurance training, either at high intensity or at low-to-moderate intensity. Testing of muscle function and cardiorespiratory fitness and collection of muscle biopsies from the vastus lateralis muscle will be performed before the first cycle of chemotherapy (or after 1 week, when not possible) (T0), halfway through chemotherapy (T1), and after completion of chemotherapy (T2). It is estimated that approximately 50% of the participants will be willing to undergo muscle biopsies. To separate the effect of the treatment itself, a usual care group with no supervised training will also be included, and in this group, testing and collection of muscle biopsies will be performed at T0 and T2 only.

Results: This study is funded by Active Against Cancer (Aktiv mot kreft) (May 2013) and the Norwegian Cancer Society (December 2018). Inclusion started in December 2016 and the last participant is expected to be recruited in December 2022. As of June 2022, we enrolled 38 (19 with biopsies) participants to the high-intensity training group, 36 (19 with biopsies) participants to the low-to-moderate intensity training group, and 17 (16 with biopsies) participants to the usual care group. Data analyses will start in fall 2022. The first results are expected to be published in spring 2024.

Conclusions: This study will generate new knowledge about the effects of different training intensities for women with breast cancer during chemotherapy treatment. It will give further insight into how chemotherapy affects the muscle tissue and how physical training at different intensities may counteract the treatment side effects in muscles. The results of this study will inform

the development and refinement of exercise programs that are effective and compatible with the multidisciplinary management of breast cancer.

Trial Registration: ClinicalTrials.gov NCT05218876; https://tinyurl.com/ysaj9dhm

International Registered Report Identifier (IRRID): DERR1-10.2196/40811

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KEYWORDS

resistance training; endurance training; muscle strength; muscle endurance; anthracyclines; taxanes

Introduction

Breast cancer is the most common type of cancer in women in Europe [1]. Advances in treatment and improved survival rates have led to an increased focus on addressing the persistent adverse effects of treatment, including cancer-related fatigue, reduced physical capacity, weight gain, and reduced quality of life [2]. A common (neo)adjuvant treatment for women with breast cancer is chemotherapy with anthracyclines or taxanes or a combination of both. Observational studies have shown an approximately 10% decrease in maximal oxygen uptake (VO_{2max}) during chemotherapy [3]. This is concerning since low VO_{2max} has been associated with higher mortality among patients with breast cancer [4]. The reduced VO_{2max} might be related to the reported cardiotoxic effects of anthracyclines [5], but reductions in VO_{2max} are also reported without any signs of impaired cardiac function [6], suggesting there are other mechanisms contributing to the observed decline. Chemotherapy including anthracyclines has been reported to reduce muscle force-generation capacity and other essential muscle functions in both animal studies [7-9] and in patients with breast cancer [10]. Anthracyclines have also been demonstrated to reduce muscle fiber cross-sectional area (CSA) [8] and mitochondrial function [11] in rodents. These findings are supported by analysis on muscle biopsies from 2 small-scale studies on patients with breast cancer undergoing chemotherapy [12,13], which confirm the deleterious effects of chemotherapy on muscle size, mitochondrial structures, and muscle function. However, it is difficult to differentiate if these negative effects on the muscle are the direct effects of chemotherapy, the cancer itself, or indirectly from the reduced levels of physical activity, which is common in patients with cancer [14]. Regardless of cause, loss of skeletal muscle mass has been associated with reduced physical functioning and increased toxicity, that is, poor tolerance to chemotherapy and thus, worse prognosis [15,16].

Our clinical experience suggests that muscle function is more affected during taxane treatment than during anthracycline treatment. One frequent comment from patients during taxane treatment is the feeling of acidification during light and moderate physical activity. Taxanes have been reported to induce peripheral neuropathies [17], and one of the main mechanisms underlying the observed neuropathy is the deleterious effects on mitochondria [17,18]. A similar negative effect on the mitochondria in the skeletal muscle fits well with the abovementioned comments from patients. However, no studies have investigated if the muscular cellular effects of treatment including taxanes are different from those of treatment without taxanes and if including taxanes in the treatment leads to a different response to an exercise intervention. We will recruit patients receiving treatment with anthracyclines, taxanes, or a combination of both. If a sufficient number of patients is given each of the different treatments, we aim to investigate if the effects of treatment including taxanes on the muscle cells are different from those of taxane-free treatment on the muscle cells.

Strength training improves muscular strength and muscle size [19], and endurance training improves mitochondrial volume and mitochondrial function [20]. Therefore, physical training is a potential effective countermeasure to the chemotherapy-induced impairments in skeletal muscle mass and function. In women with breast cancer, physical training has been shown to reduce the loss of muscle strength and cardiorespiratory fitness commonly observed during treatment [2]. However, the physiological mechanisms underlying this protective effect are largely unknown.

Endurance training has been reported to reduce the cardiotoxic effects of anthracyclines in rodents [21-23]. The possible protective effects of physical training on skeletal muscles during chemotherapy for breast cancer have only been studied in 1 small-scale study. Mijwel and colleagues [12] showed that participating in a training program that combined high-intensity intervals to either strength training or aerobic exercise (moderate intensity) during treatment had beneficial effects on muscle fiber CSA and mitochondrial enzymes in the 2 intervention groups. Furthermore, these beneficial effects showed an inverse correlation with changes in cancer-related fatigue, indicating that the training effect on muscle fiber CSA and mitochondrial enzymes during chemotherapy might reduce cancer-related fatigue [12]. However, there is a need for studies including more participants to verify these findings and to investigate the physiological mechanisms underlying this protective effect. Regular exercise during treatment also seems to have several other beneficial effects on both treatment efficiency and reducing the other side effects of treatment [24,25]. Some of these effects seems to be related to increased production of antitumor myokines in the exercising muscles [26], and this aspect will also be investigated in the analyses of muscle biopsies in this study.

To date, most studies have compared a single exercise intervention to usual care or interventions with no physical activity. High-intensity training is shown to induce larger improvements in VO_{2max} and muscle strength in both healthy individuals and in various patient populations [27-29]. However,

it is not known to which extent chemotherapy interferes with normal adaptation to physical training. A recent systematic review and meta-analysis reported that longer sessions and higher weekly volume and duration are associated with more beneficial changes in VO_{2max} after endurance training in various populations with cancer during (neo)adjuvant treatment [30]. However, the effects of different training intensities were unclear.

Data from the main study under the Physical Training in Cancer (Phys-Can) consortium showed that combined strength and endurance training with both low-to-moderate intensity and high intensity was feasible in patients with different types of cancer. Furthermore, high-intensity training led to better effects on muscle strength and VO_{2max} compared to low-to-moderate intensity training [29]. However, muscle biopsies were not included in the main study; therefore, how training with different intensities affect muscular cellular outcomes is not known. Thus, there is a need for more studies examining the effect of high versus low-to-moderate intensity training during treatment and especially those including muscle biopsies.

In summary, the direct effects of chemotherapy on muscle tissue in women treated for breast cancer are mostly unknown and previous studies that have investigated the direct effects of (neo-)adjuvant chemotherapy on muscle tissue and how these effects may interfere with the adaptations to strength and endurance training in women diagnosed with breast cancer have had small sample sizes. Furthermore, no previous study has compared the effects of different training intensities on muscle cells in women with breast cancer during (neo-)adjuvant chemotherapy and it is still uncertain whether high-intensity exercise is feasible in all phases of the treatment. Thus, the aim of this study is to evaluate and compare the effects of high and low-to-moderate intensity exercise on muscle cellular outcomes, muscle function, and cardiorespiratory fitness in women with breast cancer undergoing (neo-)adjuvant chemotherapy. We further aim to investigate if the effects of chemotherapy including taxanes on muscle cells are different from those of taxane-free chemotherapy.

Our hypotheses are as follows.

1. Both high-intensity and low-to-moderate intensity strength and endurance training during (neo-)adjuvant chemotherapy will reduce the negative treatment effects on muscle fiber CSA, mitochondrial function, cellular stress, and thus reduce the negative effects on cardiorespiratory fitness and muscle function compared to usual care. High-intensity training will be superior to low-to-moderate-intensity training in counteracting the negative treatments effects.
2. Both high-intensity and low-to-moderate intensity strength and endurance training during (neo-)adjuvant chemotherapy will increase the muscle and blood levels of potential antitumor myokines compared to usual care.
3. Treatment including taxane administration will have larger negative effects on muscle fiber CSA, mitochondrial function, cellular stress, and thus cardiorespiratory fitness and muscle function compared to taxane-free treatment, regardless of the training intensity.

Methods

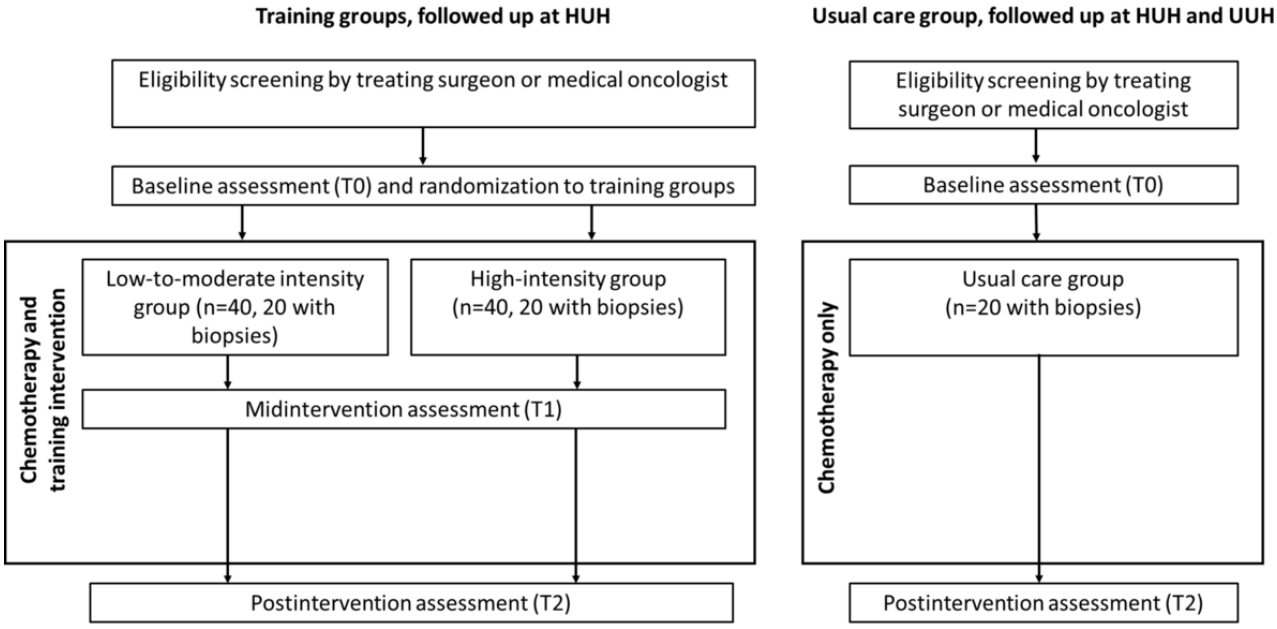
Ethics Approval

This study has been approved by the Regional Committee for Medical and Health Research Ethics South-East, Norway (2015/2360).

Study Design

This study is a 2-group randomized controlled trial (Figure 1). The participants will be randomly allocated into 1 of the 2 training groups: one group performing the combination of strength and endurance training with high intensity and the other group performing the training with low-to-moderate intensity during (neo-)adjuvant treatment for breast cancer. To measure the effect of the treatment itself, a parallel usual care group receiving no supervised training will be recruited from another pool of patients. This will be from patients living too far away from the study site to participate in training and from a usual care control group from another substudy within the Phys-Can consortium carried out at Uppsala University Hospital [31]. The usual care group will have the same inclusion and exclusion (see below) criteria as the 2 training groups in this study. Muscle biopsies, questionnaires, and blood samples will be collected from the training groups before the first chemotherapy cure (T0). The first 2-4 weeks after cure 1 will be used as a familiarization period for tests and exercises and for completing the remaining T0 tests. Testing will include measurements of physical capacity, body composition, and physical activity levels. All measurements, including muscle biopsies, questionnaires, and blood samples, will be repeated halfway into the treatment (T1) and after completion of treatment (T2). In the participants in the usual care group, measurements will be performed at T0 and T2 only. Training will start between cure 2 and cure 3 and will last throughout the treatment period, which is approximately 6 months.

Figure 1. Study flowchart. HUH: Haukeland University Hospital; UUH: Uppsala University Hospital.



Outcomes

The primary outcome for this study is muscle fiber CSA, whereas secondary outcomes include muscle function, cardiorespiratory fitness, regulators of muscle fiber size and function (including mitochondrial enzymes, heat shock proteins, protein control systems, and DNA damage), and myokines with putative antitumor effects. All outcomes are listed in Table 1.

Table 1. Outcomes and assessments.

Outcomes and specific variables	Assessment
Muscle fiber size (muscle fiber cross-sectional area)	Cross-sections of muscle biopsies
Number of myonuclei per muscle fiber (myonuclei/fiber)	Cross-sections of muscle biopsies
Number of satellite cells per muscle fiber (satellite cell/fiber)	Cross-sections of muscle biopsies
Proteins involved in muscle hypertrophy (PI3K[a]/Akt[b]/mTOR[c]-pathway, including but not limited to mTOR[c], P70s6k[d], 4EBP1[e], eIF4A[f])	Western blot
Proteins involved in muscle protein degradation (including but not limited to FOXO[g], ubiquitin ligase E2, LC3[h] (I and II), p62[i], myostatin, as well as ubiquitinated proteins)	Western blot
Mitochondrial function	
CS[j], COX4[k], HADH[l]	Western blot
Mitochondrial structure	Cross-sections and whole fiber preparations of muscle biopsies
Cellular stress	
Heat shock protein (Hsp)27, Hsp60, Hsp70	Cross-sections of muscle biopsies, western blot
DNA damage	Comet assay
Physical function	
Muscle strength	1 repetition maximum in chest press and knee extension.
Muscular endurance	Repetitions until failure at 30% of 1 repetition maximum
Cardiorespiratory fitness	Maximal oxygen uptake
Lactate threshold	Blood lactate profile
Potential antitumor myokines (including, but not limited to interleukin (IL)-6, IL-15, SPARC[m], TWEAK[n], IL-8, IL-10, IL-1β, IFN-γ[o], TNF-α[p], TNFR1[q])	mRNA levels by real-time polymerase chain reaction analyses and protein levels by western blot and enzyme-linked immunosorbent assay
Body composition	
Lean body mass, total fat mass	Dual-energy X-ray absorptiometry
BMI	Weight and height
Physical activity (level)	SenseWear Armband
Serological outcomes (hemoglobin, creatine, cortisol, high-sensitivity C-reactive protein, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, HbA^{1c})	Standard clinical measures
Quality of life and fatigue	
Fatigue	Multidimensional fatigue inventory
Pain	Brief pain inventory
Health-related quality of life	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30, The European Organization for the Research and Treatment of Cancer Quality of Life for breast cancer
Sociodemographic data (age, partnership, number and age of children living at home, education, income, work and sick leave)	Study-specific questionnaire
Lifestyle data (dietary habits, alcohol consumption, physical activity level, weight, and tobacco use)	Study-specific questionnaire
Behavioral data (motivation, self-efficacy, and barriers to training)	Study-specific questionnaire
Disease-specific information (diagnosis, type, and dose of oncological treatment, adherence to oncological treatment)	Medical records

Outcomes and specific variables	Assessment
Adverse events (adverse events occurring during exercise training sessions and during muscle biopsy sampling)	Reported by coaches/technicians

[a]PI3K: phosphoinositol-3-kinase.
[b]Akt: protein kinase B.
[c]mTOR: mechanistic target of rapamycin.
[d]P70s6k: ribosomal protein S6 kinase.
[e]4EBP1: eukaryotic translation initiation factor 4E-binding protein 1.
[f]eIF4A: eukaryotic initiation factor-4A.
[g]FOXO: forkhead box O.
[h]LC3: microtubule-associated protein 1 light chain 3.
[i]p62: ubiquitin-binding protein p62.
[j]CS: citrate synthase.
[k]COX4: cytochrome c oxidase subunit 4.
[l]HADH: 3-hydroxyacyl-CoA-dehydrogenase.
[m]SPARC: secreted protein acidic and rich in cysteine.
[n]TWEAK: TNF-related weak inducer of apoptosis.
[o]IFN-γ: interferon γ.
[p]TNF-α: tumor necrosis factor-α.
[q]TNFR1: tumor necrosis factor receptor 1.

Participant Recruitment and Eligibility Criteria

Women recently diagnosed with breast cancer starting (neo-)adjuvant chemotherapy (a combination of taxanes and anthracyclines or only one of the treatments or in combination with radiation therapy or endocrine therapy) are recruited from Haukeland University Hospital. Patients in the usual care group (see above) will also be recruited from Uppsala University Hospital. All potential participants must fulfill the following eligibility criteria: (1) diagnosed with stage I-III breast cancer, (2) >18 years old, (3) can understand and communicate in the Norwegian or Swedish language, and (4) scheduled to undergo (neo-)adjuvant chemotherapy with a combination of taxanes and anthracyclines or only one of the treatments or in combination with radiation therapy or endocrines. Women who are (1) not able to perform basic activities of daily living, (2) show cognitive disorders or severe emotional instability, and (3) experiencing other disabling comorbidities that might hamper physical training (eg, heart failure, chronic obstructive pulmonary disease, orthopedic conditions, neurological disorders) will be excluded. All eligible women will receive written information. Women who meet the inclusion criteria will be offered further information and invited to query any question about the study before being invited to participate.

Sample Size

Power calculations are based on findings in the Physical Exercise and Prostate Cancer trial [32], but findings from the study by Mijwel et al [12] strongly support similar expectations on chemotherapy in patients with breast cancer. With a similar effect on muscle fiber CSA, we need 10 participants in each group to obtain a statistical power of 80% in this study; to further enhance the power up to 95%, we need 16 participants. To account for dropouts during the intervention, we aim to recruit 40 participants to the training groups (20 in each group) willing to undergo muscle biopsies. We expect approximately 50% of the recruited participants will be willing to undergo muscle biopsy; therefore, we aim to recruit 80 participants to the training groups. To increase power on other measurements, the participants unwilling to undergo biopsy will be included in this study. In the usual care group, we also aim to include 20 participants willing to undergo muscle biopsies. This group will consist of patients living too far away from the study site at Haukeland University Hospital and participants in the usual care control group recruited to another substudy within the Phys-Can consortium carried out at Uppsala University Hospital [31].

Randomization

Participants from Haukeland University Hospital will be randomized in a 1:1 ratio into the 2 training groups stratified by treatment (neoadjuvant or adjuvant treatment). The investigator performing the analyses on muscle biopsies will be blinded for this randomization. As described, participation in the usual care group will be from patients living too far away from the study site at Haukeland University Hospital or from Uppsala University Hospital and will not be randomized.

Intervention

All participants in the training groups will perform both strength and endurance training throughout the course of treatment with chemotherapy, which is approximately 6 months. Trained coaches will guide both strength and endurance training.

Strength Training

The first 2-4 weeks after inclusion will be a familiarization period where the participants become familiar with the exercises and tests as well as how to use the Omni scale for self-reported perceived exertion [33] included in the strength training program. During the familiarization period, there will be a test of 10- and 6-repetition maximum (RM) load, which will provide the participants with individualized training loads. The strength

training will be performed as previously described [34]. Briefly, the training consists of 2 supervised sessions per week and include the following exercises: seated leg press, chest press, seated leg curl, seated row, leg extension, and standing overhead press by using dumbbells. The low-to-moderate intensity group will perform 12 repetitions for 3 sets at 50% of 6RM load in the first weekly session and 20 repetitions for 3 sets at 50% of 10RM load in the second weekly session (reporting 5-7 on the Omni scale for perceived exertion) [33]. The high-intensity training group will perform 6 repetitions for 3 sets at 6RM load in the first weekly session and 10 repetitions for 3 sets at 10RM load in the second weekly session (reporting 9-10 on the Omni scale for perceived exertion [33].

Endurance Training

During the 2-4 weeks familiarization period, participants will familiarize themselves with the use of the heart rate monitor and perceived exertion by using the Borg scale [35] for monitoring the exercise intensity and perceived exertion. All participants will perform the first session with a coach and receive training on how to use the heart rate monitor. Participants in the high-intensity training group will also be given 1-2 extra session with a coach in a gym. Thereafter, the endurance training is home-based and followed up by a coach and will be performed as previously described [34]. Briefly, the low-to-moderate intensity group perform a continuous-based exercise (running, cycling, walking uphill, or any other endurance-based activity) in bouts of at least 10 minutes at an intensity of 40%-50% of the heart rate reserve. The exercise frequency is recommended to be 2-4 times a week with the main aim to reach 150 minutes of moderate intensity per week. The high-intensity group performs high-intensity interval exercise. The sessions will consist of 2-minute intervals (running, cycling, walking uphill, or any other endurance-based activity) at an intensity of 80%-90% of the heart rate reserve (at the end of the third session) with 2 minutes of rest between intervals. During the first week, after familiarization, each session will consist of 6 intervals. Thereafter, 1 bout will be added every fourth week until 10 bouts per session are reached as the maximum, corresponding to 75 minutes of high-intensity training per week.

Procedures

Muscle Biopsy Sampling

Muscle biopsies are obtained from the midsection of the vastus lateralis muscle under local anesthesia (xylocaine adrenaline, 10 mg·ml^{-1} + 5 µg·ml^{-1}, AstraZeneca). Briefly, a 1-2-cm incision will be made in the skin and the fascia of the vastus lateralis muscle. Biopsies are collected using a 6-mm Pelomi needle (Bergström technique) with manual suction to obtain muscle samples (~200 mg). Biopsies will be rinsed in ice cold saline (0.9% NaCl) and carefully dissected free of visual fat, connective tissue, and blood. All pieces but 2 will be frozen in isopentane, precooled on dry ice, and stored at –80 °C for later analysis. The last 2 pieces (~10 mg) will be transferred to 500 µL of RNAlater stabilization solution (Invitrogen) and stored at 4 °C for at least 24 hours before 1 piece is transferred to –20 °C for long-time storage while the RNAlater solution is removed from the last piece before long-term storage at –80 °C.

Muscle Analyses

Muscle Fiber Size

Muscle fiber CSA represents the primary muscle cellular outcome. Muscle fiber CSA will be measured by immunohistochemical analysis of the cross-sections of the muscle biopsies. Briefly, transverse serial sections of the muscle biopsy (8-µm thick) will be cut using a cryostat microtome at –22 °C and mounted on glass slides. Serial cross-sections will be immunohistochemically stained for fiber types (type I, type IIa, and IIx) for CSA measurements. Muscle fiber CSA will be measured for the different fiber types separately.

Regulators of Muscle Fiber Size

The secondary muscle cellular outcomes reflecting the regulators of muscle fiber size are (1) number of myonuclei per muscle fiber, (2) number of satellite cells per muscle fiber, (3) proteins involved in muscle protein degradation (muscle breakdown), and (4) regulators of muscle protein synthesis (local growth factors). Muscle fiber myonuclear and satellite cell content per muscle fiber will be measured by immunohistochemical analysis of the cross-sections of muscle biopsies. Myonuclei and satellite cell contents per muscle fiber will be assessed for the different muscle fiber types separately. Regulators of muscle fiber size, that is, proteins involved in muscle protein synthesis and protein degradation will be measured by western blot analysis in the muscle homogenate. See Table 1 for details.

Regulators of Muscle Fiber Function and Cellular Stress

Proteins involved in protection against cellular stress (heat shock protein [Hsp]27, αB-crystallin, Hsp60, and Hsp70) as well as enzymes involved in mitochondrial function (citrate synthase, cytochrome c oxidase subunit 4, and 3-hydroxyacyl-CoA-dehydrogenase) will be assessed in muscle homogenates by western blot analysis. In addition, mitochondrial structures will be studied in cross-sections and whole fiber preparations of muscle biopsies by immunohistochemistry. DNA damage and repair will be assessed using the comet assay [36].

Myokines With Potential Antitumor Effects

Exploratory analyses on the effects of the training on the expression levels of myokines, previously proposed to have an antitumor effect, will be conducted. Relevant targets, including, but not limited to, interleukin (IL)-6, IL-15, secreted protein acidic and rich in cysteine, and TNF-related weak inducer of apoptosis will be evaluated at the mRNA level by real-time polymerase chain reaction analyses (RNA extracted from biopsies) and at the protein level by western blot and enzyme-linked immunosorbent assays (muscle and blood samples). Blood samples will be obtained by venipuncture and participants are asked to avoid smoking and alcohol and not to engage in any strenuous physical activity 24 hours before the blood sample collection. The levels of IL-6, IL-8, IL-10, IL-1β, IFN-γ, tumor necrosis factor (TNF)-α, and TNFR1 will be measured using enzyme-linked immunosorbent assay–based methods. Frozen sera will be saved for further analyses that can be included later.

Physical Functioning

1RM Testing

1RM testing will be performed as described previously [34] in chest press, leg press, and knee extension. To secure the validity of the 1RM tests, all participants will undertake a familiarization session prior to these assessments.

Muscle Endurance

Muscle endurance will be measured as the number of repetitions the patient is able to perform in a continuous set at 30% of 1RM at the corresponding time point in knee extension.

Cardiorespiratory Fitness

Cardiorespiratory fitness will be measured as VO_{2max} during maximal walking/running until exhaustion on a treadmill (PPS Med 55, Woodway Inc). The protocols start at 5 km/h with an incline of 5%. The inclination increases with 1% every minute until it reaches 12%, from which the speed increases by 0.5 km/h per minute until exhaustion. Oxygen consumption and minute ventilation will be measured continuously using an oxygen analyzer (Oxycon Pro, Erich Jaeger GmbH; Vyntus CPX, Vyaire Medical GmbH). Heart rate will be measured using a heart rate monitor (T34, Polar Electro KY).

Blood Lactate Profile

The patients will walk or run in 5 minutes at bouts with increasing submaximal workloads. Heart rate will be monitored continuously, and capillary blood samples will be taken and analyzed for lactate levels (Lactate Scout+, EKF GmbH) after each workload. The test will terminate when the patients show increased lactate concentrations by more than 1.6 mmol/L from the last workload or when the lactate increases above 4 mmol/L.

Body Composition

Total and regional lean body mass and fat mass together with bone mineral density will be measured by dual energy X-ray absorptiometry (iDXA, GE Lunar). Participants will be scanned from head to toe in a supine position, providing values for total and regional lean body mass fat mass, bone mineral content, and bone mineral density.

Assessment of Physical Activity Level and Physical Training

Participants' physical activity level will be measured using SenseWear Armband Mini (BodyMedia Inc). All participants will be instructed to wear the SenseWear Armband for 7 consecutive days. Only valid days with at least 80% wearing time will be included in the analyses. The step count cut points corresponding to moderate intensity will be 3 metabolic equivalents of task [37]. SenseWear Armband data will be analyzed with the SenseWear software (SenseWear Professional Research Software Version 8.1, BodyMedia Inc). Participants will be instructed to keep a logbook of all endurance trainings and strength trainings. In this logbook, the duration and subjective intensity measured with the Borg scale [35] of all endurance training sessions are noted. For the strength training, the load, number of repetitions, number of sets, and the perceived exertion with Omni scale are noted for each session.

Quality of Life, Fatigue, and Pain

The European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 [38] and diagnosis-specific modules (The European Organization for the Research and Treatment of Cancer Quality of Life for breast cancer) will be used to assess the quality of life. Fatigue will be assessed using the Multidimensional Fatigue Inventory [39], and pain will be assessed using Brief Pain Inventory [40].

Background Variables

Participants will provide self-reports about age, partnership, number and age of children living at home, education, income, work, sick leave, dietary habits, alcohol consumption, physical activity level, weight, tobacco use, motivation, self-efficacy, and barriers to training by using a study-specific questionnaire. In addition, past illnesses and other medical problems are recorded. Information about the medical situations such as treatment, stage of disease, and comorbidity as well as chemotherapy treatment compliance and adverse events will be collected at all 3 assessment points (T0, T1, and T2) from medical records.

Statistical Analyses

Data will be analyzed according to the intention-to-treat principle. Analyses will include standard descriptive statistics, 2-sided *t* tests, correlation, regression, and 2-way repeated-measures analysis of variance or the comparable nonparametric test as necessary to examine the differences between and within groups at T0, T1, and T2. In addition, a per-protocol analysis, that is, adherence to the protocol, will be conducted. Should imbalances in important variables be detected, sensitivity analyses will also be added including these as covariates in the model.

Results

This study is funded by Active Against Cancer (Aktiv mot kreft) (May 2013) and the Norwegian Cancer Society (December 2018). It has been registered at ClinicalTrials.gov (identifier NCT05218876). At Haukeland University Hospital, inclusion started in December 2016 and the last participant is expected to be recruited in December 2022. As of June 2022, we enrolled 38 (19 with biopsies) participants to the high-intensity training group, 36 (19 with biopsies) participants to the low-to-moderate intensity training group, and 5 (4 with biopsies) participants to the usual care group. The recruitment to the usual care group from Uppsala University Hospital started in December 2018 and is finished with a total of 12 patients completing all data collection. Data analyses of the patients from Haukeland University Hospital will start in fall 2022. Data analyses of the patients at Uppsala University Hospital started in January 2022 and is ongoing. The first results are expected to be published in spring 2024.

Discussion

The main aim of this study is to compare the effects of a high-intensity strength and endurance training program with those of a low-to-moderate intensity strength and endurance

training program on muscle cellular outcomes, muscle function, and cardiorespiratory fitness in women undergoing breast cancer chemotherapy. These results will also be compared with those of the group treated with usual care to investigate how (neo-)adjuvant treatment with chemotherapy will affect these variables and how high and low-to-moderate intensity trainings can counteract the effects of treatment. We hypothesize that the usual care control group will experience negative treatment effects on muscle fiber CSA and mitochondrial function, leading to reduced muscle function and cardiorespiratory fitness. We further expect that both high-intensity training and low-to-moderate intensity training performed by the training groups will counteract the negative treatment effects and that high-intensity training will be superior to low-to-moderate-intensity training. The results of our study are expected to provide insights on how regular exercise during treatment may counteract the side effects of chemotherapy on physical functioning and muscle tissue and how training intensity impacts these effects. Such knowledge can be used to design effective physical exercise programs, helping an increasing number of individuals with breast cancer during and following chemotherapy and possibly reducing the long-lasting side effects and ultimately improve the quality of life.

Forty women recently diagnosed with breast cancer, with 20 in each group, will give us a larger study population than those in previous studies on muscle cellular outcomes [12,41,42] to draw conclusions from. Furthermore, to our knowledge, this will be the first randomized controlled study comparing the effectiveness between high-intensity strength and endurance training and low-to-moderate intensity strength and endurance training during (neo-)adjuvant treatment on muscle cellular outcomes in patients with breast cancer. We are also recruiting participants who are not willing to undergo muscle biopsies, giving us an even larger study population when analyzing the other outcomes. As high-intensity training is shown to induce larger improvements in maximal oxygen uptake and muscle strength in both healthy individuals and in various patient populations [27,28], it should also be more effective in patients with breast cancer during chemotherapy. However, it is not known to which extent chemotherapy interferes with normal adaptation to physical training, and the high-intensity training is severely more challenging. Consequently, high-intensity training may be less feasible during chemotherapy, and lower adherence to the planned training in some periods of treatment may reduce training effectiveness. However, the feasibility of the current high-intensity training program has been confirmed in the large-scale Phys-Can study [29], in which ~75% of the participants completed the 6-month training program.

Although the primary outcome of this study is muscle fiber CSA, we are also including a wide range of biological measurements, including specific proteins involved in skeletal muscle hypertrophy, protein degradation/protein control, and regulators of muscle fiber function. These analyses will provide further insight into the underlying mechanism through which chemotherapy affects muscle tissue and therefore, muscle function, and how training with different training intensities could be used as a therapeutic measure to counteract the side effects of chemotherapy. We will recruit patients undergoing chemotherapy with anthracyclines, taxanes, or a combination of both. Given a large enough number of patients receiving different treatments, this will give us the opportunity to investigate if different chemotherapy regimens affect the adaptations to training at different intensities. Due to individual treatment protocols, there probably will be differences between participants in the treatment regimen, for example, different type and doses of chemotherapy. This might lead to differences between the 2 training groups and between the training groups and the usual care control group in treatment. The lack of randomization to the usual care control group is also a limitation. This will, together with the fact that most participants in this group are treated at a different site than the training groups, further increase the risk of differences between the training groups and the usual care control group in the treatments and other relevant factors. The results from this study are planned to be published in scientific peer review journals and at scientific congresses.

In summary, previous research underlines the positive potential of regular physical exercise during cancer treatment on outcomes such as physical function, mental health, fatigue, and quality of life in women with breast cancer [10,43,44]. However, research on the specific cellular effects of training with different intensities has not been performed. This study will provide important information on the effects of a high-intensity training versus low-to-moderate intensity strength and endurance training programs on skeletal muscle cellular outcomes, muscle function, and cardiorespiratory fitness in women diagnosed with breast cancer undergoing chemotherapy. It will also give important information about the cellular mechanisms through which chemotherapy may reduce physical performance and how training with different intensities may counteract these side effects. This knowledge can be used to design training programs that are both effective and feasible for patients with breast cancer during treatment to counteract the side effects of chemotherapy and ultimately increase the daily function and quality of life.

Acknowledgments

This study is funded by Active Against Cancer (Aktiv mot kreft) (May 2013) and the Norwegian Cancer Society (December 2018).

Data Availability

The data that will be generated from this study is planned to be included in the scientific articles that will be published. Data not included in published articles will be available from the corresponding author on reasonable request.

Authors' Contributions

TR, SB, KN, and ID conceived the original study idea and designed this study. THW, TR, SB, OV, and ES designed the data collection tools and methods. OV, THW, and TR will perform data analyses. THW and IT perform project administration. OV drafted the original manuscript while all authors reviewed and approved the manuscript. TR and IT were responsible for funding acquisition.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by: Norwegian Cancer Society (Oslo, Norway).
[PDF File (Adobe PDF File), 18 KB - resprot_v11i11e40811_app1.pdf]

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Abbreviations

CSA: cross-sectional area
Hsp: heat shock protein
IL: interleukin
Phys-Can: Physical Training and Cancer
RM: repetition maximum
T0: test period before the first chemotherapy cure
T1: test period halfway into the treatment
T2: test period after completion of treatment
TNF: tumor necrosis factor
VO_{2max}: maximal oxygen uptake

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Protocol

Reducing Cannabis Use in Young Adults With Psychosis Using iCanChange, a Mobile Health App: Protocol for a Pilot Randomized Controlled Trial (ReCAP-iCC)

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Abstract

Background: Cannabis use is the most prevalent among adolescents and young adults; frequent consumption is associated with cannabis use disorder (CUD) and psychosis, with a high prevalence (up to 50%) of CUD in individuals with first-episode psychosis (FEP). Early Intervention Services (EIS) for psychosis include face-to-face psychosocial interventions for CUD, because reducing or discontinuing cannabis use improves clinical and health care service use outcomes. However, multiple barriers (eg, staff availability and limited access to treatment) can hinder the implementation of these interventions. Mobile health (mHealth) interventions may help circumvent some of these barriers; however, to date, no study has evaluated the effects of mHealth psychological interventions for CUD in individuals with FEP.

Objective: This study describes the protocol for a pilot randomized controlled trial using a novel mHealth psychological intervention (iCanChange [iCC]) to address CUD in young adults with FEP. iCC was developed based on clinical evidence

showing that in individuals without psychosis, integrating the principles of cognitive behavioral therapy, motivational interviewing, and behavioral self-management approaches are effective in improving cannabis use–related outcomes.

Methods: Consenting individuals (n=100) meeting the inclusion criteria (eg, aged 18-35 years with FEP and CUD) will be randomly allocated in a 1:1 ratio to the intervention (iCC+modified EIS) or control (EIS) group. The iCC is fully automatized and contains 21 modules that are completed over a 12-week period and 3 booster modules available during the 3-month follow-up period. Validated self-report measures will be taken via in-person assessments at baseline and at 6, 12 (end point), and 24 weeks (end of trial); iCC use data will be collected directly from the mobile app. Primary outcomes are intervention completion and trial retention rates, and secondary outcomes are cannabis use quantity, participant satisfaction, app use, and trial recruiting parameters. Exploratory outcomes include severity of psychotic symptoms and CUD severity. For primary outcomes, we will use the chi-square test using data collected at week 12. We will consider participation in iCC acceptable if ≥50% of the participants complete at least 11 out of 21 intervention modules and the trial feasible if attrition does not reach 50%. We will use analysis of covariance and mixed-effects models for secondary outcomes and generalized estimating equation multivariable analyses for exploratory outcomes.

Results: Recruitment began in July 2022, and data collection is anticipated to be completed in July 2024. The main results are expected to be submitted for publication in 2024. We will engage patient partners and other stakeholders in creating a multifaceted knowledge translation plan to reach a diverse audience.

Conclusions: If feasible, this study will provide essential data for a larger-scale efficacy trial of iCC on cannabis use outcomes in individuals with FEP and CUD.

Trial Registration: ClinicalTrials.gov NCT05310981; https://www.clinicaltrials.gov/ct2/show/NCT05310981

International Registered Report Identifier (IRRID): PRR1-10.2196/40817

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KEYWORDS

psychological intervention; behavioral intervention; cannabis misuse; cannabis use disorder; drug use; substance use; cannabis; marijuana; young adult; teenager; psychosis; schizophrenia; mental health; disorder; dual diagnosis; telemedicine; mobile health; mHealth; digital health; eHealth; app; smartphone; mobile phone; randomized controlled trial; RCT; cognitive behavioral therapy; CBT; motivational interviewing; behavioral management; self-management; drug; substance; protocol; interview; behavior; outcome

Introduction

Cannabis Use and Psychosis

Globally, cannabis consumption has increased by 18% between 2010 and 2019, and adolescents and young adults have reported the highest levels of use [1]. In 2019, the regions with the highest past-year prevalence of cannabis use were North America (14%), Oceania (12%), and West and Central Africa (9%) [1]. The Canadian Cannabis Survey showed that in 2021, 20% and 29% of individuals aged 16-19 years and 20-24 years, respectively, consumed cannabis daily or almost daily in the last 12 months, which reflects an increase from 2017 when 15.9% and 22.5% of individuals reported identical frequencies of use in the same age groups [2,3]. Frequent and persistent cannabis consumption has been associated with an increased risk of cannabis use disorder (CUD) and psychotic disorders (eg, schizophrenia), especially in individuals with higher biological susceptibility [4,5]. Other important risk factors of first-episode psychosis (FEP) are early age of first cannabis use; consumption of cannabis products with high tetrahydrocannabinol (the main psychoactive constituent of cannabis); and environmental factors such as urbanicity, ethnic minority status, and childhood aversity [6-8]. In the general population, the prevalence of CUD is higher in men (3.5%) than in women (1.7%) [9]. Prospective studies have shown that at the beginning of treatment for FEP, cannabis is the most frequently abused drug (~50%); about 3 times more participants with a comorbid substance use disorder (including CUD) are male (78%-86%) than female and that persistent cannabis use is associated with poor clinical and functional outcomes [10-15]. Conversely, decreasing cannabis use in these individuals is an important intervention target because reducing or discontinuing cannabis use is associated with lower levels of psychotic symptoms, better occupational functioning, and a decreased likelihood of psychiatric hospitalizations [16-19].

Mobile Health Psychological Interventions for CUD in Psychosis

Early Intervention Services (EIS) for psychosis provide pharmacological treatments and psychosocial therapies for young individuals (ie, 12-35 years of age) with FEP. Psychosocial interventions are the mainstay of CUD treatment, over and above pharmacotherapy, which lack robust supporting evidence [20]. Face-to-face cognitive behavioral therapy (CBT), motivational interviewing, and motivational enhancement therapy, either alone or in combination, have been found to be moderately effective in decreasing the frequency and quantity of cannabis use, increasing the rate of abstinence, decreasing the rate of relapse, and reducing the severity of CUD and cannabis use–related problems [21-24]. However, the implementation of these interventions for CUD in EIS is variable and compounded by multiple barriers, such as low motivation of patients to change their cannabis use, heterogeneity in staff training and availability to manage CUD, varying treatment goals (eg, harm reduction vs lower cannabis consumption), high

staff turnover and workload, and limited access to treatment for patients residing in rural areas [25-28].

The widespread access to the internet and ownership of smartphones have facilitated the rapid expansion of the mobile health (mHealth) field, and it is estimated that more than 10,000 mental health apps are available for download [29]. As shown by recent systematic reviews, only 16 app-based interventions used to support the care of young adults with psychosis have undergone rigorous testing, and no study has evaluated the effects of mHealth psychological interventions for CUD in individuals with FEP [30,31]. Encouragingly, the results of 2 meta-analyses of studies that used technology-based (eg, web-based) psychological interventions to tackle cannabis misuse in individuals without psychosis have shown that these interventions were moderately effective in decreasing cannabis consumption [32,33]. Importantly, trials evaluating the effect of web-based psychological interventions on cannabis use in individuals without psychosis reported a wide range (12%-65%) of attrition rates at up to 3-month follow-up and suboptimal (30%-58%) intervention completion rates [34-38]. The high variability in attrition and completion rates in these studies can be explained by the heterogeneity in the study design and the content and intensity of the interventions. Moreover, the effect of these interventions on improving cannabis use outcomes in individuals without psychosis cannot be automatically generalized to individuals with psychosis and CUD because of differences in terms of mental health and functional status, as well as the specific beliefs of individuals with FEP related to cannabis consumption. These beliefs include (but are not limited to) limited recognition of the potential impact of cannabis use on the development or persistence of psychotic symptoms, association of cannabis consumption with relief from mental health symptoms (eg, anxiety, sleep, agitation, dysphoria), increased energy, and increased ability to form and maintain relationships [39-42].

Study Objectives

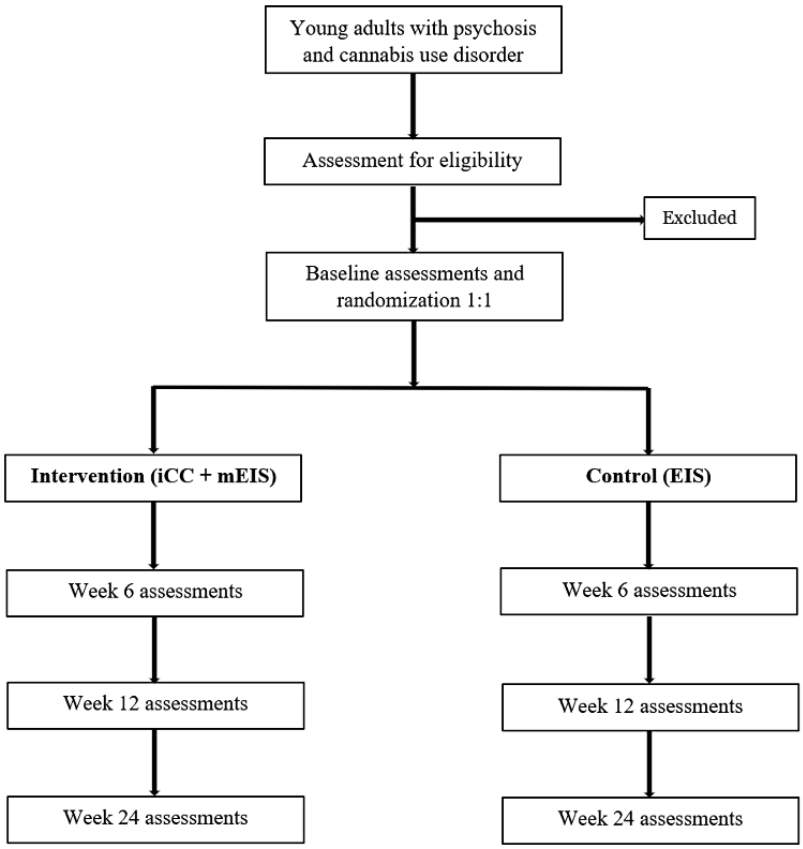
Consistent with the promising role of technology-based psychological interventions in addressing CUD in individuals with psychosis, we developed a psychological mobile app–based intervention (iCanChange [iCC]) and a pilot randomized controlled trial (RCT) to compare iCC with EIS in participants with FEP. The primary objectives are to assess intervention completion and trial retention rates. The secondary objectives are to conduct a preliminary assessment of the effect of iCC on the quantity of cannabis used, participant satisfaction, and app use and to evaluate trial recruiting parameters. We include exploratory outcomes (eg, psychotic symptoms, motivation to change cannabis consumption, and cannabis use protective behaviors) to strengthen our understanding of the benefits of using iCC in clinical settings.

Methods

Study Design

This study is a two-arm, parallel group (1:1 ratio) pilot RCT of iCC for decreasing cannabis use and modified Early Intervention Services for psychosis (mEIS) compared with EIS for young adults with FEP. Study participation may last up to 28 weeks and include a 14-day screening period (with an additional 14-day window to complete the baseline assessments), a 12-week intervention period, and a 12-week booster session and follow-up period (Figure 1). The CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) [43] guidelines were used to describe the protocol.

Figure 1. Study flowchart. EIS: Early Intervention Services; iCC: iCanChange; mEIS: modified Early Intervention Services.



Participants

Eligible participants will meet the following criteria: (1) aged 18-35 years; (2) first-episode psychosis, with diagnosis of any psychotic disorder (ie, schizophrenia, schizoaffective disorder, bipolar disorder with psychotic features, delusional disorder, psychotic disorder not otherwise specified, brief psychotic disorder, and substance-induced psychotic disorder); (3) a minimum of 3 months of follow-up at an early psychosis clinic (and still in active follow-up at study inclusion); (4) a diagnosis of CUD based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria [44]; (5) current cannabis use (at least once in the past month); (6) openness to use a mobile app–based intervention to decrease or cease cannabis use; (7) availability for the entire duration of the study and ability to comply with study procedures; and (8) ability to comprehend written French or English. The exclusion criteria were as follows: (1) any medical condition, including disabling, unstable, or acute mental condition or cognitive limitations that in the opinion of the study psychiatrist precludes safe participation in the study, the ability to provide fully informed consent, or the ability to participate in the intervention; (2) any judicial issue, pending legal action, or other reasons that might prevent completion of the study; (3) presence of a substance use disorder that precludes safe participation in the study (eg, very unstable or severe substance use disorder such as untreated opioid use disorder); and (4) current participation in another specific cannabis use–focused intervention that is not routinely offered in EIS for psychosis (eg, formal interventions for CUD and psychotherapy for CUD covered by private insurance).

Recruitment

The study will be conducted at 6 participating clinics that provide EIS for psychosis (ie, 5 sites in the province of Quebec and 1 in Nova Scotia), and additional sites may be added as needed over the course of the study to maximize recruitment.

Potential participants will be identified by the clinical staff who will document on the screening form the general eligibility and exclusion criteria and obtain permission from the participants to be contacted for research purposes. The research assistant will contact potential participants in person at the clinic or using an internet-based communication platform.

Once informed consent is obtained, the research staff will conclude the eligibility assessment by documenting on the screening form the eligibility and exclusion criteria reserved for the research staff. The enrollment process will conclude with the collection of participant contact information using the locator form.

Study Consent, Compensation, and Data Security

mHealth trial information provided during the consenting process will include the expected benefits of iCC in decreasing or ceasing cannabis use, a summary of the iCC content, expected participation in iCC (eg, number, duration, and frequency of modules), intervention services offered for CUD in both study arms, and the possibility of using iCC if randomized to the control group after the study end point assessment. Those who do not own a smartphone will be provided with a smartphone for the duration of the study. The research staff will assist participants in downloading iCC from Apple Store or Google Play Store and setting their passwords and will inform the

participant that clinical staff (eg, physicians and case managers—such as nurses, occupational therapists, social workers, or ergotherapists—henceforth *clinicians*) will be able to see the progress in the intervention on their computers (by using a customized dashboard) but are granted access to answers provided through iCC only with the participants' permission. Participants will receive information about the frequency and content of research assessments that will be performed either face to face or using telemedicine, independent of iCC use. Information about the compensation schedule (ie, CAD $30 for attending the screening visit and each of the study assessments for a possible total of CAD $150; at the time of data collection, the conversion rate was CAD $1=US $0.745) will be provided.

Before the consent form is signed, a comprehension "quiz" about the study participation will be administered to potential participants and further explanations will be provided as needed. Research personnel will inform participants that all the information collected during the research project will remain strictly confidential to the extent prescribed by law and that at no point will any individually identifiable information be revealed in any research publication or presentation. Participants' name, date of birth, and any other identifying information gathered during the study will be stored in the source documents and kept under lock. Computerized data will be encoded and held at the Centre Hospitalier de l'Université de Montréal's (CHUM) data-management core in secure, password- and firewall-protected servers.

Ethics Approval

The study was approved by the Research Ethical Committee of the CHUM (University of Montréal Health Centre; MP-02-2021-9622, 21.310) and registered on ClinicalTrials.gov (NCT05310981).

Interventions: iCanChange Mobile-Based App

Development and Content

The development of the iCC intervention was informed by the work of (and communications with) Copeland et al [45,46], who integrated CBT, motivational interviewing (MI), and behavioral self-management approaches in a brief 6-session face-to-face intervention aimed at assisting individuals who use cannabis to acquire skills to quit cannabis and maintain abstinence. In individuals without psychosis, compared with a delayed-treatment control group, the intervention was found to reduce cannabis use, decrease cannabis-related problems, and improve cannabis abstinence and control over cannabis use [47]. Members of our team with expertise in the treatment of CUD and psychosis (AW, AAB, TL, and DJA), patients partners, and a doctoral trainee (OT) integrated motivational (eg, to facilitate "change talk"), behavioral, and coping skills training approaches (eg, drug refusal skills, problem solving) described in the *Marijuana Brief Intervention* manual published by Copeland [45] and expanded the intervention by adding intervention components (modules) and activities (based on MI, CBT, and harm reduction principles) tailored to our target population.

Throughout the development process, we consulted with patient partners (individuals in different phases of recovery from psychosis and CUD who were followed up at the CHUM) to coconstruct the app, adapt the design of the app and the content based on their feedback, and pilot-test with them the preliminary versions of the app and its content. Furthermore, critical for the adaptation and development of the mobile-based intervention were the results of formative research that included (1) a qualitative methodology study (ie, focus group with individuals with psychosis and CUD and interviews with clinicians) aimed at exploring psychological intervention practices, intervention targets, and factors related to the development and implementation of a mobile-based app for CUD [48]; and (2) an electronic survey to evaluate patient preferences for participating in a mobile-based intervention for CUD. The evaluated parameters included the length and frequency of modules, total length of the intervention, preferred mode and location of receiving the intervention (eg, exclusively technology-based at the clinic), and intensity of feedback received during the intervention. On the basis of the results of the qualitative study and preliminary results of the quantitative study, we adapted the intervention to correspond to the preferred module length (15 min) and frequency (2 times per week) and the length of the intervention (3 months). The results of the formative research confirmed the importance of including the behavioral change techniques described by Copeland [45] and suggested additional intervention and app components that could facilitate behavioral change. The latter included the use of a cannabis-use journal, video testimonials about the effects of cannabis in psychosis, delivering information and skills training in video format, push notifications (Multimedia Appendix 1) to facilitate engagement with the intervention, and providing incentives (badges, see Multimedia Appendix 2) contingent with achieving intervention milestones. We provide a summary of activities and a description of behavioral change techniques corresponding to each intervention module (including boosters) based on the taxonomy published by Abraham and Michie [49] and Michie et al [50] (Tables 1-3).

Table 1. Activities and behavioral change techniques for section 1 (preparing for change).

Module and activities	Behavioral change techniques[a]
Section 1 (preparing for change)	
1. Introduction	
• Complete cannabis use diary • Select personal reasons for changing cannabis use • Read about prevalence of cannabis use and CUD[b]	• Self-monitoring of behavior • Social, personal, and emotional consequences (MI[c]) • Normative feedback • Provide contingent rewards (badge)
2. Cannabis dependence	
• Read information about CUD • Self-assessment of severity of dependence	• Provide information on consequences • Monitoring with awareness or feedback on behavior
3. Cannabis myths	
• Evaluate knowledge about health effects of cannabis consumption • Self-assessment of cannabis use consequences	• Provide information about behavior-health link • Health, social, and emotional consequences or monitoring with awareness (MI)
4. Benefits of reducing	
• Select perceived benefits (eg, social, cognitive, and emotional) of decreasing cannabis use • Prioritize these benefits	• Prompt positive self-talk • MI (preparatory change talk)
5. Believe in your strengths	
• Self-evaluate psychological strengths (eg, wisdom, bravery, and moderation) • Read a personalized feedback based on their strengths	• Focus on past success • Mental rehearsal of successful performance • Prompt self-talk • MI (preparatory change talk)
6. Triggers	
• Identify personal cannabis consumption triggers (eg, social, activities, and emotional) • Select the most important triggers • Read strategies about dealing with triggers	• Provide information • Avoiding or changing exposure to cues for the behavior • Monitoring with awareness or relapse prevention • Provide contingent rewards (badge)
7. Withdrawal	
• Watch an educational video about withdrawal symptoms • Select experienced withdrawal symptoms • Identify preferred coping strategies	• Provide information • Skills training with focus on withdrawal symptoms • Monitoring with awareness or relapse prevention • Prompt behavioral practice
8. Craving	
• Watch an educational video about craving symptoms • Select experienced craving symptoms • Read craving coping strategies • Identify preferred coping strategies	• Provide information • Skills training with focus on craving symptoms • Monitoring with awareness or relapse prevention • Prompt behavioral practice
9. Cannabis and psychosis	
• Education about cannabis and medication in psychosis • Watch 2 video testimonials about the effects of cannabis in psychosis • Report their perceptions related to the effects of cannabis on psychotic symptoms • Identify preferred psychotic symptoms coping strategies	• Provide information • Social comparison • Monitoring with awareness • Prompt behavioral practice

Module and activities	Behavioral change techniques[a]
10. Choose a cannabis use goal	
• Read a summary of all reasons and capacities of changing • Chose a cannabis use goal: stop, decrease, or maintain current use • Decide on a plan to reduce or stop cannabis use (eg, date) • Select cannabis harm reduction strategies	• MI • Prompt cannabis use goal setting or action planning and commitment • Provide general encouragement • Provide contingent rewards (badge)
Supplementary module: return to objective	
• Follow-up on their objective defined in module 10. This module can be offered for a maximum of 2 times once participants start section 2.	• Prompt barrier identification • Relapse prevention • Provide general encouragement • Prompt review of behavioral goals

[a]Corresponding to the taxonomy of behavior change techniques published by Abraham and Michie [49] and Michie et al [50].

[b]CUD: cannabis use disorder.

[c]MI: motivational interviewing.

The app is fully automatized and contains 2 sections and 3 booster modules. The first section contains 10 modules that are completed sequentially at a recommended frequency of 2 per week; however, faster progress will be permitted upon reading a prompt related to the recommended frequency. Two weeks after module 10, in which participants will self-identify a cannabis use goal, an additional module (that can be repeated after 2 weeks) will be offered to facilitate consolidating and reviewing participant goals (Table 1). Section 2 will unlock after section 1 is completed and consists of 8 modules (focusing on coping skills strategies) that can be completed in the preferred order while respecting the recommended frequency and concludes with a recapitulative module (Table 2). During the 3-month follow-up, participants will complete 1 booster session per month (which includes a summary of the content provided in the first 2 sections) to promote long-term behavioral changes (Table 3).

A summary of personalized responses provided in each module will be saved and can be accessed by the participant through the app dashboard. Additional dashboard features will include an information tab that provides links to relevant web-based resources related to psychosis and cannabis consumption; a "Profile" tab where the participant can rapidly access the most relevant information provided during module completion; a "Settings" tab where they will select their preferred language (English or French) and notification preferences; and an emergency button that will allow them to contact their case manager (see Multimedia Appendix 3 for the relevant screenshots).

The app that hosts the intervention and the video components (ie, information and storytelling) was designed in collaboration with Akufen, a Montréal-based media design company [51], and the programing for iPhone and Android was completed by Osedea, a Montréal-based software developer [52]. Following repeated content and app functionality testing by patient partners and the research team, the app underwent 2 major revisions, and the final version (iCC version 2 released in March 2022) will not undergo planned changes in structure or content until the end of the study. The app is owned by CHUM.

Table 2. Activities and behavioral change techniques for section 2 (strategies for supporting the change).

Module and activities	Behavioral change techniques[a]
Section 2 (strategies for supporting the change)	
1. Doing cannabis-free activities	
• Read about suggested distraction strategies • Decide on and plan to engage in 2 cannabis-free activities	• Behavior substitution • Prompt goal setting • Prompt behavioral practice • Behavioral activation
2. Getting social support	
• Read about the importance of having an adequate support system • Identify supportive persons	• Provide information on social support (general and emotional) • Prompt goal setting (social support) • Prompt behavioral practice • Behavioral activation
3. Taking care of yourself	
• Rank psychological and activity domains affected by cannabis use and psychosis • Read information to promote a healthy lifestyle (eg, diet and sleep) • Select a lifestyle modification goal and make a plan	• Provide information • Prompt intention formation • Prompt goal setting • Action planning • Behavioral activation
4. Managing your stress	
• Identify stress symptoms • Read about false stress triggers • Read about stress coping strategies	• Provide information • Cognitive restructuring • Monitoring with awareness • Prompt behavioral practice • Provide contingent rewards (badge, upon completion of 4 strategies) • Behavioral activation
5. Finding solutions to your problems	
• Read about problem-solving steps • Participate in exercises that incorporate problem-solving techniques	• Provide information • Skills training focused on problem-solving • Behavioral activation
6. Communicating effectively	
• Read about verbal and nonverbal communication techniques • Identify used communication techniques	• Provide information • Monitoring with awareness • Skills training focused on problem-solving • Behavioral activation
7. Being assertive	
• Read about communication modalities • Participate in exercises that exemplify the use of assertive communication	• Skills training focused on verbal and nonverbal communication • Self-affirmation • Behavioral activation
8. Valuing and rewarding yourself	
• Identify positive behavioral changes • Select preferred encouragements • Choose rewarding activities	• Self-reward • Anticipation of future rewards • Prompt goal setting (activities) • Provide contingent rewards (badge, upon completion of 8 strategies) • Behavioral activation
9. My journey	
• Self-assessment of reaching cannabis use and personal goals • Identify useful strategies and behaviors • Provide plans for future projects • Access web-based resources about cannabis and psychosis	• Provide feedback on outcomes and behavior • Prompt goal setting (activities) • Monitoring with awareness or relapse prevention • Provide general encouragement • Provide contingent rewards (badge)

[a]Corresponding to the taxonomy of behavior change techniques published by Abraham and Michie [49] and Michie et al [50].

Table 3. Activities and behavioral change techniques for follow-up modules (boosters).

Module and activities	Behavioral change techniques[a]
Follow-up modules (boosters)	
Booster 1	
• Read a personalized report about reasons or motivations for behavioral change, cannabis dependence, and goals • Self-assess their progress toward goal achievement • Read a personalized report about psychological strengths, triggers, withdrawal cravings, and stress symptoms • Identify useful strategies • Identify reasons for not reaching their goal (if applicable) and receive tailored solutions	• Review of behavioral and outcome goals • Provide feedback on outcomes and behavior • Monitoring with awareness or relapse prevention • Provide general encouragement • Prompt goal setting (for those who did not reach their goals) • Prompt behavioral practice
Booster 2	
• Reassess their severity of dependence • Set a cannabis use goal for the next month • Update preferred strategies	• Same as for booster 1
Booster 3	
• Report on positive changes and successful strategies (abstinent) • Complete questionnaires related to influence of cannabis on psychotic symptoms; cannabis use consequences (nonabstinent) • Self-report of social functioning, symptoms, and useful strategies (nonabstinent)	• Same as for booster 1

[a]Corresponding to the taxonomy of behavior change techniques published by Abraham and Michie [49] and Michie et al [50].

EIS Characteristics

Participants in the control group will receive EIS for psychosis through an interdisciplinary approach offered by teams of clinicians, including physicians and case managers with various backgrounds (eg, nurses, occupational therapists, and social workers), and interact with clinicians as per standard EIS procedures, which commonly include weekly case manager visits and follow-up visits with physicians every 3 weeks. At EIS clinics, individuals with FEP will receive intensive treatment (typically for 3 years) with the possibility of extension based on case-by-case evaluation. Services offered will comprise medication management; psychiatrist and case manager follow-up; and a range of psychosocial interventions including psychoeducation, psychotherapy (eg, CBT for psychosis), family interventions, peer support, interventions for substance use disorder (including CUD; ie, psychosocial interventions such as MI, CBT, psychoeducation, and harm reduction), support for basic life needs (eg, food and shelter), and support for improving social functioning (eg, employment and education). The receipt of interventions or services for cannabis use will be documented in the Intervention and Services Form at weeks 6, 12, and 24 assessments.

Modified EIS

Participants in the intervention arm will receive all services included in EIS, with the exception of concomitant formal psychological interventions for treating CUD, such as MI or CBT individual or group therapy sessions. Clinicians will be assigned an active supporting role, as our formative research showed that participants would like to receive support from clinicians for completing app modules or feedback related to their progress in the intervention at a frequency of approximately once per week. This implies asking about any difficulties with iCC and offering support with the content during each clinical encounter, as requested by the participants. Clinicians will use personalized login credentials to access the iCC dashboard and monitor the progress of the participants in the intervention (eg, number of modules completed and frequency) if allowed by the participant to do so.

Measurements

Schedule, Sociodemographic Data, and Social Support

Clinical research assistants will conduct all assessments at baseline and at weeks 6, 12, and 24 after consent, in person, over the phone, or using telemedicine. Data will be stored in REDCap (Research Electronic Data Capture), a secure, web-based software platform designed to support data capture for research studies [53,54] (see Figure 2 for assessment and procedure schedule corresponding to the Standard Protocol Items: Recommendations for Interventional Trials [SPIRIT] statement [55]). Sociodemographic data will be collected at baseline and will include gender identity, biological sex, ethnicity, educational attainment, employment or studying status, income, living arrangements status, and housing status. To measure social support, we will use the 10-item Social Provisions Scale, which has been validated in individuals with schizophrenia and includes 5 domains: tangible help, emotional support or attachment, orientation, reassurance of worth, and social integration [56]. Items will be measured on a 4-point Likert scale from “1-totally disagree” to “4-totally agree,” and higher total scores (range 10-40) indicate better social support.

Figure 2. Schedule of enrollment, allocation, interventions, and assessments. W: week.

	STUDY PERIOD							
	Enrolment	Baseline	Allocation	Post-allocation				
TIMEPOINT	*W -4; W -2*	*W -2; W0*	*W 0*	*W1; W5*	*W6*	*W7; W11*	*W12*	*W24*
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Locator information form **(LOC)**	X	X			X		X	X
Randomization form **(RAND)**			X					
INTERVENTIONS:								
ICanChange **(iCC)** + modified EIS **(mEIS)**				←	—	—	—	→
Early Intervention Services **(EIS)**				←	—	—	—	→
ASSESSMENTS:								
Demographics **(DEMO)**		X						
Social Provisions Scale **(SPS-10)**		X						
Intervention and Services Form **(ISF)**					X		X	X
Timeline Follow Back **(TLFB)**		X			X		X	X
Client Satisfaction Questionnaire **(CSQ-8)**					X		X	
Marijuana Problems Scale **(MPS)**		X			X		X	X
Severity of Dependence Scale **(SDS)**		X			X		X	X
Drug-Taking Confidence Questionnaire **(DTCQ)**		X			X		X	X
Precaution Adoption Process Model **(PAPM)**		X			X		X	X
Positive and Negative Syndrome Scale **(PANSS-6)**		X			X		X	X
Protective Behavioral Strategies-Marijuana **(PBSM)**		X			X		X	X
Satisfaction with Life Scale **(SWL)**		X			X		X	X
Health care utilization **(HCU)**		X			X		X	X
Adverse events **(AE)**					X		X	X

Primary Outcomes: Intervention Completion and Trial Retention Rates

For both outcomes, the denominator will represent the total number of participants randomized to the intervention or control groups. For iCC intervention completion, the numerator represents the number of participants who completed all 10 modules of the first section and at least 1 follow-up module related to involvement in reaching their cannabis use objective. This information will be collected through iCC. For participants randomized to the control group, the numerator will represent the total number of those who participated in EIS and ongoing engagement with EIS at the time of the 12-week assessment. The ongoing engagement with EIS will be documented using data collected through the Intervention and Services Form related to the receipt of services for cannabis use (at all study visits) and data from medical health records pertaining to receipt of any interventions that are offered at the clinic. For retention rate in both study groups, the numerator will be the number of participants who completed all week 12 (end point) assessments.

Secondary Outcomes

The secondary outcomes are as follows:

1. Cannabis use will be measured using a self-report tool, the Timeline Follow Back (TLFB) [57]. On the basis of the TLFB, for each day in the last 14 days, participants indicate first if they used cannabis (yes or no). To facilitate their recollection, participants will be asked about memorable days (eg, birthdays) and patterns of use (eg, more use on weekends). Then, for each day they used cannabis, they will provide the quantity of cannabis used. Participants will be reasked about the cannabis form used (dried cannabis smoked, oral spray, oral oil, dried cannabis vaporized, concentrated vapor, oral capsules, beverages, edibles, etc) and for each form, they will provide the quantity and the unit (eg, g, mg, and mL) and the concentration in tetrahydrocannabinol and cannabidiol (%, mg/mL, mg/dose, or unknown). The quantity of cannabis used on a specific day represents grams per method of cannabis use (eg, dried cannabis smoked) × number of times the method is used per day. The quantity of cannabis used in the last 14 days will be calculated. The inclusion of the quantity of cannabis use as a secondary outcome, which has been used in other similar trials [35], is justified by research suggesting that in individuals with psychosis and CUD, face-to-face psychological interventions (MI and CBT) are more effective in decreasing the quantity than the frequency of use [22].
2. Participant satisfaction with using iCC or programs for CUD offered as part of EIS (control group) will be measured with the validated 8-item Client Satisfaction Questionnaire (CSQ-8) [58]. Items (eg, “How would you rate the quality of program you received”) are scored on a scale from 1 to 4 and a higher total score reflects higher satisfaction. Participants who discontinue participation in the study will be invited to complete the CSQ-8 upon discontinuation. Other details about their experiences are collected in an open-ended format.
3. App use: Considering the importance of evaluating app use and adoption metrics in eHealth trials [43], data will be collected automatically through iCC for the entire 24-week participation in the intervention. The following outcomes will be monitored: number of iCC modules and strategies completed, number of times a particular module was opened and completed, time spent on individual iCC modules, time elapsed between the initiation and completion of individual iCC modules, and total time spent completing the iCC intervention and boosters. For each participant, iCC data will be synchronized with a password-protected Amazon

Web Services account for a period of 24 weeks. Data related to clinicians' use of the dashboard (ie, number of logins) are synchronized with the Amazon Web Services account and will be used for exploratory analyses of clinician involvement in monitoring participant progress during the intervention.

4. Trial parameters: Information collected during enrollment and study visits (stored in REDCap) will allow us to calculate the number of participants who were referred to the study, screened, eligible, provided informed consent, randomized, initiated the intervention (ie, who both logged into iCC and complete module 1), and completed baseline and follow-up assessments.

Exploratory Outcomes

The exploratory outcomes are as follows:

1. Cannabis use frequency (and abstinence) will be measured using the TLFB. Participants who declare using alcohol will be asked about the frequency and quantity of use, and those who consume other substances (eg, cocaine, amphetamine, opioids) will be asked about the frequency of use and route of administration.
2. Cannabis-related negative social, occupational, physical, and personal consequences will be assessed using the 19-item unidimensional self-report instrument, the Marijuana Problems Scale (MPS) [59,60]. Higher MPS scores (range 0-38) denote more negative cannabis use consequences.
3. Cannabis use disorder severity will be measured with the 5-item Severity of Dependence Scale (SDS), which has been validated in people with early psychosis [61,62]. Higher total scores (range 0-15) indicate more severe dependence symptoms.
4. Confidence in resisting cannabis use in 8 different situations (eg, "if other people treated me unfairly or interfered with my plans") will be measured using the validated Drug-Taking Confidence Questionnaire (DTCQ) [63], with higher scores denoting higher confidence levels to resist cannabis use.
5. The measurement of intentions to stop using cannabis has been informed by and adapted from the Precaution Adoption Process Model [64], a theoretical stage-based model that allows participants to place themselves in one of 6 nominal stages: (1) unengaged (ie, "As of right now, I haven't thought about if I want to stop using cannabis"); (2) undecided (ie, "I'm still unsure if I want to stop"); (3) decided not to act (ie, "I do not want to stop"); (4) decided to act (ie, "I want to stop"); (5) acting (ie, "I recently stopped"); and (6) maintenance (ie, "I stopped using cannabis over a month ago").
6. The severity of positive and negative symptoms of psychosis will be measured using an interviewer-administered scale, the Positive and Negative Syndrome Scale (PANSS-6) [65]. This well-validated short version of the PANSS has been chosen rather than the complete 30-item version to reduce the burden of data collection. A total score of 6 reveals no psychotic symptoms, and a total score of <14 will be considered the cutoff for remission of schizophrenia [65].
7. To measure cannabis-related harm, we will use the 17-item Protective Behavioral Strategies-Marijuana (PBSM) questionnaire, which has been shown to be valid and free of bias in terms of gender, sex, race, ethnicity, and recreational marijuana use legal status [66]. We use the table provided by Pedersen et al [66] to convert the sum score into Item Response Theory scale scores, with higher scores indicating higher-risk behaviors [66].
8. Participants will report their Satisfaction with Life pertaining to 4 domains (ie, living situation, social relationships, work, self, and present life) using the 18-item Satisfaction with Life questionnaire (SWL), which has been validated for schizophrenia and schizophrenia-related disorders [67]. In each domain, higher mean scores indicate greater satisfaction.
9. Self-reported health service use data using the Health Care form will include emergency department visits and hospitalizations for psychological, emotional, or mental health issues in the last 30 days (yes or no). In the case of hospitalization, additional data will be collected (ie, number of admissions, duration of stay, reason for admission, and confirmation using medical records).

Sample Size

Sample size calculations were guided by the results of studies that used psychological app-based interventions targeting cannabis use in individuals without psychosis [68] or with subthreshold psychosis [38], in which attrition was lower than 33% and the intervention completion rate was approximately 50%. We will use a CI approach with binomial SEs and normal approximation [69] to calculate the number of participants needed to reject the null hypothesis that at 12 weeks, the attrition will be ≥50% (expected maximum attrition of 30%) and intervention completion will be ≤50% (the minimum expected proportion of participants who download the app and complete at least 11 out of 21 intervention modules—excluding the 3 boosters—is 70%). We calculated that at least 33 participants must be randomized per study arm to maintain 80% power to detect hypothesized effects with a 1-sided significance level of 5%. For the intervention completion outcome, we adjusted the sample size for an estimated 30% attrition and calculated that a total of approximately 100 participants will be needed for this study ($2 \times 33 / 0.7 = 94$).

Randomization and Blinding

Once baseline assessments are completed, participants will be randomized to either (1) iCC+mEIS or (2) EIS. Within each stratum, based on biological sex, a random 1:1 group allocation sequence is generated using a permuted block design with blocks of varying sizes to decrease the likelihood of predictability of group assignment. The group allocation will not be masked, and the baseline visit concludes with participants logging into iCC and completing the introductory module. If a participant drops out of the study at any point following randomization, the randomization slot will not be reallocated to a new participant. The randomization schedule is concealed within the secure REDCap system and was created by the CHUM Center for the Integration and Analysis of Medical Data (CITADEL). The study participants, clinicians, and research

staff conducting assessments will not be blinded to the group assignment, while individuals performing analyses will be blinded.

Statistical Analyses

The 1-sided chi-square 95% CI will be calculated to estimate the lower bound of iCC completion and trial retention rates. We will consider participation in iCC acceptable if more than 50% of the participants completed at least 11 out of 21 intervention modules at week 12. The trial will be considered feasible if the attrition at week 12 does not reach 50%. An analysis of covariance model will be used to provide a preliminary assessment of the effect of treatment on the quantity of cannabis use (dependent variable) at 12 weeks (end of intervention). The independent variables will be the quantity of cannabis use at baseline and a dichotomous variable reflecting arm allocation. The second model will include covariates that were found to be different between the groups at baseline. For participants' satisfaction with the intervention, we will calculate the CSQ total scores as well as the mean and SD. The groups will be compared using a mixed-effects model with random intercepts for each site. For app use and trial parameters, we will use univariate analyses and report the distribution (frequency tables), central tendency (mean, median, and mode), and dispersion (range and SD).

For exploratory outcomes, we will compute descriptive statistics and bivariate and multivariable analyses using generalized estimating equation (GEE) models. The generalized estimating equation is a repeated-measures regression model that accounts for the correlations between repeated measures for each person [70]. We will use different types of GEE modeling depending on the distribution of the outcome. For cannabis frequency (count data), we will use Poisson; for the abstinence (binary), we will use binomial; and for continuous variables (ie, scores calculated for MPS, SDS, DTCQ, PANSS, PBSM, SWL, and SPS), we will use linear GEE modeling. Using this analytic approach, we will estimate the multivariable associations between the outcomes and study visits (ie, baseline and end of intervention), study condition (the reference group will be the control arm), and their interaction, as well as other predictors and covariates, such as sociodemographics, social support, CUD severity, behavioral stage of change, medication status, and other substance use. We will use the chi-square test of proportions to compare behavioral stages at different time points and between the 2 study arms.

Missing entries for fields where missing values account for <5% of the sample may be imputed using the sample mean for continuous variables and sample mode for categorical variables. Fields with >5% missing entries may be excluded from multivariate models. In the case of missing visits, the proposed types of analyses (linear mixed-effects models and GEE models) will include all participants with at least one nonmissing visit, which may increase statistical power and reduce estimation bias. Our analysis plan includes both intention-to-treat and per-protocol analyses.

Training Activities

The study staff will receive training on all assessments and procedures as per protocol, and include assessments, study interventions, safety procedures, data management, and collection. Special training sessions will be organized for clinicians to support the use of iCC and include a description of the functionalities of the app, content, and structure. In addition, clinicians will receive free access to the app for a period of 7 days (using a special account) to facilitate the use of the dashboard and discussions with participants about iCC use. Additional training sessions will be organized throughout the study as needed.

Other Information

An independent Data and Safety Monitoring Board (DSMB) will conduct periodic reviews (every 9 months) to monitor the safety of the interventions and the validity and integrity of the data from the study. On the basis of the DSMB's recommendations, alterations can be made to the study design (eg, increase or decrease in the number of sites, sample size) based on poor accrual or recruitment, retention, or iCC acceptability. The DSMB may recommend stopping the study early because of an excess of adverse events.

Patient partners will also be involved during the trial with the lead site team, providing input and feedback on study conduct and any challenges that may arise.

Results

Study enrollment began in July 2022. We expect to complete participant enrollment in January 2024 and data collection in July 2024. The main results are expected to be submitted for publication in 2024. We will engage patient partners and other stakeholders in creating a knowledge translation plan and developing plain language summaries, reports, briefing notes, and other documents that will be used to disseminate our results to a wider audience.

Discussion

Study Strengths and Challenges

The manuscript describes the protocol of a pilot RCT that aims to evaluate the acceptability of iCC, a new mobile-based psychological intervention for helping young adults with psychosis and CUD decrease their cannabis use, and the feasibility of conducting the study in participants who receive EIS for psychosis. In addition, the trial will provide preliminary data related to cannabis use and other outcomes relevant in clinical practice. To our knowledge, this is the first RCT of an mHealth intervention that incorporates CBT and MI approaches to address CUD in this population.

We adapted the content and design of the app based on the results of our formative research [48] and the continuous feedback and input from patient partners. Although these approaches may improve the likelihood of meeting the intervention acceptability and completion targets, many challenges may arise with mobile health apps. For example, flexibility in the pace of module completion, although desired

by the target population, may lead to suboptimal content uptake by participants. Progressing too fast through the intervention could represent a barrier toward increasing cannabis coping skills and correcting maladaptive cannabis use behaviors. Nevertheless, our decision to not limit the number of new modules that can be completed per week is also supported by the recommendations (for the development of mental health smartphone apps) published by Khazaal et al [71], who advocate against restricting the utilization flow of a mental health smartphone app as it can reduce participant concentration in performing the activity and decrease their satisfaction with achievements. Whether this flexibility will be beneficial toward app use and utility in the context of young adults with psychosis and CUD remains to be determined. To evaluate our approach, we will conduct exploratory subgroup analyses based on participants' compliance with the recommended frequency of 2 modules per week [72] and assess differences in cannabis use outcomes and satisfaction with iCC.

To consider the trial feasible, at least 50% of participants must complete all study assessments at week 12, which corresponds to the end of the iCC main intervention (excluding booster sessions). In the absence of similar trials in our target population, we chose this cutoff conservatively, as it is close to the maximum attrition rate of 65% reported in studies using app-based interventions for decreasing cannabis use in individuals *without psychosis* [34-36]. Our approach is justified by the clinical characteristics of participants attributable to psychosis and CUD, which could represent a barrier in complying with the study procedures. However, we expect an attrition rate closer to 30% because we tailored the iCC intervention to participants' needs, restricted inclusion criteria to participants interested in using an app-based psychological intervention, and planned to offer iCC to participants allocated to the control arm at the end of the study. In addition, the intensive clinical follow-up that is offered in EIS for psychosis could contribute to lower attrition rates. Other implemented strategies that could reduce loss to follow-up include maintaining an updated record of participant contact information throughout the study, scheduling study visits according to participant availability, and offering flexible in-person or web-based study visit assessments.

In individuals with psychosis, face-to-face psychological interventions were found to be more effective in decreasing the quantity than frequency of cannabis used [22]. However, no study has evaluated the effects of mHealth interventions on the quantity of cannabis used in individuals with CUD and psychosis. In their RCT that included a web-based psychological intervention in individuals without psychosis, Rooke et al [35]) found a small effect (Cohen d=0.19) of a short 6-module intervention on the quantity of cannabis consumed at the 12-week follow-up [35]. Similar to the intervention used by Rooke et al [35], iCC incorporates behavioral and motivational approaches tested by Copeland et al [47]. Our pilot study will offer valuable information related to using a higher-intensity 19-module intervention and offering support during clinical encounters to participants who have difficulties in completing iCC.

Our study has some limitations. Due to the centralized randomization method, the variability in the number of clinicians at participating sites, and expected differences in enrollment activity across sites, it is possible that some clinicians may have patients in both study groups, which increases the risk for iCC components to be incorporated into the treatment of participants in the control group, resulting in type II errors. To document possible crossover effects, we will explore differences in outcomes between participants in the control group whose clinicians have patients in the iCC group and those whose clinicians do not. Despite being assigned an active supporting role for iCC completion, we expect a variable level of clinician involvement that could impact iCC completion rates. We will use dashboard use parameters (eg, number of logins) as a proxy for clinician support with iCC and explore the association between clinician engagement and iCC completion. To measure cannabis use, we relied exclusively on participants' self-reports and the TLFB instrument. However, we estimated a relatively low risk of measurement bias associated with our approach, as the TLFB has been shown to have high levels of agreement with biological measures [73]. As EIS does not include a mobile app–based psychosocial intervention, participant blinding was not possible. Clinicians cannot be blinded because the participants in the iCC arm receive mEIS. Research staff collecting data are not blinded to the group assignment because they offer help with technical issues related to trial participation. However, groups will be labeled with nonidentifying terms to ensure the blinding of individuals performing data analysis. Moreover, because we only included individuals interested in participating in an app-based intervention, the results of this study may not be applicable to all young adults who receive treatment for FEP and CUD. Finally, we acknowledge the limitations of efficacy assessments in pilot trials and the risks associated with using such data to design large-scale trials. Therefore, we will carefully contextualize these data when interpreting them to avoid misguiding decision making in future trials using iCC.

Conclusions

Given the dearth of mHealth interventions for CUD in individuals with psychosis, the results from this pilot trial will inform the adaptation of iCC to increase its acceptability and usability and provide critical data for designing a larger trial to evaluate the efficacy of the intervention in improving outcomes that are most relevant in this population. This study aligns with the current strategies of major research funding authorities to stimulate the development and rigorous testing of innovative mHealth interventions for individuals with mental health issues.

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Data Availability

The data sets generated during or analyzed during this study are not publicly available because the trial is ongoing but will be made available from the corresponding author upon reasonable request.

Authors' Contributions

OT drafted the first version of the manuscript, tables, and figures. OT, AA-B, AW, TL, J Copeland, PL-T, SC-M, J Côté, DC, SD, SL'H, CO-P, M-AR, PGT, MV, and DJ-A contributed to the conception and design of the study, development of the app-based intervention, and development of the study protocol. DJA obtained funding and supervised study development and conduct. All authors critically reviewed and approved the manuscript.

Conflicts of Interest

PGT declares speaker fees and advisory board honoraria from Otsuka Lundbeck, Janssen, Abbvie, Teva Canada, in the last 2 years. DJ-A receives study material from Cardiol Therapeutics for a clinical trial funded by the Quebec Ministry of Health and Social Services. All other authors have no conflicts of interest to declare.

Multimedia Appendix 1
iCanChange push notifications.
[PDF File (Adobe PDF File), 117 KB - resprot_v11i11e40817_app1.pdf]

Multimedia Appendix 2
iCanChange badges.
[PDF File (Adobe PDF File), 108 KB - resprot_v11i11e40817_app2.pdf]

Multimedia Appendix 3
iCanChange screenshots.
[PDF File (Adobe PDF File), 2095 KB - resprot_v11i11e40817_app3.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
CHUM: Centre Hospitalier de l'Université de Montréal
CSQ: Client Satisfaction Questionnaire
CUD: cannabis use disorder
DSMB: Data and Safety Monitoring Board
DTCQ: Drug-Taking Confidence Questionnaire
EIS: Early Intervention Services
FEP: first-episode psychosis
GEE: generalized estimating equation
iCC: iCanChange
mEIS: modified EIS
MI: motivational interviewing
MPS: Marijuana Problems Scale
PBSM: Protective Behavioral Strategies-Marijuana
RCT: randomized controlled trial
SDS: Severity of Dependence Scale
SWL: Satisfaction with Life
TLFB: Timeline Follow Back

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Protocol

A Digital Health Intervention for Stress and Anxiety Relief in Perioperative Care: Protocol for a Feasibility Randomized Controlled Trial

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Abstract

Background: Stress and anxiety are psychophysiological responses commonly experienced by patients during the perioperative process that can increase presurgical and postsurgical complications to a comprehensive and positive recovery. Preventing and intervening in stress and anxiety can help patients achieve positive health and well-being outcomes. Similarly, the provision of education about surgery can be a crucial component and is inversely correlated with preoperative anxiety levels. However, few patients receive stress and anxiety relief support before surgery, and resource constraints make face-to-face education sessions untenable. Digital health interventions can be helpful in empowering patients and enhancing a more positive experience. Digital health interventions have been shown to help patients feel informed about the possible benefits and risks of available treatment options. However, they currently focus only on providing informative content, neglecting the importance of personalization and patient empowerment.

Objective: This study aimed to explore the feasibility of a digital health intervention called the Adhera CARINAE Digital Health Program, designed to provide evidence-based, personalized stress- and anxiety-management methods enabled by a comprehensive digital ecosystem that incorporates wearable, mobile, and virtual reality technologies. The intervention program includes the use of advanced data-driven techniques for tailored patient education and lifestyle support.

Methods: The trial will include 5 hospitals across 3 European countries and will use a randomized controlled design including 30 intervention participants and 30 control group participants. The involved surgeries are cardiopulmonary and coronary artery bypass surgeries, cardiac valve replacement, prostate or bladder cancer surgeries, hip and knee replacement, maxillofacial surgery, or scoliosis. The control group will receive standard care, and the intervention group will additionally be exposed to the digital health intervention program.

Results: The recruitment process started in January 2022 and has been completed. The primary impact analysis is currently ongoing. The expected results will be published in early 2023.

Conclusions: This manuscript details a comprehensive protocol for a study that will provide valuable information about the intervention program, such as the measurement of comparative intervention effects on stress; anxiety and pain management; and usability by patients, caregivers, and health care professionals. This will contribute to the evidence planning process for the future adoption of diverse digital health solutions in the field of surgery.

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KEYWORDS

CARINAE; digital health; perioperative process; patient empowerment; stress and anxiety management; mobile health; mHealth; virtual reality; VR; health recommender system; HRS

Introduction

Background

Patients undergoing surgical operations exhibit symptoms of severe stress, anxiety, and fear as common physiological and psychological reactions to potentially threatening situations associated with surgeries [1,2]. Family caregivers are expected to assume a complex caregiving role for these patients and are therefore confronted with emotional distress and physical decline as well [3].

Surgeons and health care professionals (HCPs) use a variety of stress-coping strategies, as stressors that affect surgical performance and contribute to complications [4]. Psychological support and patient education have proven to be very effective in reducing this stress and anxiety [5,6]. Provision of information about their surgery constitutes an essential part of the preoperative experience both in patients and their caregivers because it helps decrease anxiety levels as well as surgical complications [7,8]. Patient empowerment improves self-care management, encourages patients to take an active role in managing their diseases, and expands outcomes such as satisfaction, cost, health status, and function [9]. Addressing caregiver strain is also an important aspect of care for pediatric patients [10] and those with special health care needs [11].

Advances in digital health interventions have been a great support for enhancing awareness about health conditions and for the management of mental health by relying on both nonimmersive systems (eg, mobile apps) and immersive systems (eg, virtual reality [VR]) [12]. These include aspects such as supporting patients in the management of anxiety, stress [13], and pain [14,15]. VR has been used in multiple health care applications, including reducing stress and pain, training medical practitioners, patient counseling, cognitive rehabilitation, physical therapy in medicine, diagnostic and treatment needs in dentistry, in mental health management, and surgery [16]. A multiuser immersive VR (IVR) system was developed and used during presurgical discussions in a prospective patient cohort undergoing cerebrovascular surgery [17]. An IVR intervention adopted in pediatric patients to manage pain and anxiety provides a new, easy, and cost-effective intervention that can be applied to other painful and stressful medical procedures [18]. Pain is a highly distressing symptom for patients in all clinical settings, and it is influenced by stress and anxiety levels. VR applications have proven to be efficient in stress relief and pain management mainly because of their distractive properties [19].

Digital health interventions generate substantial amounts of data that can be used for personalization, relying on artificial intelligence (AI) techniques [20-24], including applications in perioperative care users [25]. A particular type of AI-based system is the health recommender systems (HRSs), which enable the personalization of patient interventions based on their unique behavioral and health needs [26,27]. For example, perioperative stress is perceived very differently from patient to patient and varies largely with the severity of the illness and the required surgery type. Therefore, the effort to assess stress levels and interventions to develop the skills needed to better cope with it should be a personalized experience related to health behavior theories. HRSs incorporate behavioral change models such as I-Change to guide the personalization of educational and behavioral intervention [28,29].

There is a lack of understanding of the feasibility of combining VR with mobile-based technologies as the main channel for the provision of digital health intervention [30]. In this study, what is explored is the feasibility of a digital health intervention that leverages latest mobile and VR technologies within the use case of helping patients to manage stress and anxiety during surgery while promoting healthy recovery.

On the basis of these premises, the aim of this study was to explore the trial design and effect of a new digital health intervention called the Adhera CARINAE Digital Program that combines evidence-based perioperative stress management, anxiety, and pain relief techniques grounded in behavioral science with relevant education and information resources. As such, this study aimed to explore whether using an advanced digital health platform, which provides evidence-based, personalized stress- and anxiety-management methods, through the designed intervention can reduce perioperative stress. The results of the intervention were measured through a series of self-reported measurements and compared with versus of a control group to determine the effect of the intervention.

The Adhera CARINAE Digital Health Program Overview

Digital health interventions designed to help patients before, during, and after surgery reduce their stress and anxiety levels and improve their overall self-management, including support for positive lifestyle changes [29]. Within the context of this study, the selected clinical use cases were cardiac, traumatological, and oncology surgeries, including both pediatric and adult patients. In the case of pediatrics, the key users include caregivers.

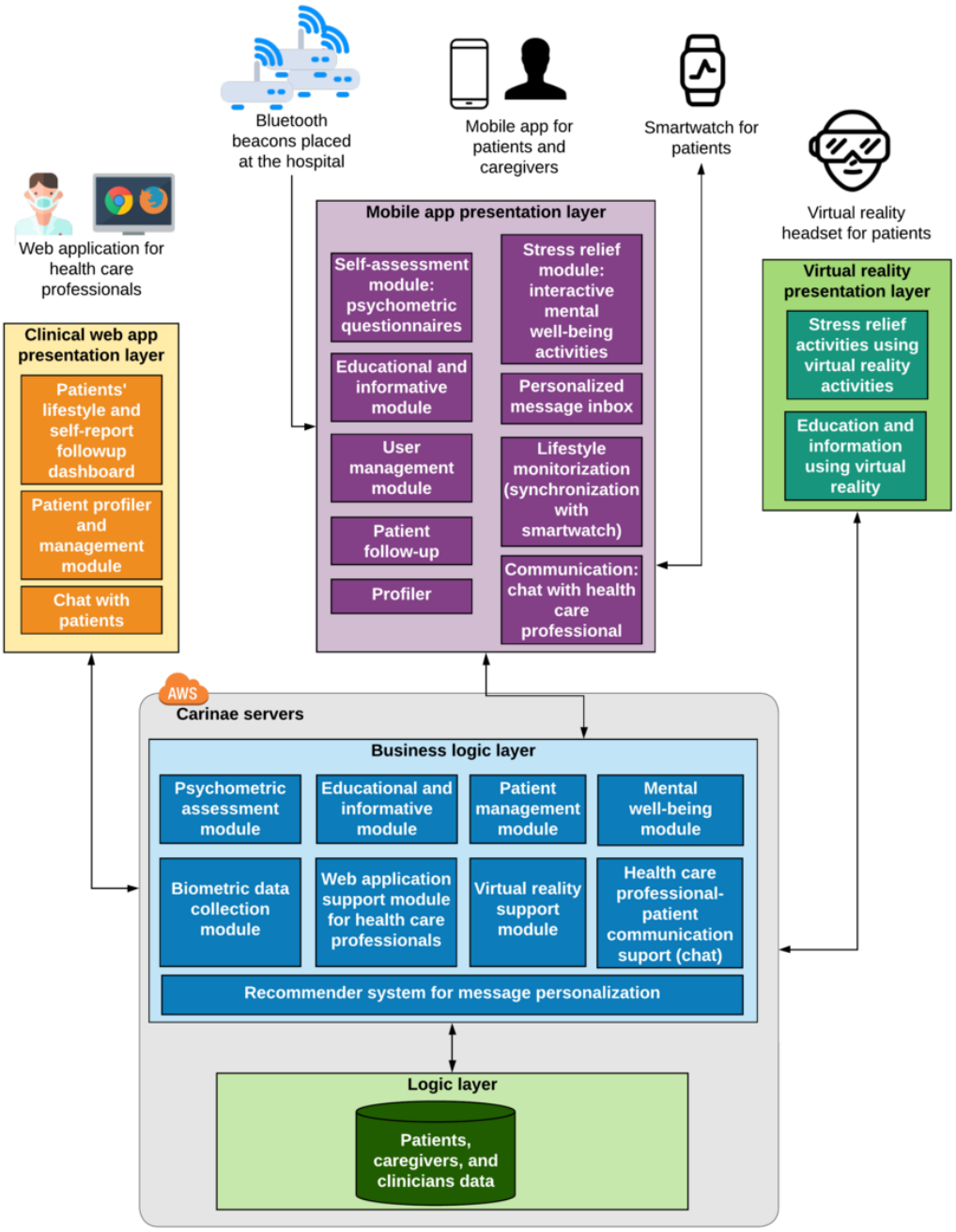
The development of digital intervention has followed an iterative, detailed requirement elicitation process involving end users and capitalizing many years of work on personal health systems [31-34]. It combines various multichannel technologies as well as evidence-based content to support patients (including children and older adults) in their perioperative journey, as well as caregivers and HCP. The targeted surgeries include, but are not limited to, cardiopulmonary and coronary artery bypass surgery, cardiac valve replacement, prostate, kidney, and bladder cancer surgery, hip and knee replacement, maxillofacial surgery, orthognathic surgery, and scoliosis surgery. The design of the intervention was based on input from (1) personalized recommendations and educational content, (2) communication with HCPs, and (3) activities on mental well-being [26,35]. All modules were designed to be flexible and adaptable to accommodate national, regional, local, and institutional policies and guidelines. The embedded educational content is based on clinical guidelines and approved by clinicians, whereas the content has been generated by a multidisciplinary team including HCPs, surgeons, and psychologists. Interoperability is a key advantage of the system, as it can export or import data using both existing standards and proprietary mechanisms.

The digital intervention program delivers nonmedical intervention to patients, including (1) personalized health education to improve patient self-management skills addressing surgery needs and recovery, (2) behavioral motivational messages aimed at promoting healthier lifestyles, (3) mental well-being support to reduce stress and anxiety, and (4) a collaborative platform to enable collaboration between patients, caregivers, and HCPs (Figure 1). The program is delivered using a digital health ecosystem that leverages the following key elements:

- Mobile app: This incorporates AI-based behavioral coaching based on the Adhera Health Precision Digital Companion Platform that incorporates an advanced HRS, which is complemented by educational content and mental well-being exercises based on cognitive behavioral therapy. The mobile solution also integrates wearable technologies (a Withings Pulse HR smartwatch) and Internet of Things (IoT) technology (location beacons in the hospital) to support patient monitoring and personalization.
- VR component: This provides a combination of educational content and mental well-being exercises.
- Clinical web application: This provides patient support dashboards and tools for HCPs involved in patient care (eg, chat and monitoring).

Patient information required for digital intervention includes minimal demographic information, patient medical records, and preferences and is securely stored in European Amazon Servers, respecting all national, international, and European regulations and aligned with ISO 27001. Data are encrypted, both in transit and at rest, and only minimal personal information required is stored.

Figure 1. Architecture overview and functionalities embedded into the Adhera CARINAE Digital Program intervention. AWS: Amazon Web Services.



The Digital Health Program: Mobile App Component

The intervention mobile app (iOS and Android app) was designed to support patients before, during, and after surgery with a set of features (Figure 2). The underlying principle of the mobile component is to support (1) patient self-management education, (2) stress reduction techniques via mobile-based exercises, (3) behavioral motivation, and (4) collaboration between clinicians and caregivers.

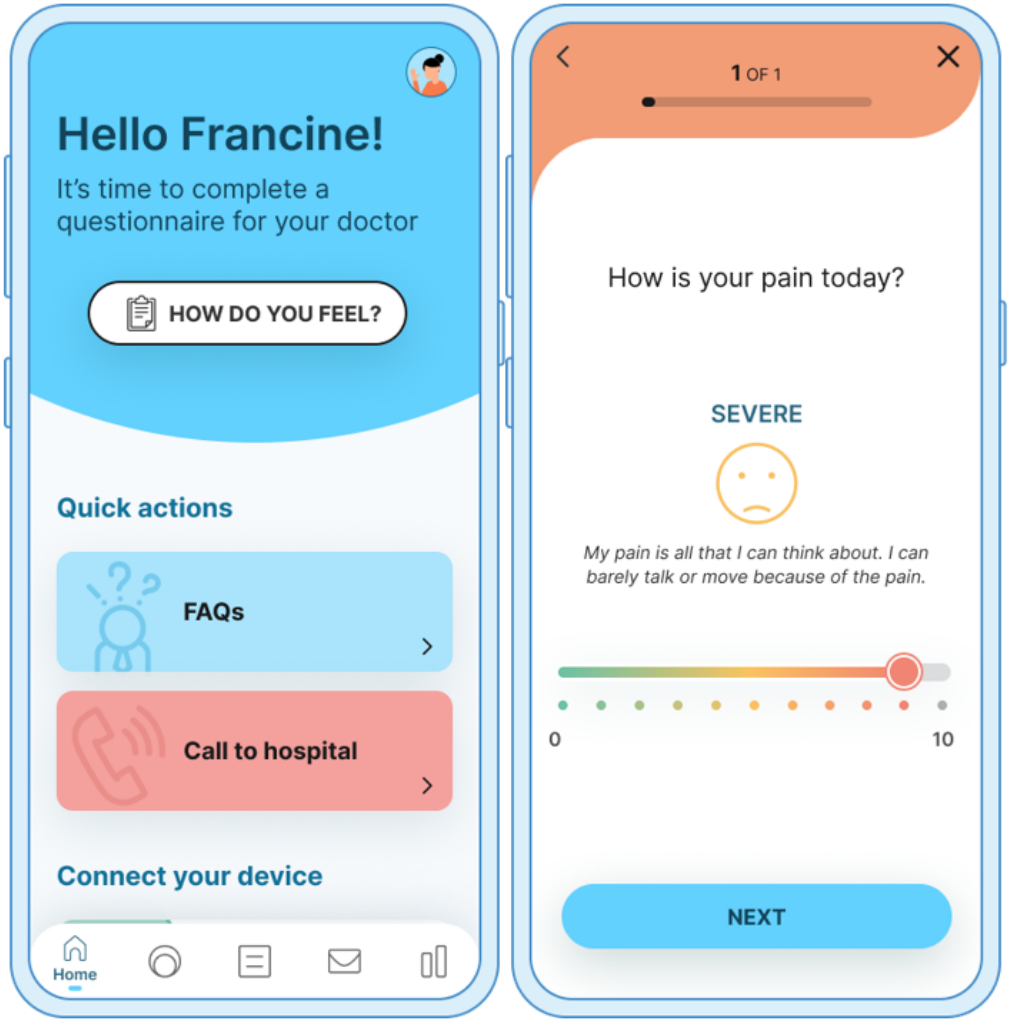
The educational and information modules of the mobile solution are designed to support self-management skills and related knowledge using principles set up by the Patient Education Materials Assessment Tool recommendations regarding understandability and actionability [33]. These modules leverage the patients' profile details to present a set of relevant educational contents about their surgery as well as beneficial information to prepare patients physically and emotionally. These contents were complemented with related quiz questions to maximize knowledge retention. The psychoeducational and information modules support patients throughout the 3 main stages of the patient journey: (1) thirteen educational modules aimed at preparing for the surgery (eg, knowledge about the surgery, coping mechanism for fear and stress, self-care for preparation for the surgery, awareness about smoking cessation and other lifestyles, and admission day tips); (2) five educational modules with aspects related to the surgery, which are designed to be used during hospitalization; and (3) eight modules addressing aspects related to postsurgery recovery (eg, skin and wound care, healthy eating, rehabilitation, physical activity). The educational content is personalized based on the patient profile, so contents are related to the specific surgery of the

patient and adapted to the patient's health care provider clinical workflow.

The mobile app also includes *mental well-being activities* designed for stress relief based on mindfulness principles and cognitive behavioral therapy (see Multimedia Appendix 1 for a screenshot). These include a combination of multimedia content, such as nature and music mindfulness exercises, breathing relaxation training, and meditation. When a mobile app detects high levels of reported stress, mental well-being exercises are recommended to users.

The mobile app also addresses the importance of *patient monitoring* of health status and lifestyle to provide personalized care and tailored content. For this reason, the mobile app provides both subjective (eg, patient-reported outcomes based on psychometrics) and objective monitoring using a smartwatch (Withings Pulse HR, Withings France SA) to monitor biometric variables of health outcomes and relevant behaviors (eg, physical activity; refer to Multimedia Appendix 2 for a screenshot). HCPs can monitor these patient parameters via a web application (see the next subsection). In the context of supporting patients during hospitalization, the solution relies on automatic patient tracking using an IoT-based indoor location. Patient monitoring includes multiple questionnaires enabling pain and stress self-assessment as well as wound healing progress. The questionnaires already available include the visual analogue scale (VAS) for stress, VAS for pain, and Bluebelle Wound Healing Questionnaire [34]. Through this module, patients can report potential complications while monitoring the wound healing and recovery time after discharge.

Figure 2. The Adhera Health CARINAE Digital Program mobile app.



As part of the integration with the existing clinical workflow, the mobile solution provides a *communication module* where patients can chat with their health care team through an asynchronous chat.

One of the key elements of a mobile solution is *personalization*, which maximizes patient engagement. A core element of the personalization strategy is the use of the Adhera HRS, which provides personalized messages to patients based on behavioral change models such as the I-Change model [26]. These messages are tips and pieces of advice about how to adopt healthy behaviors such as quitting smoking before and after surgery to improve recovery length. Patients are guided to adhere to healthier habits and reduce their stress and anxiety levels before and after surgery.

The motivational messages of the digital program have been designed by expert psychologists, clinicians, and researchers in the field of behavioral change models for stress and anxiety relief (refer to Multimedia Appendix 3 for a screenshot). The

messages were based on specific motivational and behavioral change factors represented by attitudes. These include factors such as social influence and support in reducing stress and anxiety symptoms, self-efficacy (patients' perception of their ability to manage stress and anxiety situations), personal skills for self-regulation (in stress and anxiety events), and action planning (actions to perform the desired behaviors and coping or maintaining planning). These factors are encountered in the 3 phases of the behavioral change process: enhancing awareness, increasing motivation, and leading to intentional behavioral change. According to this theoretical framework, the message meta-features were designed first, for each phase and factor, ensuring at least one message for each meta-feature and for each combination of meta-features. Second, motivational messages have been defined also considering sex and age differences, as well as the type of surgery and patient. To provide motivational messages, we relied on the I-Change model, which provides guidance on personalizing motivational messages according to individual patient profiles. These recommendations are sent with the frequency preferred by users and when the AI-based solution detects that a subjective or physiological parameter has increased or decreased (eg, reported high stress level and sensor-derived physical activity), these parameters are only used for personalization of the AI-based recommendations and not for assessing the stress levels. In this case, a stress-relief technique is recommended to the patient depending on the nature of the source of stress. The HRS relies on a profiler module that gathers relevant information from patients about their desired level of detail with regard to surgery information (eg, general or graphical), preferences for techniques to manage stress (music preferences, virtual places, etc), and other relevant information to create personalized interventions (education level, age, medical condition, etc). The stored information is used to adapt the educational and motivational content to individual needs and preferences that the user can change or modify at any time.

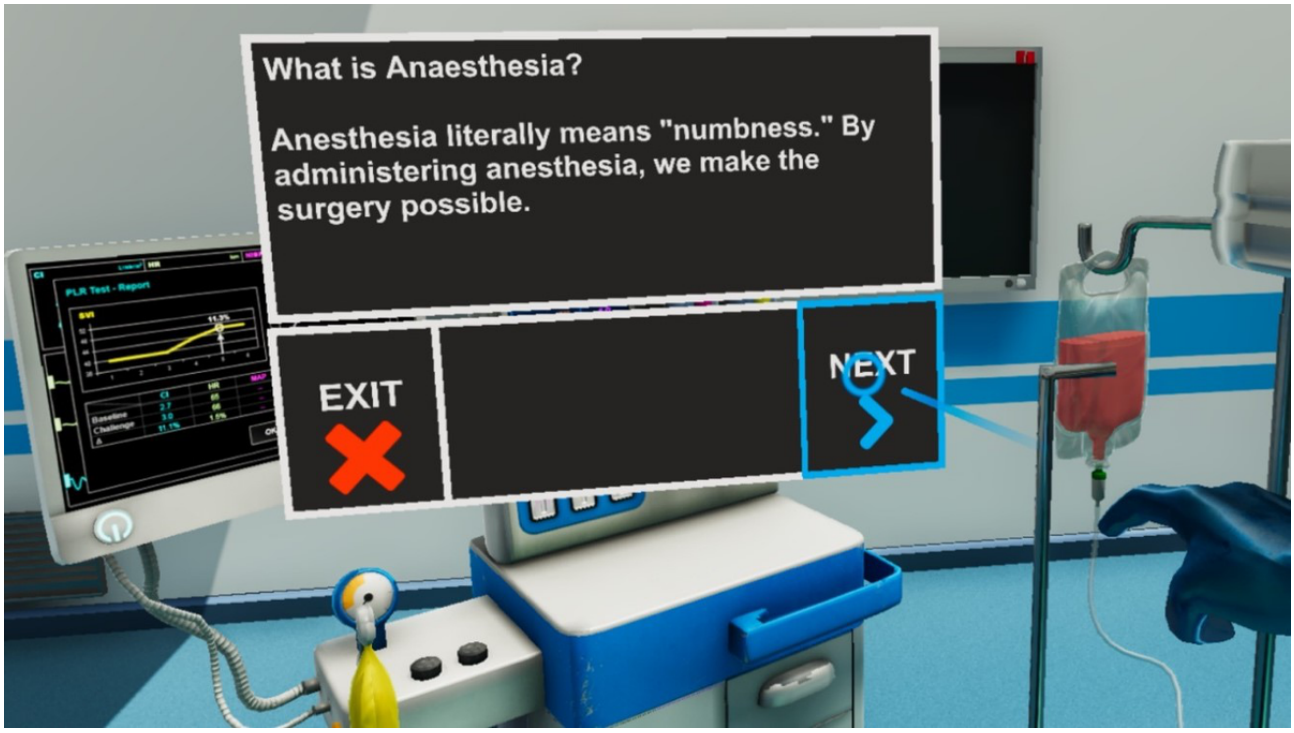
The data from the patient profile (type of surgery, preferences, specific requirements, etc) are combined with lifestyle monitored data and implicit and explicit user interaction patterns with the content. This allows the updating of patient information and helps to tailor the best stress management strategy. Furthermore, a real-time location system based on 4 Bluetooth low-energy beacons installed at the hospital entrance, admission desk, ward, and surgery area provides the mobile app with the patient location, so context-aware content is recommended to the patient based on that location (eg, how to navigate the hospital and preparation after admission). IoT-based functionality is not required at home.

The Digital Health Program: VR Component

Overview

The digital health program used a VR component as an additional channel for delivering patient education, perioperative stress management, and pain relief. The information was presented to the patient via step-by-step guidelines and gamified scenarios, representing learning instructions and procedures to prepare the patient for the actual surgical procedure and the period that will follow the surgery. This content is presented in a gamified way, delivering body and mind exercises, instructions for postsurgery diet, and a postsurgery exercise program. VR implementation represents a novel approach for delivering educational content and knowledge about perioperative care procedures while empowering patients to combat stress. It provides (1) an immersive, gamified educational VR preoperative simulation of the proposed medical procedure to familiarize the patients with each step of the patient journey (Figure 3) and (2) a mindfulness and wellness VR layer for coping with the postoperative effects. This reinforces and complements the interventions delivered by the mobile app.

Figure 3. A screenshot of the digital health virtual reality component displaying anesthesia information inside the "OR" environment.



The CARINAE VR is powered by the Unity-based 3D engine provided by the ORAMA VR M.A.G.E.S. platform [35]. The CARINAE VR component guides users with a virtual companion, who is a friendly robot that addresses users in their native language using both audio and textual feedback. To encourage adoption by health care institutes, the CARINAE VR component is integrated into the Pico G2 4 K headset, which provides a cheaper, easier-to-use, yet high-quality alternative available in the VR headset market.

Users are transported to a serene and calm location (CARINAE Mansion), inviting them to explore and interact with their content. VR applications consist of interactive means in IVR environments. Such activities are complemented by features designed to distract the patient with short, fun exercises and activities aimed at occupying the patient's focus, reducing stress (in case of an upcoming operation), and distracting them from pain (after surgery). The CARINAE VR component features the following contents:

- The patient enters the *virtual environment*, the CARINAE mansion, located on a remote island during a sunny and relaxing day. When the application was launched, the medical robot introduced basic controls and interacted with the virtual environment. The user becomes familiar with VR controllers and how to access the features of the mobile component. A *multimedia screen* allows the selection of the desired playlist or video organized by genre.
- The patients' *recommended meals* for each day along with their nutritional facts are provided on the interface table (refer to Multimedia Appendix 4 for a screenshot). The board included the recommended perioperative physical exercises for the patient. Exercises can be selected, and a pop-up window containing additional information and recommendations can be opened for the instructions. Outside the CARINAE mansion, there is also a yoga mat in which the user can perform breathing exercises following animated instructions.
- Maps for in-hospital education and familiarization:
  - An *interactive hospital map* guides patients to the hospital. The patient can click the "up" and "down" buttons to see the different floors of the hospital. At the bottom side of the panel, there are selected areas of the hospital that the patient visits during hospitalization, for example, cardiology, surgery room, etc. By clicking on these buttons, the map automatically focuses on and shows the selected position in the hospital.
  - The educational module included a *virtual visit to the operating room*. Users can access the "Operation preview" button located on top of the surgical bed to be teleported to the virtual operating room, where a number of information points pose contents related to their upcoming surgery. These information points also include material regarding the risks and possible complications of the surgery, as well as the anesthesia machine, by addressing the most commonly asked questions about the anesthesia process.
- Stress relief VR applications: The VR environment encompasses various *mini games and interaction points*. In particular, a remote-controlled toy robot allows patients to navigate around the room and playfully interface with multiple types of objects in the scene. Entertainment with physical simulations through virtual characters makes the function feel more natural.
  - Mini games: A mini game called "whack-a-mole" is available with the VR tool. The game consists of taking a wooden mallet and hitting "animatronic" rodents (moles) that protrude out of holes carved on the playing surface and described in the scientific literature as a beneficial tool to improve essential cognitive skills. Another game, known as stone balancing, allows users to balance, or "stack" stones on top of one another to produce various "sculptures." This activity is often used in mindfulness-based stress reduction, as it improves patients' moment awareness.
  - Traveling Exercise: A powerful *visualization* (guided imagery) technique integrated into the VR module engages users to bring their imagination into play to mentally "travel" to a positive, peaceful, and calming setting. Guided imagery has been scientifically linked to effective postoperative pain management.
  - Whiteboard: This VR application allows users to grab pens of different colors and draw them. Coloring has been suggested to have many mental health benefits, one of which is stress relief. It enables users to focus on a task or moment while stimulating creativity and logic.

The Digital Health Program: Clinical Web Application

The web application targets health care providers and provides them with the necessary tools to enroll patients into the digital health program, as well as a tool for following up and communicating with patients. The web application features content about the profile of each patient and their preferences, such as the level of detail that they are interested in about their upcoming surgery, stress management preferences such as music and virtual places, information about their medical history and demographics to facilitate the personalization of the stress-relief content, as well as a dashboard for physicians to facilitate the visualization of patient-reported input over time, such as anxiety and pain levels.

This web application is mainly used to enable HCPs to manage, monitor, and follow patients enrolled in digital health programs. Whenever available, it connects to the electronic health record of the client to automatically retrieve useful information of the users (credentials) and patients enrolled (eg, demographics, medical history, clinical reports, and laboratory tests) as well as to provide relevant information about patients undergoing surgery such as their stress level. The web application includes the following modules.

Profiler for Personalization Module

The profiler module gathers relevant information from patients about (1) the level of information they would like to receive regarding their surgery (general, more detailed, and graphical); (2) how they would prefer to manage stress (music preferences, virtual places, etc); and (3) other relevant information to create

personalized intervention (education level, age, medical condition, etc). The information stored is adapted to individual needs and preferences that the user can change or modify at any time. All necessary actions were taken to ensure equality of use and avoid age and gender discrimination. Data from the patient profile (type or surgery, preferences, specific requirements, etc) are combined with lifestyle monitored data and implicit and explicit feedback of patients and caregivers when using the mobile app to update patient information and tailor the best stress management coach strategy in accordance with physicians' recommendations.

Communication Module

This module enables communication with the mobile app users. It is based on asynchronous chat that can be used to exchange messages with health providers and contact them in case of an emergency. In addition, predefined messages can be configured to be sent to users at specific time points of the patient journey (ie, the day before the surgery, remind clinical appointments, etc).

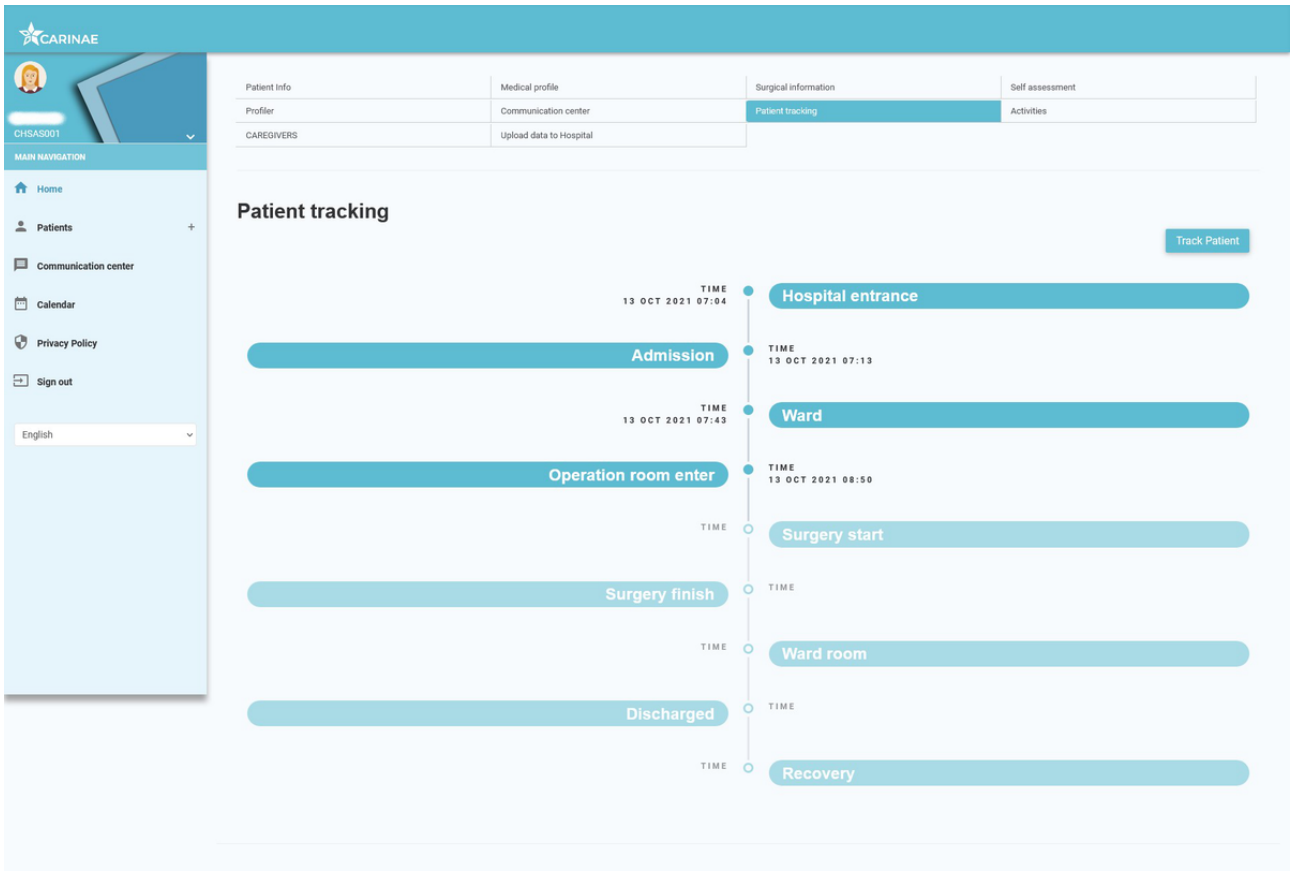
Lifestyle Monitoring Module

This module enables the longitudinal visualization of the biometric information gathered through the mobile app, including physical activity and other information helpful in understanding patient behavior along the patient journey and monitoring his or her progress between clinical visits.

Patient Tracking Module

The patient tracking module helps HCPs track patient location and elapsed times between specific steps of the patient journey from admission to hospital discharge. Patients are automatically tracked using BLE beacons strategically installed in the hospital entrance, admission, surgery ward, and presurgery room. From that point onward, HCPs manually update patient tracking, which also triggers notifications to the caregiver's mobile app, helping them to monitor their relative along the surgical journey (Figure 4).

Figure 4. A screenshot of the Digital Health Program web application.



Self-assessment Module

The self-assessment module facilitates visual monitoring of psychometric information through validated patient-reported outcome measures and questionnaires by HCPs. This information includes the VAS for stress and pain and the Bluebelle Wound Healing Questionnaire, which includes pictures of the wound taken with the mobile app. The sampling frequency of these questionnaires was preset according to the advice of psychologists and surgeons.

Methods

Overview

The Adhera CARINAE Digital Health Program will be tested in a multicenter trial, including 5 clinical settings across 3 European countries, and will use a stratified randomized controlled design including 30 intervention participants (6 per clinical site) and 30 control group participants (6 per clinical

site; Multimedia Appendix 5). This study aimed to obtain objective answers to the following 2 research questions:

1. Is the designed protocol feasible for conducting a future definitive randomized controlled trial? Accordingly, to what extent does the program affect patients' and caregivers' stress, anxiety, and pain levels, and secondarily, well-being and overall quality of life, compared with patients receiving the standard of care only?
2. What is the overall usability of the digital health solution based on the experience of patients, caregivers, and HCP?

Study Setting

After approval from the ethics board, the study will be conducted at the 5 departments of the following European hospitals:

1. Maastricht University Medical Center+ (UMC+; the Netherlands)—Cardiothoracic Surgery Department
2. Hospital Universitario Reina Sofia (SAS; Spain)—Cardiothoracic Surgery Department
3. Instituto di Ricovero e Cura per Anziani (INRCA; Italy)—Urology Department
4. Sant Joan de Déu Hospital (Spain)—Orthopaedics and Traumatology Department for Children
5. Fundació Parc Taulí (Parc Taulí; Spain—Orthopaedics and Traumatology Department for Adults.

Eligibility Criteria

Inclusion Criteria

The study included participants aged 8 to 65 years who underwent one of the following surgeries: cardiopulmonary bypass surgery (Maastricht UMC+); coronary artery bypass surgery (Maastricht UMC+); cardiac valve replacement (SAS, Maastricht UMC+); prostate, kidney, or bladder cancer surgery (INRCA); hip or knee replacement (HSJD; Parc Taulí); maxillofacial surgery (HSJD); orthognathic surgery (HSJD); or scoliosis (HSJD). Furthermore, adult study participants will have to have an Android smartphone and demonstrate basic digital literacy (eg, know how to communicate through instant messaging apps or similar). For children, their caregivers should have an Android smartphone and demonstrate basic digital literacy.

Exclusion Criteria

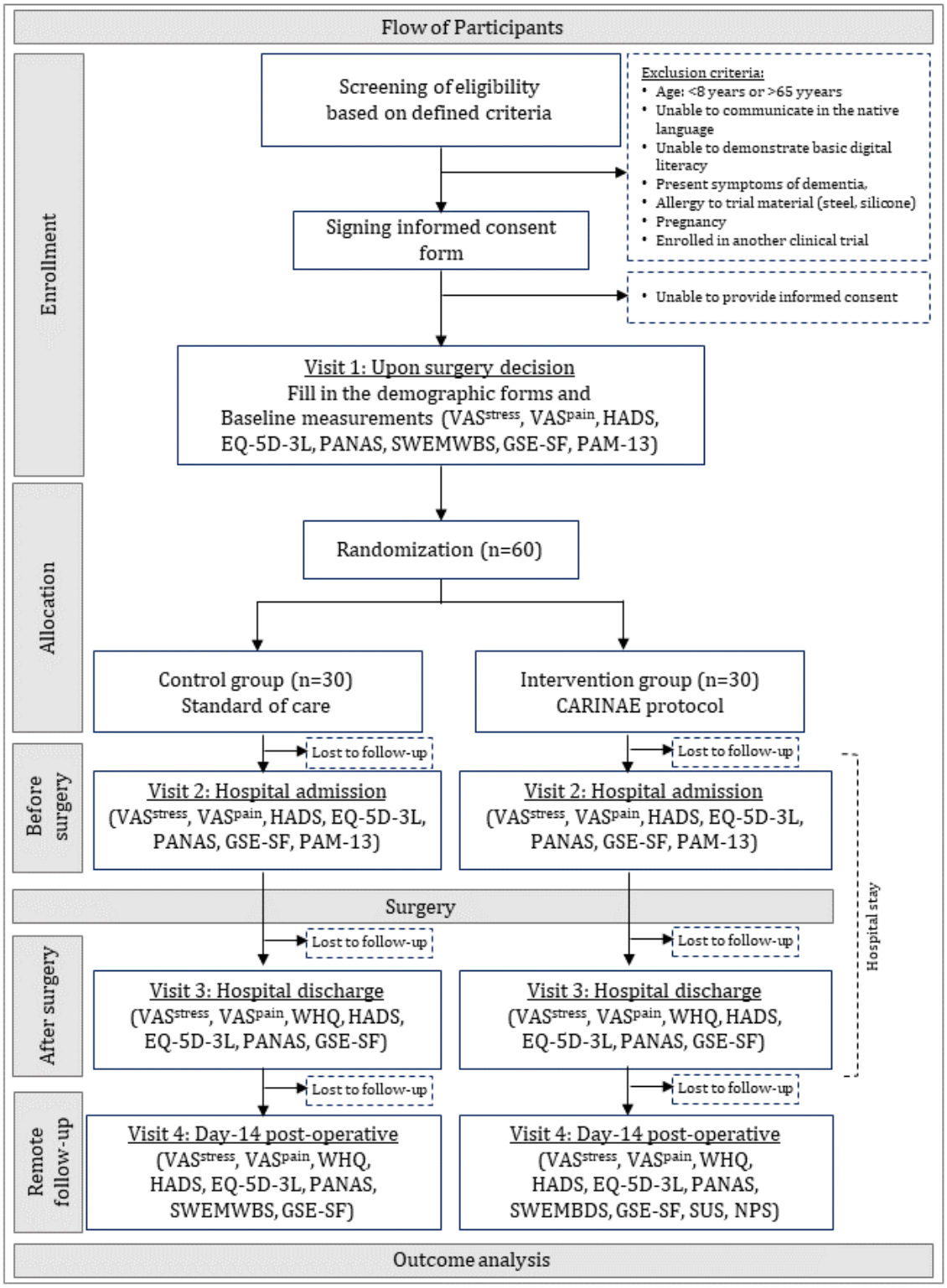
Potential participants who are unable to provide informed consent; communicate in the native language; demonstrate basic digital literacy; present symptoms of dementia; are allergic to dedicated wearable materials, such as steel and silicone; are pregnant; and are enrolled in another clinical trial will be excluded.

Interventions

Overview

Eligible participants will be randomly assigned to the experimental group or the control group following block randomization of size 4 using the Sealed Envelope web-based tool [36]. The digital health solution includes 3 distinct components—that is, the mobile app, a VR component, and a clinical web application. The first and second components will be used by the participants in the experimental group, whereas the third will be used only by HCPs for those patients. Both the control and the experimental groups underwent the same visits. The trial was organized as shown in Figure 5.

Figure 5. Flow of participants. GSE-SF: General Self-Efficacy Short Form; HADS: Hospital Anxiety and Depression Scale; NPS: Net Promoter Score; PAM-13: Patient Activation Measure short form; PANAS: Positive and Negative Affect Schedule; SUS: System Usability Scale; SWEMWBS: Short Warwick Edinburgh Mental Well-Being Scale; VAS: visual analogue scale.



Control Group

The control group will not use the digital solution and will receive standard care consisting of visits to the health care provider. Patients in the control group were provided with instructions on diet and healthy lifestyle habits; however, in current health care settings, it is not very common to provide patients with stress and anxiety perioperative relief support. Assessments of the control group will be performed during the following visits:

1. The initial visit on which the HCP communicates to the patient the need for surgery (2-4 weeks before surgery);
2. Hospital admission (1-3 days before surgery);
3. Hospital discharge (approximately 1 week after surgery);
4. Remote follow-up 14 days after the surgery.

Following each visit, several questionnaires will be administered to patients with a duration ranging from 15 to 45 minutes according to the visit (Table 1).

Table 1. Key parameters and measurements: baseline is 2-4 weeks before surgery, (hospital) admission is 1-3 days before surgery, (hospital) discharge is 1 week after surgery, and postoperative is 2 weeks after surgery.

Variables	Participants	Measurements	Baseline	Admission	Discharge	Postoperative
Primary outcomes						
Self-reported stress	Patients and caregivers	VAS[a,stress]	Yes	Yes	Yes	Yes
Self-reported pain	Patients	VAS[pain]	Yes	Yes	Yes	Yes
Anxiety and depression	Patients	HADS[b]	Yes	Yes	Yes	Yes
Secondary outcomes						
HRQoL[c]	Patients	EQ-5D-3L	Yes	Yes	Yes	No
Emotional status	Patients	PANAS[d]	Yes	Yes	Yes	Yes
Mental well-being	Patients and caregivers	SWEMWBS[e]	Yes	No	No	Yes
Self-efficacy	Patients and caregivers	GSE-SF[f]	Yes	No	No	Yes
Activation status	Patients	PAM-13[g]	Yes	Yes	No	Yes
Usability outcomes						
CARINAE's usability	Intervention group patients, HCPs[h] and caregivers	SUS[i]	No	Yes	Yes	Yes
Recommendation grade for CARINAE	Intervention group patients, HCPs and caregivers	NPS[j]	No	Yes	Yes	Yes
General satisfaction with CARINAE	Intervention group patients, HCPs and caregivers	Ad hoc	No	Yes	Yes	Yes
Covariates						
Demographics	Patients	Self-report assessment questionnaire	Yes	No	No	No
Clinical data	HCPs	HCP report	Yes	Yes	Yes	Yes
Length of hospital stay	Patients	HCP report	No	Yes	Yes	No

[a]VAS: visual analogue scale.

[b]HADS: Hospital Anxiety and Depression Scale.

[c]HRQoL: health-related quality of life.

[d]PANAS: Positive and Negative Affect Schedule.

[e]SWEMWBS: Short Warwick Edinburgh Mental Well-Being Scale.

[f]GSE-SF: General Self-Efficacy-Short Form.

[g]PAM-13: Patient Activation Measure short form.

[h]HCP: health care professional.

[i]SUS: Stem Usability Scale.

[j]NPS: Net Promoter Score.

Experimental (Intervention) Group

The experimental group will receive a digital health solution during the first visit, and training on how to use this tool will be provided. Patients will take the digital health solution home with them and can use it as often as they like. The experimental group, after each 1 of the 4 standard care visits, will complete the same questionnaires as the control group.

Outcome Variables

Research Question 1 (Primary and Secondary Outcome Variables)

Stress, anxiety, and pain represent the primary outcome variables that will be measured using paper-and-pencil questionnaires.

The secondary outcome variables were overall quality of life, emotional status, mental well-being, self-efficacy perception, and patient activation during and after hospital stay.

To assess the primary outcome variables, the following questionnaires will be used after each standard care visit and will be administered by paper and pencil:

- Patients' and caregivers' *self-reported stress* was measured using a VAS at enrollment (baseline), at admission for surgery, at hospital discharge, and 2 weeks after surgery. Operationally, a VAS is usually a horizontal line, 100 mm in length, anchored by word descriptors at each end, such as no stress versus highest stress possible [37].
- Patients' *self-reported pain* was measured using a VAS for pain measurement at enrollment (baseline), at admission for surgery, at hospital discharge, and 2 weeks after the surgery. The VAS for pain is a validated single-item scale that is anchored by "no pain" (score of 0) and "pain as bad as it could be" or "worst imaginable pain" (score of 100). The VAS presents a high internal consistency, as shown by a Cronbach α of 0.9117 [38].
- Patients'*Hospital Anxiety and Depression Scale* (HADS) scores were measured at admission for surgery, at hospital discharge, and 2 weeks after surgery. The HADS consists of 2 dimensions with 7 questions each, one representing the anxiety subscale and the other representing depression, with both psychopathological concepts of anxiety and depression being independent. Each item was rated on a 4-point frequency scale, ranging from 0 to 3. The internal consistency of the HADS, as measured by the Cronbach α coefficient, was found to be .78 for the anxiety subscale and .86 for the depression subscale, indicating satisfactory reliability [39].

To assess the secondary outcome variables, the following questionnaires will be used after each standard care visit and will be administered paper and pencil:

- Patients' *health-related quality of life* (HRQoL) was measured using the EQ-5D-3L questionnaire at enrollment, admission for surgery, and at clinical discharge. EQ-5D-3L measures HRQoL across 5 dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression [40]. These dimensions are scored as "no problems," "moderate problems," or "severe problems."
- Patients' *emotional status* was measured at enrollment (baseline), at admission for surgery, at hospital discharge, and 2 weeks after surgery using the Positive and Negative Affect Schedule (PANAS). The PANAS is represented by 10-items evaluating positive and negative affectivity in terms of descriptive adjectives (eg, active or upset). Responses ranged from 1 ("never") to 5 ("very much"). Cronbach α indicated excellent internal consistency for both factors (.90 and .91, respectively) [41].
- Patients' and caregivers' *mental well-being* was measured at enrollment and 2 weeks after the surgery using the "Short Warwick Edinburgh Mental Well-Being Scale." This instrument specifically targeted positive mental functioning. The scale is composed of 7-items (eg, "I've been feeling useful") with a 5-point response range from ("none of the time" to "all of the time"). The questionnaire has high internal consistency reliability, with a Cronbach α of .89 [42].
- Patients' and caregivers'*self-efficacy* measured at enrollment and 2 weeks after surgery using the General Self-Efficacy in Short Form (GSE) questionnaire. Self-efficacy refers to the general perception of one's capability to handle adversities. The GSE-SF is a 6-item scale wherein several self-descriptive sentences are scored from 1 ("not at all true") to 4 ("exactly true"). The questionnaire presents high internal consistency reliability with a Cronbach α of .85 [43].
- Patients' *activation status* was measured using a self-reported questionnaire, the Patient Activation Measure short form (PAM-13), at enrollment, admission for surgery, and 2 weeks after surgery. PAM-13 is an instrument that assesses patient knowledge, skills, and confidence in the management of chronic conditions [44]. Response options ranged from (1) strongly disagree to (4) strongly agree, and an additional "not applicable" option. The questionnaire presents high internal consistency reliability with a Cronbach α of .81.

Research Question 2 (Usability Outcome Variables)

The usability of the intervention tools will be monitored during hospital stay and posthospitalization using well-validated and ad hoc metrics. The *System Usability Scale*, *Net Promoter Score*, and an ad hoc *usability questionnaire* will be administered to the intervention group patients and caregivers as well as the HCPs who are involved in the care management of the intervention group [45,46].

The System Usability Scale is a 10-item evaluation based on a 5-point Likert scale measuring the strength and agreement of usability [45].

The ad hoc *usability questionnaire* assessed 4 dimensions: (1) functionalities, (2) design, (3) manual and instruction for use, and (4) general usability on a Likert scale (1-10). Each dimension also contained open fields to which participants responded qualitatively.

Net Promoter Score is used to assess general satisfaction with the question, "How likely are you to recommend this service?" [46]. The response format ranged from –100 to +100. Specific satisfaction was measured using a Likert scale (0-100) on a single question ("Did the user like the CARINAE solution?").

Independent Variable

The independent variable in this study was the type of intervention. This variable is allocated to 2 levels: control and intervention.

Confounding Variables

Patient age, sex, surgery type, medication use, length of hospital stay, and health outcomes, such as postoperative complications, reoperation, mortality, and groups in which the patients were involved during the intervention, will be used as confounding variables.

Participant Timeline

This feasibility trial consisted of an 8-week intervention treatment phase, including 4 visits; the last 2 weeks will be a follow-up phase, and visit 4 will be performed remotely. The total trial data collection period will be 2 months. The measurements were performed as shown in Table 1.

Sample Size

As this was a feasibility study, a sample size calculation is not required. However, we can estimate the number of participants we will be able to recruit during the data-collection period. In this feasibility study with a statistical power of 0.8, an α of .05, and an effect size of 1.20, the minimum required sample size will be 60 participants (30 in each group). Sample size calculations are estimated using G*Power (version 3.1.9.2).

Recruitment

Participants

Clinical investigators will prescreen the eligibility of the participants that they have available in their pool of subjects proposed for one of the surgeries in the inclusion criteria. Whenever they find a potentially eligible participant, they will invite them to participate in the study, either by phone or during routine consultation, whichever is more convenient. If the patient shows interest in participating in the study, then he or she will be referred to the research coordinator of the study that will facilitate him or her the patient information letter and the informed consent form and will solve any questions and concerns the patient may have. Upon obtaining informed consent, the patients will be considered recruited for the trial.

Randomization and Allocation

Participants-patients will be randomized through the prestratified randomization method to achieve balance between the 2 groups (intervention and control groups) according to the type of surgery and baseline characteristics (covariates). Stratified randomization was achieved by generating a separate block for each combination of covariates and participants were assigned to the appropriate block of covariates. The specific covariates in the clinical trial were represented by the type of surgery (3 surgeries) and sex (2 levels: male and female). With these 2 covariates, the possible block combinations totaled 6 (eg, male, cardiac valve replacement). According to this, the participants' allocation will be blinded through an Excel file spreadsheet (RAND function) using permuted block randomization with a ratio of 1:1 between the intervention and control groups. Allocation concealment will be ensured, as we will not release the randomization code until the patients are recruited for the trial.

Data Analyses

The analyses will be conducted in Python 3.9.5 through the IDE PyCharm Community Edition 2021.2.1 Software and intention-to-treat principles. Descriptive statistics will be used to characterize the groups during the 4 visits. Furthermore, owing to the small sample size, Spearman correlations will be performed with all the variables to check, first, for potential associations between the variables and, second, differences between the intervention versus control groups. Further potential differences between these groups will be analyzed as follows:

- Stress (VAS), pain (VAS), and mood state (PANAS-short form) will be subjected to a multivariate mixed analysis of variance (split-plot ANOVA) with "time" as a within-subject factor (ie, 4 time points) and "group" as a between-subject factor (intervention vs control).
- Patient activation (PAM-13) and self-efficacy (GSE-SF) will also be submitted to a multivariate mixed analysis of variance with "time" as a within-subject factor (Ie, 3 time points) and "group" as a between-subject factor (intervention vs control).
- Mental well-being (Short Warwick Edinburgh Mental Well-Being Scale) and HRQoL (EQ-5D-3L and EQ-5D-Y) will be analyzed using multivariate mixed analyses of covariance. As measurements of these 2 variables are based on a pre-post design, postmeasurements will be used as the dependent variable and premeasurements as covariates.

Finally, it is of interest to explore the effects as a function of different types of surgery. To this end, 2 different statistical approaches will be used:

- Cluster analyses per surgery type. Data will be split for each of the surgeries, and variables will be analyzed individually using time and group as within and between factors, respectively.
- A different statistical approach from the approach described above will also be used. In this case, analyses are performed within a linear mixed model (LMM) framework. LMM allows for the flexible handling of unbalanced data, outliers, or missing observations without averaging the data of participants. In addition, LMM enables the modeling of data using different fixed and random factors. Accordingly, each of the variables will be submitted to an LMM analysis wherein "time," "group (intervention vs control)" and their interaction (time × group) will be included as fixed factors. In contrast, "subjects" and "surgery" will be submitted as random factors. This analysis enables the calculation of regression estimation parameters by considering that participants differ in the surgery type. In addition, the participants' age or sex may also be used as control covariates.

Ethics and Dissemination

Ethics Approval and Consent to Participate

All procedures were approved by the ethics committees of the 5 clinical sites in the 3 countries involved (Italy, Netherlands, and Spain):

1. Maastricht UMC+ (the Netherlands)—Cardiothoracic Surgery Department
2. Hospital Universitario Reina Sofia (SAS; Spain)—Cardiothoracic Surgery Department
3. INRCA (Italy)—Urology Department
4. Sant Joan de Déu Hospital (Spain)—Orthopedics and Traumatology Department for Children
5. Fundació Parc Taulí (Parc Taulí; Spain)—Orthopedics and Traumatology Department for Adults.

Spanish regulation allows only 1 ethics committee to be requested per country, and its approval applies to the national territory. Approval in Spain was requested by the Hospital Reina Sofía (SAS) ethical committee (Stars-car-0320-5113) and has been acknowledged by both Hospital Sant Joan de Déu and Parc Taulí ethical committees.

Signed consent was obtained from all participants in the study. For those who are unable to provide informed consent, the caregiver will approach each potential participant and his or her substitute decision maker to provide information on the study. If these potential participants and their substitute decision makers provide their consent, the substitute decision makers will sign the consent form, and the HCPs will seek the potential participants' assent. Participants will not receive any incentive to participate in this study.

Withdrawal From the Study

The participants and substitute decision makers can request to withdraw from the study at any time, either orally or in writing. The participants will be able to withdraw from the study at any time before the group analysis is calculated. If a participant withdraws, his or her information will not be considered in the analysis. If a participant requests to have his or her data be destroyed, the research team will honor this request by shredding and recycling the paper records and erasing any records stored on a computer hard drive using commercial software applications designed to remove all data from storage devices. However, once all the participants' data were analyzed, the participant could not withdraw. Participants will be informed of this condition in a consent letter. The deadline date for withdrawal will be determined once all participants' data have been collected, and data analysis is underway. This will occur during the 6 months of the study.

Consent or Assent

Signed consent will be obtained from all participants in the study. For those who are unable to provide informed consent, the caregiver will approach each potential participant and his or her substitute decision maker to provide information on the study. If these potential participants and their substitute decision makers provide their consent, the substitute decision makers will sign the consent form, and the HCPs will seek the potential participants' assent.

Confidentiality

Participants will be assigned an alphanumeric code instead of using their names or other identifiers. Only the study coordinator will have access to the master list, where these codes are linked to the participants' first names. With the exception of direct conversations with each participant, their names will not be used, only their numbers. Hard copies of the consent forms, questionnaires, and study notes will be stored in a locked filing cabinet in the 5 departments of the 5 hospitals. All of the deidentified electronic study documents will be encrypted and stored on a password-protected computer drive.

Access to Data

Participating HCPs will be given access to cleaned data sets. The master list will be stored on a password-protected computer. Only the study coordinator will have access to the master list. The data will be retained for 5 years and will be published in peer-reviewed journals and conferences. The data will not become part of a data repository and will not be involved in the creation of a research database or registry for future research. After 5 years, the data will be destroyed.

Quality Assurance and Safety

We will follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines for clinical trial feasibility.

Results

The recruitment process started in January 2022 and has been completed. The primary impact analysis is currently ongoing. The expected results will be published in early 2023.

Discussion

Overview

The primary objective of the proposed study is to assess the feasibility of a digital health support program and its related technologies, that is, wearables, mobile apps, and VR for reducing perioperative stress. The results of this project will inform the development of best practices for patients' stress relief during the perioperative process.

Several strategies and techniques have been proposed to manage preoperative stress and anxiety, which can be effective in supporting patients to cope with a wide range of stressful health situations. In current health care settings, however, it is not very common to provide patients with stress and anxiety relief support before a surgical procedure. The available VR apps focus only on providing informative content, neglecting the importance of patient empowerment with a more robust educational curriculum. This study will be among the first to evaluate the potential effectiveness of complete IVR technology for reducing perioperative stress.

This protocol describes a complete digital health solution that offers a unique combination of end points and the integration of knowledge derived from several domains, including stress and anxiety management, patient empowerment, communication with medical professionals, adaptation to illness, self-regulation, self-management, and adaptation to medical procedures.

This digital health solution allowed participants to receive constant feedback to improve their appraisal and coping skills in an entertaining and motivating manner. It focuses on patient empowerment through active participation in the process and is dynamically adapted according to operation type, patient preferences, needs, and medical history throughout the preclinical phase, admission, and discharge in a continuous and personalized manner. Simultaneously, it facilitates effective interactions between patients and HCPs through user-friendly and intelligent communication. It uses the spaced learning methodology to help patients understand and learn the diverse aspects of their surgical process, from presurgery requirements to recovery steps with stress management throughout the process and provides multichannel anxiety and stress-relief personalized content.

The authors believe that the digital health solution, combining mobile health and VR technologies with a web application, can provide positive results in reducing perioperative stress and creating effective collaborations between physicians, surgeons and their patients, while supporting them in improving their knowledge in related domains. The Adhera CARINAE Digital Health Program has the potential to improve physical and emotional reactions to stressors, such as surgical operations, increase the levels of calmness, promote a sense of well-being, and empower patients in preoperative conditions. Information provided through the platform advances and enhances health literacy and digital competence and increases the participation of the patient in the decision-making process. Integration with third-party apps can facilitate the exchange of important information between patients and physicians as well as between personal applications and clinical health systems.

Limitations

Information provided through the digital health solution is not offered in the control group. Moreover, the digital health solution offers personalized information to the intervention group, which was not possible in the control group. This introduces a bias in the measurement results. Furthermore, for pediatric patients, as the intervention was observed and materialized through their caregivers, additional bias was introduced in the measurements.

Conclusions

This protocol defines the application of a very innovative approach to the management of stress associated with painful and stressful medical procedures, such as surgery. The project depicted in this manuscript proposes an excellent tool that companies and the health care system can use to collaborate on promoting the entry of this valuable technology into the global health care system market.

In conclusion, this study will provide valuable information on the effects of digital health interventions in comparison with the standard of care. A great deal of insights on the comparative effects of the tool on relevant outcomes and the usability of the comprehensive digital health solution by patients, caregivers, and HCPs will be acquired. This will contribute to the evidence planning process, which is crucial for future adoption of digital health programs.

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The work presented in this paper is part of the STARS joint precommercial public procurement project that has received funding from the European Union's Horizon 2020 Research and Innovation Programme. With the STARS project, 5 leading European hospitals (AZM, Maastricht, the Netherlands: Dianne de Korte and Esther Lacko; Instituto di Ricovero e Cura per Anziani, Ancona, Italy: Lorena Rossi; Parc Tauli, Sabadell, Spain: Andrea Vallejo; Sant Joan de Déu, Esplugues del Llobregat, Spain: Clara Hérnandez-Cera and Cristina Ruiz Herguido; and Hospital Universitario Reina Sofia, Cordoba, Spain: Juan J. Ferres) have implemented cross-border joint precommercial procurement to challenge and stimulate the European industry to design and develop innovative resilient support tools to be applied in the field of patients, planned for surgery, with the aim of reducing stress continuously during the entire care plan. The precommercial procurement, therefore, awarded R&D contracts to a number of competing contractors at the same time, in order to compare different approaches to solving the common need, for which either no commercially stable solutions yet existed on the market, or existing solutions exhibited structural shortcomings that require further R&D. Adhera Health is one of the two competing awardees in phase 3. The content of this study reflects only the authors' views.

Finally, this work was realized thanks to the collaboration and involvement of software developers and programmers of Adhera Health Inc and FORTH. In particular, for Adhera Health Inc thanks to Waqas Razzaq, Jesus Perez Cremona, Saruchi Hunjan and for FORTH In particular, for Adhera Health Inc thanks to Waqas Razzaq, Jesus Perez Cremona, Saruchi Hunjan and for FORTH thanks to Artemis Sfakaki, Yannis Petrakis, Vassilis Tzikoulis, George Kavlentakis, and Fokion Logothetidis.

Data Availability

Data sharing is not applicable to this study because no data sets were generated or analyzed during the study protocol generation.

Authors' Contributions

HK, IACC, and HA contributed equally to the manuscript drafting. AK, SHF, RMBR, LFL, and FJNB contributed equally to the study protocol and critical review of the manuscript. DGK, GP, PZ, KCA, and CS contributed to the final critical review of this manuscript.

Conflicts of Interest

All authors, except HA and RMBR, have been or are employees in organizations taking stake in the potential commercial exploitation of the CARINAE Digital Health solution.

Multimedia Appendix 1
Mental well-being activities.
[PNG File , 228 KB - resprot_v11i11e38536_app1.png]

Multimedia Appendix 2
Mobile health app biometric synchronization.
[PNG File , 185 KB - resprot_v11i11e38536_app2.png]

Multimedia Appendix 3
Personalized motivational messages.
[PNG File , 169 KB - resprot_v11i11e38536_app3.png]

Multimedia Appendix 4
A screenshot of the CARINAE virtual reality app displaying perioperative nutrition information inside the “mansion” environment.
[PNG File , 155 KB - resprot_v11i11e38536_app4.png]

Multimedia Appendix 5
Summarized SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) table.
[DOC File , 80 KB - resprot_v11i11e38536_app5.doc]

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Abbreviations

AI: artificial intelligence
CONSORT: Consolidated Standards of Reporting Trials
HADS: Hospital Anxiety and Depression Scale
HCP: health care professional
HRQoL: health-related quality of life
HRS: health recommender system
INRCA: Instituto di Ricovero e Cura per Anziani
IoT: Internet of Things
IVR: immersive virtual reality
LMM: linear mixed model
PANAS: Positive and Negative Affect Schedule
UMC+: University Medical Center+
VAS: visual analogue scale
VR: virtual reality

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Protocol

Motivational Design for Web-Based Instruction in Health Professions Education: Protocol for a Systematic Review and Directed Content Analysis

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Abstract

Background: Web-based instruction plays an essential role in health professions education (HPE) by facilitating learners' interactions with educational content, teachers, peers, and patients when they would not be feasible in person. Within the unsupervised settings where web-based instruction is often delivered, learners must effectively self-regulate their learning to be successful. Effective self-regulation places heavy demands on learners' motivation, so effective web-based instruction must be designed to instigate and maintain learners' motivation to learn. Models of motivational design integrate theories of motivation with design strategies intended to create the conditions for motivated engagement. Teachers can use such models to develop their procedural and conceptual knowledge in ways that help them design motivating instruction in messy real-world contexts. Studies such as randomized controlled trials (RCTs) and other quasi-experimental designs that compare different motivational design strategies play a critical role in advancing models of motivational design. Synthesizing the evidence from those studies can identify effective strategies and help teachers and researchers understand the mechanisms governing why strategies work, for whom, and under what circumstances.

Objective: The planned review aims to analyze how studies comparing motivational design strategies for web-based instruction in HPE support and advance models of motivational design by (1) controlling for established risks to internal validity, (2) leveraging authentic educational contexts to afford ecological validity, (3) drawing on established theories of motivation, (4) investigating a wide breadth of motivational constructs, and (5) analyzing mediators and moderators of strategy effects.

Methods: The planned review will use database searching, registry searching, and hand searching to identify studies comparing motivational design strategies for web-based instruction, delivered to learners in HPE. Studies will be considered from 1990 onward. Two team members will independently screen studies and extract data from the included studies. During extraction, we will record information on the design characteristics of the studies, the theories of motivation they are informed by, the motivational constructs they target, and the mediators and moderators they consider.

Results: We have executed our database and registry searches and have begun screening titles and abstracts.

Conclusions: By appraising the characteristics of studies that have focused on the motivational design of web-based instruction in HPE, the planned review will produce recommendations that will ensure impactful programs of future research in this crucial educational space.

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KEYWORDS

medical education; nursing education; e-learning; serious games; instructional design; motivation; health care; health professional; professional education; digital learning; web-based learning

Introduction

Learning remotely is here to stay. Web-based instruction, which encompasses remote lectures, asynchronous interactive modules, virtual patient simulations, and serious games, plays an essential role in health professions education (HPE): it digitally mediates learners' interactions with educational content, teachers, peers, and patients, when it would otherwise be too costly, infeasible, or impossible for in-person interactions to occur [1,2].

Learners typically access web-based instruction from remote, unsupervised settings, such as home, coffee shop, or library. Accordingly, learners often have a great deal of control in terms of *how* to engage with instruction. They can choose which learning strategies to use (eg, by taking notes in a notebook), when to revisit content (eg, returning to a previous slide), whether to access help from a peer or teacher (eg, by asking questions or leaving a comment), and how long to spend on learning. Under these conditions, learners must self-regulate their learning effectively [3]. Theoretical models of self-regulated learning (SRL) construe learning as a process whereby learners set goals for their learning and then strategically monitor and control aspects of their cognition, motivation, behavior, and environment toward attaining their goals [4]. A growing body of literature in HPE has demonstrated positive relationships between facets of SRL and academic achievement in unsupervised settings [5-7].

Effective SRL requires significant effort. Learners engaged in SRL do not learn "on autopilot" by following the directions of others or by defaulting to their usual approach to learning. Rather, they actively monitor and adapt their approach to learning as necessary [8]. Consequently, SRL relies heavily on a learner's motivation to learn [9]. Motivation refers to the energetic force that instigates and sustains goal-directed action [10]. Several studies in HPE provide evidence for links between motivational constructs, facets of SRL, and academic achievement [6,11-16].

A learner's motivation to learn will ebb and flow depending on situational factors such as what they are learning, with whom, where, and the challenges they face along the way [17,18]. Consequently, learners may sit down at their computer to complete web-based instruction only to find themselves less than optimally motivated. In such situations, they cannot rely on a teacher to recognize they are facing a motivational deficit, nor to help them address it. Instead, motivational support can, and should, be built into instruction itself [19].

Motivational design, a subprocess of instructional design, is a systematic, goal-directed, problem-solving process that involves (1) specifying the conditions under which learners will become and remain motivated to engage with instruction and (2) designing instruction to facilitate these conditions [20]. Models of motivational design integrate (1) an underlying theoretical account of how motivated engagement in learning unfolds with (2) a set of evidence-based strategies that teachers can use to facilitate the conditions for motivated engagement [21]. While theories of motivation describe *how* learners instigate and sustain goal-directed action, models of motivational design prescribe strategies for *how to help* instigate and sustain learners' goal-directed action toward desirable learning outcomes [21]. For example, Keller's attention, relevance, confidence, and satisfaction (ARCS) model of motivational design, commonly used across many educational contexts, including HPE [22,23], integrates a theory of motivation (Keller's macro model of motivation) with an organized set of strategies targeting four key motivational conditions derived from the ARCS theory [20].

Owing to their theoretical grounding, models of motivational design can help teachers build both *procedural knowledge* regarding design strategies that can be applied when designing instruction, and *conceptual knowledge* regarding why design strategies ought to be effective, based on an underlying theoretical account of how motivated engagement in learning unfolds. We argue that with an integrated body of procedural and conceptual knowledge, teachers can more flexibly apply and adapt previously learned design strategies and invent new ones in the messy, real-world contexts of HPE [24]. Therefore, we propose that a key objective of HPE research should be to advance models of motivational design.

Many kinds of studies can advance models of motivational design [25]. "Basic science" studies conducted in highly controlled lab environments can advance our understanding of the motivational processes underpinning learning [26,27]. Single-group quantitative, qualitative, and mixed-methods studies can investigate learners' perceptions of, and reactions to, instructional designs, to support our theoretical understanding of how certain designs operate to support motivation [28]. We propose that studies that aim to compare different motivational design strategies, including randomized controlled trials (RCTs)

and other quasi-experimental designs, play an essential role in advancing models of motivational design. They uniquely afford the potential for identifying the effects of different design strategies, which can then be integrated into models of motivational design. Research comparing motivational design strategies can also investigate mediating processes and moderating factors to determine why a strategy works, for whom, and under what conditions, thus helping to test and refine the theory that underlies a model of motivational design [29]. Accordingly, motivation researchers in HPE have called for greater use of RCTs to investigate strategies to enhance learners' motivation [29,30].

In this review, we aim to appraise studies that compare motivational design strategies for web-based instruction in HPE, to enhance the quality of future research toward refined models of motivational design. Comparative studies can advance models of motivational design when they generate high-quality evidence regarding what motivational strategies work, why, for whom, and under what circumstances. Accordingly, our review will be guided by the following research questions: (1) How well do existing studies control for established risks of bias (eg, allocating participants to different instructional designs randomly)? To afford drawing *internally valid*, causal conclusions regarding the effects of a design strategy, studies must be conducted in a manner that avoids known risks of bias [31]. For instance, Lazowski and Hulleman [32] found that quasi-experimental studies of motivational interventions reported stronger, more positive effect sizes than RCTs, suggesting that quasi-experimental studies may be subject to positive bias. (2) To what extent are existing studies conducted in authentic educational contexts? For studies to draw *ecologically valid* conclusions regarding the effects of a design strategy, they are best conducted in authentic educational contexts rather than in fabricated lab environments that do not resemble the "real world" [31,32]. For instance, findings of attenuated effects may be due to lower levels of engagement with aspects of an instructional design in an authentic versus a lab context [28,33]. (3) How frequently, and to what extent, are existing studies explicitly informed by a theory of motivation or model of motivational design? Theories of motivation and models of motivational design can serve to "organize" design strategies by associating them with motivational processes sketched out in the theory or model. Doing so permits an understanding of how the effects of a strategy relate to the underlying motivational processes sketched out in the theory or model. Further, an established theory of motivation or model of motivational design can help researchers identify potential mediating processes and moderating factors that could be the subject of investigation [29]. (4) Which motivational constructs have studies targeted with their instructional designs? Theories of motivation propose many proximal determinants of motivation, such as competence beliefs and value beliefs [29]. In models of motivational design, such constructs can be considered the *conditions* under which learners will become and remain motivated to engage with instruction, and which should be facilitated by instruction. Constructs may be influential depending on the characteristics of learners, the task, and the context in which learning takes place; therefore, it is important that teachers are able to draw on design strategies targeting a wide breadth of constructs. (5) Which hypothesized mediators or moderators of motivational design have studies operationalized or analyzed? Studies outside of HPE have demonstrated that motivational interventions can have differential effects on engagement and learning, depending on learner characteristics such as perceived competence for learning [34,35]. We will catalogue the data researchers collect on potential mediating variables (eg, self-regulated learning processes) and moderating factors (eg, baseline motivational characteristics).

We have chosen a systematic review as the most appropriate review methodology for answering our research questions, given our focus on RCTs and other quasi-experimental comparisons and our interest in appraising the quality of the included studies. Like other previous reviews, our analysis will profile each study's conceptual foundations, intervention characteristics, and chosen study designs, rather than aggregate study outcomes [36-39].

To increase the feasibility of our review, we will restrict our focus to studies that compare design strategies targeting motivation for web-based instruction. This focus is warranted; researchers have argued that effective SRL is more critical in web-based learning environments than in other, in-person learning environments, due to their unsupervised nature [39]. Further, as studies coming out of the COVID-19 pandemic have shown, learners' motivation may be particularly vulnerable in remote, web-based learning environments [40].

Methods

Overview

The protocol for this systematic review is reported in accordance with PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) [41]. However, we omit items 16 (meta-biases) and 17 (confidence in cumulative evidence), given we will not synthesize the outcomes of studies. The protocol for this systematic review has been registered (PROSPERO #CRD42022359521).

Eligibility Criteria

Study Characteristics

We will consider primary studies published in English, from 1990 to 2022. We selected this range based on the review strategy adopted by the Digital Health Education Collaboration, which recently published several reviews on digital education in HPE [42]. They argued computers were rarely used for educational purposes prior to 1990. We will consider study designs, including individual RCTs, cluster RCTs, cross-over trials, and other quasi-experimental designs. Notably, protocols for *ongoing* studies are also eligible for inclusion.

Participants

Studies will be eligible for inclusion if their sample was limited to learners in the health professions or was included but was not limited to learners in the health professions. Learners in the health professions may be preregistration or postregistration, following the distinction made by the Digital Health Education Collaboration [42]. *Preregistration* learners are those enrolled

in an educational program (eg, university degree program and vocational training program) that, upon completion, renders them eligible for a qualification permitting them to work in a health care setting under a regulated professional designation. *Postregistration* learners are those already working in a health care setting under a regulated professional designation and whose learning focuses on maintaining, updating, or broadening their existing knowledge and skills with respect to their practice discipline. Our list of eligible health professions is based on a triangulation from two sources. First, we referenced the list of regulated health professions in Ontario, Canada under the *Regulated Health Professions Act, 1991*. Then, we cross-referenced this list with the list of regulated health professions in the United Kingdom. We included all the regulated professions on either list, which are as follows: audiology; arts therapy; chiropody or podiatry; chiropractic care; dental hygiene; dental technology; dental therapy; dentistry; denturism; dietetics; hearing aid dispensing; homeopathy; massage therapy; medical laboratory technology; medical radiation technology; medicine; midwifery; naturopathy or osteopathy; nursing; occupational therapy; operating department practitioner; opticianry; optometry; orthodontic therapy; orthoptics; paramedicine; pharmacy; pharmacy technology; physiotherapy; psychotherapy; prosthetics, pedorthists, or orthotists; respiratory therapy; speech-language pathology; and traditional Chinese medicine and acupuncture. We also consider social work (which is a regulated profession in Ontario) to be an eligible health profession. Although biomedical scientists, clinical scientists, kinesiologists, and psychologists are regulated health professions, many learners in these fields do not intend to pursue a health care professional designation. Consequently, we excluded these from our list of eligible health professions.

Interventions

We will adopt the levels of instructional design framework proposed by Cook [43], who argued that instructional design choices can be conceptualized at three levels: the instructional medium, configuration, and strategy. An *instructional medium* refers to a mode of delivery. Examples include face-to-face instruction, paper-based instruction, and web-based instruction. We define web-based instruction as any instruction that leverages internet-based technologies to digitally mediate learners' interactions with educational content, teachers, patients, or peers [2]. An *instructional configuration* refers to a type of instruction within a given medium that has several distinguishing features from other configurations. Examples of different web-based instructional configurations include virtual lectures, asynchronous tutorials, and web-based discussion forums. An *instructional strategy* refers to a technique employed within a given configuration that is intended to facilitate the learning process. Examples of different strategies within a virtual patient simulation on communication skills include recording a transcript of the patient interview for later reflection or asking learners to set certain goals before interacting with the virtual patient.

Within studies using the medium of web-based instruction, our inclusion criteria will require that authors evaluate the effects of an instructional configuration or strategy that explicitly targets a specific motivational construct, or motivation more generally. That is, studies will be eligible if the intervention's effect on learning is hypothesized to occur through effects on motivation. Strategies targeting the timing of instruction (eg, before or after an in-person simulation experience) or the delivery of instruction (eg, supplemented with email reminders) will also be eligible for inclusion.

Studies will be judged ineligible if an instructional configuration or strategy does not intend to enhance or maintain learners' motivation *to learn*, but rather enhance or maintain their motivation toward some other aim. For example, a study that evaluates how an instructional strategy impacts learners' self-efficacy to apply a new procedure in clinical practice (versus their self-efficacy for learning more about the procedure) will be excluded from this review. We are interested in identifying evidence-based methods for designing web-based instruction to energize the process of SRL *during* instruction, not in energizing the self-regulated application of learned knowledge and skills in practice.

We will also include studies if an instructional configuration or strategy is investigated within a computer-based environment that could be made available to learners via internet-based technologies but was not done so for the study. For example, a study that investigated the motivational effects of a strategy within an instructional environment made available to learners via a CD-ROM would be eligible for inclusion, as such an environment could be readily replicated and delivered to learners via the web. By contrast, a virtual learning environment that requires a head-mounted display connected to a powerful computer would not be considered an environment that could be made available to learners via the web, and thus would not be eligible for inclusion. Finally, the device (eg, computers or smartphones) that learners use to access web-based instruction will have no bearing on study eligibility.

Comparators

Studies will be eligible for inclusion if they compare (1) an instructional configuration with another configuration, (2) an instructional strategy with another strategy while holding the configuration constant, or (3) an instructional strategy with the absence of the strategy while holding the configuration constant. Cook [43] argued that comparisons between configurations (eg, a virtual lecture versus an asynchronous interactive module) are inherently confounded given the many points of differentiation, making it nearly impossible to connect configuration features to any differences across outcomes. Consequently, such comparisons are less informative than comparisons at the strategy level, which feature a single point of differentiation. However, our primary interest is in mapping the literature to date, so both sorts of comparisons will be included. Further, based on prior reviews, we expect most comparisons will occur at the configuration level [44].

Outcomes

Similar to the meta-analysis of motivation interventions in education by Lazowski and Hulleman [32], studies will be eligible for inclusion if they assess the effect of an instructional configuration or strategy on a learner outcome, including

motivation, SRL, and achievement outcomes. Motivational outcomes include self-reports regarding specific motivational constructs or of motivation more generally. SRL outcomes are highly varied; based on established models of SRL [45] and prior reviews [46,47], SRL outcomes may relate to goals (including goal level and goal content), metacognitive processes (including goal setting, planning, self-monitoring, self-control, self-judgements, and self-reactions, which may relate to aspects of cognition, motivation, emotion, behavior, or the environment), cognitive strategy use (including rehearsal, organization, and elaboration strategies, or any other procedures a learner uses to control how they process task-relevant information), and resource management (including effort regulation, persistence, time management, environmental structuring, help seeking, peer collaboration, or any other procedures one uses to control their external environment or their internal environment, including their motivation and emotion). In HPE, the related construct of *engagement* has been conceptualized and operationalized to encompass a broad range of SRL processes. For example, engagement has been framed as having an experiential dimension (ie, reflecting a learner's subjective experience while playing a game) and a behavioral dimension (ie, reflecting a learner's time on task) [44]. From an SRL perspective [48], experiential engagement could map onto several motivational constructs, whereas behavioral engagement maps to persistence. Finally, studies are eligible if they collect any available achievement measure (eg, retention or transfer and course grades), assessed at any time (ie, immediately after instruction or delayed). Studies that only include non–learner outcomes (eg, instructor satisfaction and cost) will not be eligible for inclusion, as we do not consider these studies to be investigations of designs targeting *learners'* motivation to learn.

Information Sources

Database Searching

Relevant studies will be identified by searching the following databases: MEDLINE, Embase, Emcare, PsycINFO, ERIC, and Web of Science. Articles addressing the education or training of each health profession appear in the journals of these respective fields. For this reason, databases with significant coverage of the medical, nursing, allied health, as well as education literature were selected, with the addition of the multidisciplinary database platform Web of Science. These databases are also broadly consistent with those selected for similar reviews [32,44,49]. Our search strategy was developed by a health sciences librarian in collaboration with subject specialists and informed by prior reviews [32], using MEDLINE initially to assess the quality and quantity of our search returns. The search strategy was then adapted and applied to the other databases. Categories of terms included those related to learners in eligible health professions, web-based instruction, and motivation. Unlike the review by Lazowski and Hulleman [32], we did not include theories of motivation in our search terms, as theory use was not a criterion for inclusion. Further, we did not include specific motivational constructs (eg, value, relevance, confidence, and interest) in our search terms, as we expected this would greatly increase the number of nonrelevant studies required to screen, as many motivational constructs are common words used in nonmotivational contexts. Rather, we assume that any study targeting motivation and referencing a specific motivational construct will also mention motivation, and thus will be covered in our search. Our search strategy for MEDLINE can be found in Multimedia Appendix 1.

Registry Searching

Relevant studies will be identified by searching Open Science Framework Registries.

Hand Searching

Studies will also be identified by hand searching the reference lists of previous systematic reviews related to web-based instruction in HPE [38,44,49-58].

Reference Searching

The reference lists of the included studies will also be screened for additional studies.

Study Records

Data Management

All records identified through database and hand searching will be managed and screened using Covidence web-based software. After title and abstract screening, the full texts of the included studies will be uploaded for screening and, if necessary, data extraction.

Selection

The titles and abstracts of all records identified through database and hand searching will be independently screened by 2 team members, who will be blinded to each other's decisions. Team members will periodically meet to review conflicts, identify any systematic reasons for conflicts, and come to decisions regarding how to handle these issues. With these decisions in mind, conflicts will then be resolved by one team member not involved in the initial decision. The same process will occur for full-text screening. Reason for exclusion at the full-text screening stage will be documented and reported in a PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flow diagram. Percent agreement at the abstract and full-text screening stages will be calculated.

Risk of Bias Assessment

The risk of bias for the included studies will be independently rated by 2 team members using the Cochrane Effective Practice and Organization of Care standard risk of bias criteria [59]. The 9 criteria involved in a risk of bias assessment include the following: random sequence generation, allocation concealment, similar baseline outcome measures, similar baseline characteristics, incomplete outcome data, blind assessment of outcomes, protection against contamination, selective outcome reporting, and other risks of bias. Each criterion will be given a rating of "low risk," "high risk," or "unclear risk" at the study level. Team members will be blinded to each other's rating. Team members will periodically meet to review conflicts, identify any systematic reasons for conflicts, come to decisions regarding how to handle these issues, and resolve conflicts in ratings. Percent agreement for risk of bias ratings will be calculated.

Data Extraction and Synthesis

Data will be extracted and synthesized using a directed content analysis with each individual study as the unit of analysis [60]. We will use content analysis to systematically code the content of each article into categories for the purpose of identifying patterns in the data [60,61]. We will code deductively, meaning we will use existing theory or prior research as a foundation for developing our initial coding categories [60]. Our coding scheme will likely not remain static, given we will iteratively adapt it when relevant data are not congruent with existing categories [61]. Study data will be independently extracted by 2 team members using a comprehensive extraction and coding tool, developed through a consultation of the theoretical and empirical literature. The extraction and coding tool will be piloted and, as necessary, updated by having 2 team members independently extract data from a few studies and comparing their results. Team members will be blinded during the extraction process. Team members will periodically meet to review variability in the extracted data, identify any systematic reasons for this variability, and decide how to handle these issues. Primary study authors will be contacted in the case of unclear or missing data. Percept agreement for extracted items will be calculated.

Our extraction and coding tool will facilitate the collection of the following data items: study title, first author, publication year, geographic location in which the study was completed, study design, health profession of participants, training status of participants, sample size, topics of instruction, length of instruction, setting in which instruction was delivered to participants, device on which instruction was accessed, technology used to deliver instruction (eg, internet or CD-ROM), instructional configuration, instructional strategy (if relevant), theory of motivation used to inform the configuration or strategy, motivational constructs targeted by a configuration or strategy, definition of the constructs (if applicable), other learning processes targeted by a configuration or strategy (eg, cognitive processes), comparison, moderators, outcomes (including hypothesized mediating variables), and moderator or outcome measures.

Two items relevant to our research questions are the theory of motivation used and the motivational constructs targeted by a configuration or strategy. We have developed a list of 7 of the most established theories of motivation in education, to be used as our initial codes, as follows: (1) expectancy-value theory [62]; (2) achievement goal theory [63]; (3) self-determination theory [64,65]; (4) social cognitive theory [66,67]; (5) attribution theory [68]; (6) control-value theory [69,70]; and (7) the Keller macro model of motivation and performance (underpinning the ARCS model of motivational design) [20,71]

Based on this list of theories, we also developed an initial list of motivational constructs, which comprises the following: (1) achievement goal orientations; (2) competence beliefs (including confidence, self-efficacy, action-control expectancies, outcome expectancies, action-outcome expectancies, control of learning beliefs, and expectancies for success); (3) value beliefs (including relevance, perceived instrumentality, task value, extrinsic value, utility value, attainment value, and cost); (4) interest (also curiosity and attention); (5) outcome attributions; (6) the self-determination theory taxonomy of motivation (intrinsic motivation, extrinsic motivation, external regulation, introjected regulation, identified regulation, integrated regulation, autonomous motivation, and controlled motivation); and (7) basic psychological needs satisfaction or frustration (including feelings of autonomy, competence, and relatedness).

These codes are by no means restrictive; we anticipate that they will inductively grow and change through the data extraction process. The results of our deductive content analysis will be presented in tabular and graphical form, representing the frequency of different study characteristics, the frequency with which different motivational constructs have been targeted in the literature, including as mediators and moderators, and the theories of motivation that have informed these studies. We will also present stratified results by type of health professional, participants' training status, and study characteristics. These tabular and graphical presentations will be accompanied by narratively presented exemplars of strategies targeting different constructs.

Results

As of September 2022, we have completed our database searches (executed on August 2, 2022) and registry searches (executed on September 15, 2022) and have begun hand searching. Our initial search yielded 10,590 studies. We selected a purposive sample of 30 studies for team members to practice screening. Following practice, we began screening titles and abstracts. We aim to complete screening by the end of 2022.

Discussion

Overview

Through conducting this review, we expect to produce a list of understudied or poorly studied conceptual foci to support the growth of a robust evidence base in motivational design, and to provide guidance regarding methodological advancements in future studies of motivational design (eg, greater use of moderation analyses). By establishing a foundation to guide future theory-based research in this area, our review will provide more fertile grounds for future knowledge syntheses that include other sources of evidence (eg, qualitative studies) and that focus on understanding mechanisms of motivational design (eg, realist reviews).

Although previous reviews have focused on motivational design features of web-based instruction in HPE [38,44,49-58], none have sought to (1) achieve the specific goal of using existing evidence to refine models of motivational design, (2) propose which types of evidence will be required to meet this goal, (3) identify the study designs that can generate such evidence (eg, studies comparing motivational design strategies), and (4) appraise the degree to which studies have generated such evidence. Thus, the value of our review lies in its ability to appraise where we have been and to inform where we ought to go. We anticipate our findings will inform a program of research that includes future experimental studies, qualitative studies, and additional knowledge syntheses.

Conclusion

In his book on motivational design, Keller [20] posed the question "Is motivation like a boulder – stable and unwavering, or a pile of dry leaves – unstable and in flux?" The answer appears to be *both*, depending on the level of generality at which motivation is assessed [18]. Most learners in the health professions report being highly motivated to improve their knowledge and skills [72], a consistent finding across disciplines that has likely perpetuated a belief that learners are *always* motivated to learn. However, from situation to situation, learners in HPE likely experience fluctuations in their motivation, depending on what they are learning, the context in which learning takes place, and the challenges they face along the way [18]. Viewing motivation at the situational level demands that we understand ways of designing web-based instruction to enhance and maintain learners' motivation. Through this systematic review, we aim to support future research regarding the motivational design of web-based instruction in HPE by appraising the characteristics of RCTs and other quasi-experimental comparisons that have been conducted to date. We believe this new era of remote learning demands that we set a strong foundation for researchers to generate the highest quality evidence toward ensuring HPE learners flourish rather than languish when learning online.

Conflicts of Interest

None declared.

Multimedia Appendix 1
MEDLINE search strategy.
[DOCX File , 19 KB - resprot_v11i11e42681_app1.docx]

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Abbreviations

ARCS: attention, relevance, confidence, and satisfaction
HPE: health professions education
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
RCT: randomized controlled trial
SRL: self-regulated learning

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Protocol

The Changes That Occur in the Immune System During Immune Activation in Patients With Prediabetes From All Ethnicities, Aged 25-45 Years: Protocol for a Systematic Review and Meta-analysis

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Abstract

Background: Prediabetes is an asymptomatic, intermediate state between normoglycemia and the onset of type 2 diabetes mellitus. Recent reports indicate that during prediabetes, there are subclinical changes to immune cells and inflammatory markers. Therefore, this systematic review will provide a synthesis of the available data on the changes in the concentration of immune cells and selective inflammatory markers. It will also give evidence of a demographic impact on changes or complications in the prediabetes state.

Objective: The objectives of this study are to create a protocol that will be used to analyze the collected data of previously published research based on immune cells such as neutrophils, lymphocytes, monocytes, eosinophils, and basophils, as well as inflammatory markers such as C-reactive protein, tumor necrosis factor-alpha, interleukin-6, P-selectin, cluster of differentiation 40 ligand, and fibrinogen. Additionally, an impact of demographics will be determined using the previously published data collected.

Methods: This protocol was prepared through adhering to the PRISMA (Preferred Reporting Items for Systemic Reviews and Meta-Analysis) 2015 guidelines for reporting protocols. Published clinical studies that involve observational (cross-sectional, comparative cross-sectional, case-control, or cohort) study designs that include normal or nondiabetic and prediabetes reports will be used in this systematic review and meta-analysis. This will be accomplished by using clinical Medical Subject Headings to search on MEDLINE, Cochrane library, and African Journal Online. Reviewers (NCM, AMS, and AK) will screen all the results and select the studies that meet the eligibility criteria. Downs and Black Checklist will be used to check the risk of bias, and then a Review Manager v5.4 forest plot will be used for meta-analysis. Additionally, the forest plot will also be used for sensitivity analysis. The strength of evidence will then be assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Results: Since July 5, 2020, there are no participants recruited. Publicly available data will be used in the review and will be collected after this protocol publication. No ethics approval is required as no subjects will be used, and analysis will be based on reported data. Authors will be contacted if there was a misunderstanding related to reading their reported data.

Conclusions: The findings will clarify changes that might be observed in a study of interest based in the eThekwini district in South Africa.

Trial Registration: International Prospective Registry of Systematic Reviews (PROSPERO) CRD42020184828; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=184828

International Registered Report Identifier (IRRID): PRR1-10.2196/31619

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KEYWORDS

systematic review; meta-analysis; prediabetes; immune cells; inflammatory markers; diabetes; inflammatory response; immunology; demographics; risk factors

Introduction

Type 2 diabetes (T2D) is a metabolic disorder characterized by chronic hyperglycemia, which gives rise to metabolic and signaling abnormalities [1-3]. According to Kayal and Graves [3], these metabolic and signaling abnormalities have been reported to cause dysregulated innate immunity. Chronic dysregulated immunity includes changes in immune cells such as neutrophils, lymphocytes, monocytes, eosinophils, and basophils [4-7]. Upon activation, these immune cells play a different role, including secretion of inflammatory markers such as C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), P-selectin, cluster of differentiation 40 ligand (CD40L), and fibrinogen [4,5,8-11]. The chronic immune activation in T2D results in a suppressed immune system [3,12]. According to Lam and LeRoith [13], a fundamental change in the population with T2D is witnessed by the health care communities. This was confirmed by the International Diabetes Federation statistics, reporting that in 2019, there were 19 million people with diabetes in Africa aged 20-79 years [1]. The International Diabetes Federation also reported that there were 12 million Africans aged 20-79 years living with undiagnosed diabetes in 2019 [1]. South Africa is the highest with 4.6 million adults with diabetes (20-79 years) [1]. In 2017, the Indian population was reported to have the highest prevalence of diabetes in South Africa by 11%-13%, followed by people of color by 8%-10%, then Black people by 5%-8%, and White being the lowest by 4% [14,15]. The Indian population among people with diabetes has been shown to be high due to their strong diabetes genetic predisposition [14,15]. However, the onset of T2D arises from the progression of prediabetes [16]. Prediabetes has been reported to be an asymptomatic state, creating a research complication in its documentation of the statistics and prevalence. There is less evidence on the changes in immune cells and selective inflammatory markers at the prediabetes stage [17-20]. However, in our laboratory, research has been conducted on animals in addition to the available research reporting the metabolic and signaling abnormalities, including immune activation during prediabetes [21-24]. This then raised a debatable issue if the same abnormalities occur during prediabetes in human individuals owing to limitations in the animal models, even though the research mimicked the human diet. From the search conducted, we found no report or evidence of the systematic review that reports on the changes in immune cell concentration and the level of secretion of selective inflammatory markers that occur during immune activation during prediabetes. Therefore, our research presents an opportunity to compile a systematic review that will yield an exhaustive synthesis obtained from the available studies that previously reported on immune cells and selective inflammatory markers of interest in prediabetes. Additionally, this systematic review will give reports on the impact of demographics on changes of immune cells and secretion of selective inflammatory markers during prediabetes.

The objectives of this study are as follows: (1) to determine the changes in concentration of immune cells, such as neutrophils, lymphocytes, monocytes, eosinophils, and basophils during prediabetes; (2) to investigate if there are changes in concentration on selected inflammatory markers, such as CRP, TNF-α, IL-6, P-selectin, CD40L, and fibrinogen, during prediabetes; and (3) to assess the variation of prediabetes-associated changes in immune function among different demographic groups.

Methods

This protocol was prepared by adhering to the PRISMA (Preferred Reporting Items for Systemic Reviews and Meta-Analysis) 2015 guidelines for reporting protocols [25].

Systematic Review Registration

The protocol has been registered with PROSPERO with registration number “CRD42020184828,” dated July 5, 2020.

Ethics Approval and Consent to Participate

The data analyzed will be those that have already been published, and there will be no data collection from individuals. The authors declare that there will be no informed consent required to be signed; therefore, no ethics approval is required for the systematic review and meta-analysis.

Eligibility Criteria for the Study

Studies with a minimum of 100 participants (N=100) and the studies that report community-based clinical cross-sectional study will be eligible. The inclusion and exclusion criteria will be as follows: inclusion—the information reported from nondiabetic adult patients aged 25-45 years from all ethnicities will be used; exclusion—information reported from people with a history of liver disease, kidney disease, heart disease, and depression will not be used. Information from pregnant women will also not be used. Additionally, no samples from professional sports athletes will be allowed in the study. Full-text articles or reports indicating that individuals who were used were free from all the mentioned criteria will then be eligible.

Prediabetes Diagnosis Criteria

Diagnostic criteria for prediabetes will be as follows (participants should meet 1 of the following diagnoses): fasting blood glucose—5.6 to 7.0 mmol/L; 2 hours postprandial blood glucose (2 hours oral glucose tolerance test)—7.8 to 11.0 mmol/L with glycated hemoglobin (5.7% - 6.4%).

Study Design

Participants

Intervention

These will be clinical studies that involve observational studies if they are cross-sectional, comparative cross-sectional, case-control, or cohort study designs that involve normal (nondiabetic) and prediabetes reports. The reported information that involves one or more immune cells (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) in the prediabetic state will be eligible for this systematic review. Additionally, studies that report information that involves at least one or more inflammatory markers of interest, which are CRP, TNF-α, IL-6, P-selectin, CD40L, and fibrinogen, will also be eligible for this systematic review.

Comparators

In this systematic review, the eligible comparing control groups will be normal (nondiabetic) control and T2D control groups.

Outcomes

This systematic review is expected to show the following results: (1) the changes in concentration of immune cells such as neutrophils, lymphocytes, monocytes, eosinophils, and basophils during prediabetes (reported as odds ratio and 95% CI); (2) the changes in concentration of selected markers such as CRP, TNF-α, IL-6, P-selectin, CD40L, and fibrinogen during prediabetes (reported as odds ratio and 95% CI); and (3) variations in markers of immune function among different demographic groups based on gender, age, and race (reported as the mean).

Search Strategy

The electronic search strategy will be used as an identification for studies involving cohorts that have been studied that are related to the study of interest [26]. This strategy will be accomplished by search on MEDLINE (from 1963 to 2020), Cochrane library displaying results of trials from PubMed, CT.gov, Embase, ICTRP (from 1963 to 2020), as well as African Journal Online (from 1998 to 2020) [26]. In addition to these search strategies, clinical MeSH (Medical Subject Headings) and text will be applied to filter the available information. For all search conducted, the keywords to be used will be “pre-diabetes and immunity,” “pre-diabetes and immune cells,” “pre-diabetes and leucocytes,” and “pre-diabetes and inflammation.”

Identification of Eligible Studies

The title and abstracts of all the obtained results will be screened by reviewers (NCM, AMS, and AK), and the studies that meet the eligibility criteria will then be selected. Each reviewer will be responsible for screening all the selected study reports before the decision-making of the eligible reports. The PRISMA flowchart for selection of studies will then be provided in the reports from the systematic review.

Patient and Public Involvement

No patient was involved.

Data Management

Study Records and Data Extraction

The data of the study records that are selected as eligible reports will then be extracted and recorded in an Excel (Microsoft Corp) file. The predefined list of variables to be considered in each report will be used as categories in an Excel file. Considering the research of interest, the outcome of interest will mainly be the immune cell response and concentration of selected markers in both genders, at an age parameter of interest, and in all ethnicities. However, the value of the baseline characteristic of the data reported will also be considered. Therefore, the baseline characteristics of the eligible research reports obtained will be author, year of publication, country, and study setting. The methodology of the study reported will also be considered with categories including design, period, sampling strategy, and whether participants are from a normal or prediabetic population. Finally, the outcomes from different genders, ages, ethnicities, and immune cell changes or inflammatory markers will then be extracted.

Data Simplification

Studies that report on the immune cells (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) will be combined into a single group. Additionally, the studies that report on selected inflammatory markers (CRP, TNF-α, IL-6, P-selectin, CD40L, and fibrinogen) will also be combined into a single group.

Risk of Bias

The potential risk of bias in individual studies will be obtained using the Downs and Black Checklist [27]. The scores will be rated as follows: excellent (25-26), good (20-24), moderate (14-19), poor (11-13), and very poor (<10). Three reviewers (NCM, AMS, and AK) will be responsible for the independent judgments, which will be based on the 4 domains of the Black and Downs checklist tool, which are reporting bias (10 items), external validity (3 items), internal validity (6 items), and selection bias (7 items). In a situation where there will be a difference of opinions between NCM, AMS, and AK, author PSN will be responsible for adjudication. In situations where the data are not clear, the investigator who reported the data will be contacted 3 times. If no response is obtained, data will be then excluded from the eligible report.

Data Synthesis

For the meta-analysis of reported data, a forest plot will be used from Review Manager software version 5.4 (RevMan) [28-30]. Using this forest plot, eligible data from all reported studies will be analyzed depending on their sample size and the mean of the concentration of immune cells or inflammatory markers in prediabetic and control groups. Additionally, an odds ratio and CI will be used to make the forest plot where the solid lines will represent the 95% CI. Each reported study will be represented as a horizontal line on the y-axis to list the primary author and year of study. The forest plot will also include the weight of the study results that will be automatically obtained using the Review Manager software.

Sensitivity Analysis

RevMan forest plot will also test for heterogeneity, where greater homogeneity will be indicated by a greater overlap between the CIs [30]. Using the forest plot, I^2 will then be calculated where a value between 0% and 100% will be obtained. A value obtained less than 25% will be an indication of a strong homogeneity, and a value obtained greater than 75% will be an indication of a strong heterogeneity. However, a value of 50% will be considered as an average value.

Assessment of Strength of Evidence

NCM, AMS, and AK will then be responsible for the assessment of the strength of evidence. The studies included in the review will then be evaluated using the Grading of Recommendations Assessment, Development, and Evaluation approach (GRADE) [30-32]. Furthermore, the summary of findings table will then be created using a GRADEpro (McMaster University and Evidence Prime Inc) tool.

Results

As of July 5, 2020, no participants have been recruited as publicly available data will be used. These data will be collected when this protocol has been published. There will be no ethics approval required as the review is based on published data, and authors will be contacted if there is a misunderstanding from reading their reported data for clarity of their published work.

Discussion

Principal Findings

The synthesis of previous study reports obtained from this systematic review and meta-analysis will clarify the complications on the immune system at prediabetes such as the changes that have been reported on immune cells, which are neutrophils, lymphocytes, monocytes, eosinophils, and basophils. This systematic review and meta-analysis will also give an outstanding synthesis of data from previous reports based on selected inflammatory markers of interest.

Conclusion

The synthesis from this systematic review and meta-analysis will create a hallmark of association between demographics and prediabetes. This will clarify changes that might be observed in a study of interest based in the eThekwini district in South Africa.

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Authors' Contributions

NCM, AMS, and AK were responsible for brainstorming, designing the study, and drafting the protocol. NCM, AMS, PS, and AK were responsible for reviewing the eligible study and final draft of the manuscript. Funders had no role in developing the protocol.

Conflicts of Interest

None declared.

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Abbreviations

CD40L: cluster of differentiation 40 ligands
CRP: C-reactive protein
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
IL-6: interleukin-6
MeSH: Medical Subject Headings
PRISMA: Preferred Reporting Items for Systemic Reviews and Meta-AnalysisT2d: type 2 diabetes
TNF-α: tumor necrosis factor-alpha

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Protocol

The Differences Between Same-Day and Staged (Circumferential) Fusion Surgery in Adult Spinal Deformity: Protocol for a Systematic Review

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Abstract

Background: Adult spinal deformity (ASD) is a deformity in the curvature of the adult spine. ASD includes a range of pathology that leads to decreased quality of life for patients as well as debilitating morbidities. Treatment can range from nonoperative management to long-segment surgical corrections and depends greatly on the deformity and patient profiles. If surgical treatment is indicated, circumferential (a combined anterior and posterior approach) fusion is one of the tools in the spine surgeon's armamentarium. Depending on the complexity, the procedure is either completed on the same day or staged. Determining whether to perform a circumferential surgery in a staged fashion is based largely on the surgeon's preference and perception of the individual case complexity; at present, there is no high-quality evidence that can be used to support that decision.

Objective: This paper presents the protocol for a systematic review that aims to investigate the differences between same-day versus staged circumferential fusion surgery in ASD both in patient selection and in outcomes.

Methods: Searches will be performed on MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, and Scopus. Gray literature and the reference lists of articles included in the full-text screening will also be screened for inclusion. Results will be exported to Covidence. Data will be collected on demographics, type of procedures performed, surgery levels, blood loss, total operation time, length of stay, disposition, readmissions (30 days and 90 days), and perioperative complications. Patient-reported outcomes will also be assessed. Data quality assessment of randomized controlled trials will be performed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials, and nonrandomized studies will be assessed with the ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions) tool. All screening, quality assessment, and data extraction will be done by 2 independent reviewers. A descriptive synthesis will be performed, and data will be evaluated for further analysis.

Results: This study is currently in the screening phase. There are no results yet. The search strategy has been developed and documented. Information has been exported to Covidence. Upon conclusion of the critical appraisal stage, screening and extraction, as well as a synthesis of the results, will be performed.

Conclusions: The intended review will summarize the differences in perioperative outcomes and complications between same-day and staged (circumferential) fusion surgery in adult spinal deformity. It will also describe the patients selected for such procedures based on their demographics and pathology. Identified gaps in knowledge will provide insight into current limitations and guide further studies on this topic.

Trial Registration: PROSPERO CRD42022339764; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=339764

International Registered Report Identifier (IRRID): PRR1-10.2196/42331

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KEYWORDS

spinal surgery; scoliosis; kyphosis; protocol; circumferential; adult spinal deformity; differences; fusion; fusion surgery; spinal curvature; spine deformity; spinal deformity; surgery; surgical; perioperative; review methodology; systematic review; search strategy; protocol

Introduction

Background

Adult spinal deformities (ASDs) are defined as abnormalities in the spinal curvature or alignment in the adult population that deviate from normal limits [1]. ASD can include any combination of spinal deformities, such as kyphosis, lordosis, and scoliosis. ASD is becoming more prevalent with the increasing age of the population [1-4]. Once conservative management has failed, surgical correction is considered. Common indications for surgery are pain with substantial abnormality in spinal curvature, significant deformities that are esthetically unacceptable to the patient, documented curve progression with imbalance in one or more planes, and significant loss of pulmonary function attributed to the deformity [5-9].

Depending on the complexity and patient-specific surgical risk profile, ASD surgeries, such as circumferential procedures, can be done on the same day or staged and completed on a different date [10-17]. Differences in outcome between same-day and staged surgery have been a topic of interest for surgeons.

Rationale and Objective

To our knowledge, no systematic review of published literature on this topic has been performed. Our study aims to shed light on the current literature, highlight limitations, identify gaps in knowledge, and guide future studies on the management of ASD with either same-day or staged circumferential fusion.

Methods

Protocol and Registration

The protocol was developed based on the PRISMA-*P* 2015 (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) methodology (see checklist in Multimedia Appendix 1) [18,19]. The protocol is registered in PROSPERO (International Prospective Register of Systematic Reviews; CRD42022339764).

Eligibility Criteria

The PICO (population, intervention, comparison, and outcome) framework was used to formulate the eligibility criteria:

- Population: patients with adult spinal deformity;
- Intervention: staged (circumferential) fusion surgery;
- Comparison: same-day (circumferential) fusion surgery;
- Outcome: differences in perioperative outcomes, complications, length of stay, disposition, readmissions, and patient-reported outcomes.

Inclusion and Exclusion Criteria

We will include all clinical studies of patients with ASD who underwent staged (circumferential) fusion surgery. Studies that include nonhuman subjects or a nonadult population, compare different types of surgery that do not differ in timing (same day vs staged), case reports, case series, studies presenting a technical report of the procedure performed without reporting any original data, and conference abstracts will be excluded. Additionally, only literature in English will be considered.

Search Strategy

A comprehensive systematic search strategy has been developed in conjunction with an external librarian. MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, and Scopus will be searched. We will also search Google Scholar for gray literature and screen the references of articles included in the full-text screening for inclusion in our systematic review. A sample search strategy specific to MEDLINE has been generated and is presented in Textbox 1, including database-specific search information, such as controlled vocabulary and keywords. All results will be exported and deduplicated on Covidence [20].

Textbox 1. Complete search strategy for MEDLINE.

- Search #1: (“spinal curvatures”[MeSH Terms] OR “spinal curvatures”[MeSH Terms] OR “adult spinal deformity”[tiab] OR “adult degenerative deformity”[tiab] OR “asd”[tiab] OR “spinal deformity”[tiab])
- Search #2: (“staging”[tiab] OR “staged”[tiab] OR “same day”[tiab] OR “stag*”[tiab])
- Search #3: (“circumferential”[tiab] OR “anterior posterior”[tiab] OR (“anterior”[tiab] AND “posterior”[tiab]) OR “posterior”[tiab] OR “anterior”[tiab])
- Search #4: (“fusion”[tiab] OR “spinal fusion”[tiab] OR “spinal surgery”[tiab] OR “spinal fusion surgery”[tiab])
- (#1 AND #2) OR (#2 AND #3 AND #4)

Data Selection and Extraction

Two independent reviewers will participate in a title and abstract screen on Covidence. A third reviewer will resolve any disagreements. After completion of the title and abstract screen, the results will be exported to EndNote 20 (Clarivate), and institutional access will allow for automatic integration of the full-text PDFs [21]. Thereafter, the references will be reimported to Covidence. Full-text review will commence, and data extraction will subsequently be performed.

Key data for extraction will include, but will not be limited to, study information (first author and date of publication), study design, number of participants included in the study, demographics, type of procedures being performed, surgery levels, blood loss, total operation time, length of stay, disposition, readmissions (30 days and 90 days), patient-reported outcomes (eg, the Neck Disability Index, the Oswestry Disability Index, and EQ-5D), intraoperative complications (eg, intensive care unit admissions and stays), and postoperative complications (eg, medical, surgical) [22-24].

Data Quality

The methodological quality and risk of bias of eligible studies will be critically appraised by 2 independent reviewers. A data quality assessment of randomized controlled trials will be performed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [25]. Nonrandomized studies will be assessed with the ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions) tool [26].

Data Synthesis

Due to the nature of this review and expected paucity of data, a descriptive synthesis will be performed. Therefore, data will be presented descriptively in tables. Additionally, graphical formats will be used as appropriate. This is subject to change depending on the extracted data. An internal statistician will evaluate a best-practice approach.

Results

This study is in the critical appraisal stage. No results have been obtained yet. At the time of writing, the developed search strategy had been used. Information from databases has been extracted to Covidence and records have been deduplicated. The screening stage has not concluded yet.

Discussion

To our knowledge, this will be the first systematic review on the differences between same-day and staged circumferential fusion surgery in ASD focusing on the current evidence and its limitations. The decision to stage a surgery for a complex deformity case comes with certain tradeoffs for the surgeon and patient. Some surgeons prefer to minimize complexity by staging and, in theory, minimize the morbidity associated with long operative and anesthesia times. Others elect to combine approaches on the same day to theoretically limit anesthesia events and blood loss, reduce total operative time, and reduce the overall length of stay and hospital costs.

The available literature on staging ASD procedures is limited by small sample sizes and inclusion of diverse pathologies (degenerative, infectious, neoplastic, or traumatic), making interpretation difficult. Nearly 30 years ago, Shufflebarger et al [27] reported a retrospective review of staged (n=35) versus same-day (n=40) surgery for ASD that showed significantly less total blood loss, lower postoperative complication rates, and a more favorable deformity correction. Another small retrospective study of 11 patients per group showed that same-day surgeries were associated with less blood loss, decreased postoperative morbidity, and shorter lengths of stay [28]. With regard to extended hospitalization, Stephens et al [29] demonstrated that it is independently associated with increased costs after ASD surgeries. A national population-based discharge database was used to analyze outcomes in 11,265 circumferential spine surgeries with a subgroup analysis of same-day versus staged procedures. The staged group was associated with increased perioperative complications, including postoperative venous thrombosis and acute respiratory distress syndrome [30]. The authors then performed a propensity-matched analysis of a retrospective cohort comparing same-day versus staged spine surgery in ASD with similar complication rates between groups. However, the staged group also required more revision surgery at the 2-year follow-up than the same-day group [16].

A limitation of this study is the relative paucity of high-quality evidence in this domain given the retrospective nature of many studies investigating this issue. Additionally, there are external factors that may influence the decision to perform same-day or staged surgery, such as surgical training, operating room availability, organizational practice patterns, and patient preference, which cannot be directly studied in this review.

Our systematic review will provide surgeons with a rigorous analysis of the available data on same-day versus staged procedures for circumferential fusion. The decision to stage a procedure has thus far been largely driven by the individual surgeon's practice patterns or because of the complexity of a patient's deformity or medical comorbidities. With the aging population and the increase in ASD, evidence-based practice will promote the best outcomes for our patients and avoid unnecessary and costly complications. Understanding the literature available at this point and its limitations will help to guide future prospective trials to deepen our understanding of this complex problem.

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No funding was received for this study.

Authors' Contributions

WCW is the guarantor of this study. MMD and AA conceptualized this study. MMD and SN generated the search strategy and wrote and revised the protocol. KM provided expertise on the methodology and identified pitfalls. GS, CW, and YGG reviewed and revised the manuscript. DM provided input on the statistical analysis. AKO and WCW provided critical guidance at all stages of the protocol preparation. All authors reviewed the manuscript and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.
[DOC File , 97 KB - resprot_v11i11e42331_app1.doc]

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Abbreviations

ASD: adult spinal deformity
PICO: population, intervention, comparison, and outcome
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PROSPERO: International Prospective Register of Systematic Reviews
ROBIN-I: Risk of Bias in Non-randomized Studies of Interventions

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Protocol

Passive Sensing in the Prediction of Suicidal Thoughts and Behaviors: Protocol for a Systematic Review

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Abstract

Background: Suicide is a severe public health problem, resulting in a high number of attempts and deaths each year. Early detection of suicidal thoughts and behaviors (STBs) is key to preventing attempts. We discuss passive sensing of digital and behavioral markers to enhance the detection and prediction of STBs.

Objective: The paper presents the protocol for a systematic review that aims to summarize existing research on passive sensing of STBs and evaluate whether the STB prediction can be improved using passive sensing compared to prior prediction models.

Methods: A systematic search will be conducted in the scientific databases MEDLINE, PubMed, Embase, PsycINFO, and Web of Science. Eligible studies need to investigate any passive sensor data from smartphones or wearables to predict STBs. The predictive value of passive sensing will be the primary outcome. The practical implications and feasibility of the studies will be considered as secondary outcomes. Study quality will be assessed using the Prediction Model Risk of Bias Assessment Tool (PROBAST). If studies are sufficiently homogenous, we will conduct a meta-analysis of the predictive value of passive sensing on STBs.

Results: The review process started in July 2022 with data extraction in September 2022. Results are expected in December 2022.

Conclusions: Despite intensive research efforts, the ability to predict STBs is little better than chance. This systematic review will contribute to our understanding of the potential of passive sensing to improve STB prediction. Future research will be stimulated since gaps in the current literature will be identified and promising next steps toward clinical implementation will be outlined.

Trial Registration: OSF Registries osf-registrations-hzxua-v1; https://osf.io/hzxua

International Registered Report Identifier (IRRID): DERR1-10.2196/42146

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KEYWORDS

suicide prediction; passive sensing; review; systematic review; sensors; suicidal thoughts and behaviors; digital markers; behavioral markers

Introduction

Suicide Prevention

Suicide is a common cause of death, resulting in over 700,000 deaths worldwide each year, while the total number of suicide attempts is even higher [1]. Especially among adolescents and young adults, suicide is a leading cause of death [1]. Identification of suicidal thoughts and behaviors (STBs) can support help seeking to prevent suicide attempts [2]. Years of research have been conducted to identify risk factors to meet this demand of health care [3-7]. Yet, a recent systematic review of prediction models for suicide attempts and deaths reported that the predictive validity associated with a positive result for suicide mortality was extremely low (≤0.01 in most models) [8]. Additionally, Franklin and colleagues [4] found that research on suicide risk factors in the past 50 years carries almost no predictive power due to several reasons. First, the prediction of a suicidal event is difficult in general because of the low probability of the occurrence of suicide [2,6]. Second, a major shortcoming of prior investigations was the repeated focus on an identical set of risk factors that have been shown to produce little predictive value for when an attempt might occur. For example, while the first suicidal thoughts or ideas about specific suicide methods often occur years before a suicide attempt, the transfer from ideation to action often occurs within days or hours before the attempt [9]. Third, similar measurement methods were repeatedly used, predominantly questionnaires [4]. However, questionnaires fall short in describing the strong fluctuations in risk factors for suicidal behavior like emotional distress, hopelessness, or suicidal thoughts [10,11], making short-term prediction nearly impossible. In addition, it is difficult to model the complex interactions of different risk factors using questionnaire data [12].

Passive Sensing

In recent years, promising new ways to identify STBs have emerged. The widespread use of smartphones in everyday life provides a source of data that allows real-time monitoring [13]. Passive sensing is one of many terms that are used to describe the passive collection of behavioral data via smartphones or other wearable devices [14]. Depending on the type of device, different sensors can be used to collect a variety of data points. In general, behavioral (eg, movement via GPS), physiological (eg, heart rate), and social (eg, social media engagement) signals can be measured through the sensors [13]. The objectivity and seamless provision of information over a period of time brings advantages compared to subjective questionnaires at a certain point in time [15,16]. Therefore, research has focused on the potential and feasibility of passive sensing in mental health [16-19]. Machine learning methods can then build predictive models from these huge data sets [20,21].

Previous Research

Despite a number of unanswered questions and methodological challenges [22], some researchers have explored the potential of passive sensing for mental health. Studies investigating the relationship between passive sensing and psychological symptoms have been conducted [18,23,24]. For example, Zulueta and colleagues [25] found that increased accelerometer activity was correlated with a change in mood disturbances. Furthermore, increased social media use was found to be positively correlated to depressive symptoms [25]. Quantitative variables such as the number of outgoing calls, unique numbers texted, or absolute distance traveled showed a predictive value for depressive symptoms in an investigation by Place and colleagues [26]. Across several studies, there is a promising trend that passive sensing can be reliably used to predict some symptoms or behaviors. However, other studies report less-promising results, which tempers expectations and highlights the need for replication trials to confirm preliminary findings [27,28].

The Proposed Review

Prior reviews have been conducted to summarize the possibilities and limitations of passive sensing in suicide prediction [15,29,30]. Given the dynamic development of the field, an updated review is needed to observe the latest advances in the field. The proposed systematic review aims to summarize the research on passive sensing in suicide prediction and identify both major advances and obstacles. In particular, we intend to create a better understanding of how current findings may translate into practice. For this purpose, the review will address (1) whether passive sensing data show the ability to improve the prediction of STBs compared to traditional methods of data collection, (2) what the comparative predictive power of different sensor types is, and (3) what analysis methods have been reported in the literature.

Methods

This protocol is based on the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist [31].

Eligibility Criteria

We will include studies that addressed passive data generation via smartphones or wearables in the context of STBs. All individuals regardless of age or gender with any STB (suicidal ideation, suicide attempt, death by suicide) will be included. Studies reporting on nonsuicidal self-injury will be excluded. If studies investigate both STBs and nonsuicidal self-injury, they will be included. Studies will be included regardless of whether or not the participants were receiving treatment. Studies will be eligible if they report results on the association between passive sensing and STBs. In addition, we will include study protocols and conduct a search of international study registries to preview upcoming research. Articles will be translated into English if necessary.

Search Strategy

A web-based systematic database search will be performed using the following search terms: (mobile sens* OR smart sens* OR smartphone sens* OR passive sens* OR passive monitor* OR sensor OR sensors OR digital phenotyp* OR wearable* OR passive data OR real-time data OR real-world data) AND suicid*. To ensure the sensitivity of the search, the search string was validated by a test set of 7 hand-searched relevant articles (Multimedia Appendix 1 [32-38]). The search string was optimized using an iterative process until a coverage rate of

100% was reached. In July 2022, the search will be conducted via the databases MEDLINE, PubMed, Embase, PsycINFO, and Web of Science (Multimedia Appendix 2). We will perform forward searches via Google Scholar and backward searches in the reference lists. Gray literature will not be searched.

Selection Process

The selection of relevant articles will be conducted by 2 independent researchers using the online tool Covidence. First, all titles and abstracts resulting from the search will be screened against the eligibility criteria. Second, the full texts of the articles selected in the first step will be obtained and screened in more detail. Disagreements will be resolved in discussion with a third reviewer. Duplicates will be identified and excluded. In the case of multiple reports of the same study, all available data will be reported. All steps of the selection process will be described in detail and will be visualized in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart [39].

Data Extraction

All data will be managed via Covidence, which will be used for the whole selection process. At the end of the process, the 2 independent reviewers will extract information according to a data extraction sheet. The following variables will be extracted from all included articles: authors, publication year, journal, population variables (age, gender, STBs), data collection device (smartphone, smartwatch, smart home, etc), type and frequency of passive data (social media, text messages, screen time, etc), analysis methods (machine learning, predictive models, qualitative techniques, etc), and assessment length. If any important data are missing, the authors will be contacted. Any qualitative or quantitative data describing the predictive ability of passive sensor data will be extracted. Results on the practical relevance and feasibility of passive sensing will be considered as secondary outcomes.

Risk of Bias Assessment

To assess the risk of bias at the study level, 2 independent reviewers will use the signaling questions of the Prediction Model Risk of Bias Assessment Tool (PROBAST) [40]. According to the tool, 4 domains will be analyzed: participants, predictors, outcome, and analysis. In total, 19 signaling questions will be answered with “yes,” “probably yes,” “no,” “probably no,” or “no information.” Afterward, the level of risk of bias will be estimated. Disagreement between the reviewers will be solved via discussion. If discussion does not lead to agreement, a third reviewer will be consulted.

Data Analysis

All extracted characteristics of the identified studies will be described narratively. The relevant results will be presented in text form and visualized in tables. If an appropriate number of studies report associations between identical sensor data and a quantitative measure for STBs, we will perform meta-analytic pooling. The meta-analytic pooled correlation will be estimated using a random-effects model with a maximum likelihood estimator. We will treat the heterogeneity (ie, the variability between the studies in terms of methodology and sample characteristics) as random [41]. In this way, we will estimate both the average true effect and the amount of heterogeneity among the true effects [41]. If heterogeneity is zero, the average true effect displays the true effect.

Results

The selection process started in July 2022. Data extraction started at the beginning of September 2022. Results are expected in December 2022.

Discussion

The aim of this systematic review is to summarize the potential of passively generated data to predict STBs. Research in this area is new but has developed rapidly in recent years. Consequently, we expect a rather heterogenous set of reports and trial designs. Therefore, one aspect of this review will be to identify key variables that future trials should report in order to increase comparability in future systematic reviews. For example, an extended form of the TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) Checklist [42] for sensing data could be developed. In addition, this review offers a chance to identify valuable predictors to improve the prevention of suicide. It will present an updated summary of existing knowledge in this fast-growing field and exceed prior reviews’ quality through preregistration and by using a systematic approach. Next to predictive values of quantitative sensor data, feasibility aspects of sensing studies will be pointed out as well. Hence, new inspirations for further research regarding methodological possibilities of data collection and study design will be stimulated. At the same time, recent evidence will be critically evaluated in order to create further demands for research that will advance the path to clinical applicability.

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Data Availability

All study data will be made publicly available on the Open Science Framework website.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The test set of 7 hand-searched relevant articles.
[DOCX File , 21 KB - resprot_v11i11e42146_app1.docx]

Multimedia Appendix 2
Database search strings.
[DOCX File , 16 KB - resprot_v11i11e42146_app2.docx]

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Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PROBAST: Prediction Model Risk of Bias Assessment Tool
STB: suicidal thoughts and behavior
TRIPOD: Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis

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Protocol

Smart Continence Care for People With Profound Intellectual and Multiple Disabilities: Protocol for a Cluster Randomized Trial and Trial-Based Economic Evaluation

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Abstract

Background: People with profound intellectual and multiple disabilities (PIMD) cannot communicate the need to change their incontinence products. The smart continence care (SCC) product Abena Nova signals caregivers when change is needed. This provides the opportunity for more person-centered care, increased quality of life, and a decreased number of leakages. However, there is a need for evidence of the effectiveness and cost-effectiveness of such technology compared with regular continence care (RCC) for people with PIMD.

Objective: This paper presents the research protocol for an effectiveness and cost-effectiveness study with people with PIMD living in long-term care facilities in the Netherlands.

Methods: A cluster randomized trial will be conducted in 3 consecutive waves across 6 long-term care providers for people with disabilities and 160 participants with PIMD. Long-term care providers are randomized at a 1:1 ratio, resulting in an intervention group and a group continuing RCC. The intervention group will receive implementation guidance and use SCC for 3 months; the other group will continue their RCC as usual and then switch to SCC. This study consists of three components: effectiveness study, economic evaluation, and process evaluation. The primary outcome will be a change in the number of leakages. The secondary outcomes are quality of life, the difference in the number of changes, the work perception of caregivers, cost-effectiveness, and cost utility. Data collection will occur at T0 (baseline), T1 (6 weeks), T2 (12 weeks), and T3 (9-month follow-up) for the first 2 intervention groups. An intention-to-treat analysis will be performed. The economic evaluation will be conducted alongside the trial from the societal and long-term care provider perspectives. Qualitative data collection through interviews and field notes will complement these quantitative results and provide input for the process evaluation.

Results: This research was funded in December 2019 by ZonMw, the Netherlands Organization for Health Research and Development. As of June 2022, we enrolled 118 of the 160 participants. The enrollment of participants will continue in the third and fourth quarters of 2022.

Conclusions: This study will provide insights into the effectiveness and cost-effectiveness of SCC for people with PIMD, allowing long-term care providers to make informed decisions about implementing such a technology. This is the first time that such a large-scale study is being conducted for people with PIMD.

Trial Registration: ClinicalTrials.gov NCT05481840; https://clinicaltrials.gov/ct2/show/NCT05481840

International Registered Report Identifier (IRRID): DERR1-10.2196/42555

(JMIR Res Protoc 2022;11(11):e42555) doi:10.2196/42555

KEYWORDS

care technology; implementation; disability care; profound intellectual and multiple disabilities; economic evaluation; continence care; smart diaper

Introduction

Background

People with profound intellectual and multiple disabilities (PIMD) depend entirely on professional care. Their disability is characterized by profound intellectual disability, that is, a developmental age of up to 24 to 36 months depending on the definition [1], profound motor disability, and, usually, secondary disabilities or impairments [2]. The Netherlands has approximately 9500 (April 1, 2013) people with severe intellectual disabilities or PIMD (developmental age of up to 4 years), of which 95% live in a long-term care facility [3].

People with PIMD commonly experience urinary and fecal incontinence. The percentage of incontinence ranges from 45% in people with severe intellectual disabilities [4] to 56% in people with PIMD. An incidence of 61% was reported in females with a specific form of PIMD: the Rett syndrome [5]. There is a correlation between an increased level of intellectual disability and a higher rate of incontinence [4,6] and between an increased level of physical impairment and a higher rate of incontinence [7]. There are methods to promote continence in people with PIMD, such as toilet routine training [4,8]. This training can take a long time and might not be successful for all persons with PIMD, as it requires a combination of communicative skills, mobility, and cognitive ability, skills which are commonly underdeveloped in people with PIMD [2]. In Dutch long-term care facilities, most people with PIMD who are incontinent wear pads, adult diapers, or catheters. When a person cannot notify when change is needed, the material is often changed at scheduled moments. However, these scheduled moments result in leakages when the material is oversaturated, leading to an additional change of clothing or bed sheets, and the person may need to be washed or showered.

Furthermore, long exposure to wet incontinence materials could result in skin problems, such as incontinence-associated dermatitis [9]. In addition, scheduled changes could result in unnecessary changes when the pads or diapers are still (relatively) dry. Leakages, skin problems, and unnecessary changes cause an extra burden to people with PIMD, resulting in agitation and additional transfers, and their caregivers, as unnecessary time is spent on continence care and related activities.

Person-Centered Continence Care by Using Technology

The Health and Youth Care Inspectorate (Dutch Ministry of Health, Welfare, and Sports) emphasizes the importance of providing good care for people with PIMD, as they fully depend on their caregivers. The key point in providing good care to people with PIMD is to recognize the needs of the person and act accordingly, which is known as person-centered care [10,11]. However, it is complex to recognize these needs [12], and a caregiver must have known the person for many years [10]. The needs of people with PIMD regarding continence care can be communicated using technology (smart continence care [SCC]). Sensors in the incontinence material signal when a change of the material is needed. If the use of person-centered continence care decreases the number of leakages and unnecessary changes, it has the potential to increase the quality of care provided for people with PIMD, and it may also save the time spent on continence care and reduce the workload of the caregivers. This is even more important given the increasing shortage of health care workers [13], especially because PIMD care in the Netherlands has difficulties finding and keeping caregivers [14].

Several solutions have been developed to inform caregivers of when to change incontinence products. Some examples of such solutions are analog indicators on the material itself; a strip on the outside of the incontinence product that shifts color with changes in saturation [15]; smart continence products using sensor technology, such as a 72-hour observation of the voiding pattern registered by a small device attached to the incontinence product with an integrated sensor [16]; solutions for continuous monitoring and notification of the need for change with reusable sensors that are attached on the outside of the product [16]; and solutions with integrated sensors and removable clip [17]. To check the color change on the analog indicator, the caregiver should physically inspect the product. With the 72-hour observation technology, there is no real-time notification of the need for change. Both can be considered disadvantages. With the last 2 solutions, caregivers and people with PIMD can benefit from real-time notification sent to a mobile phone when a change of continence material is needed. This study investigates a smart continence product with integrated sensors and a removable clip (Abena Nova).

Previous studies on SCC, mostly pilot studies, have investigated its effect on the number of leakages, number of changes, and quality of life of the user [18,19]. However, these studies were small and had different target groups (ie, older people and people with intellectual disabilities), and in one of the studies [18], the supplier was involved in the research. Therefore, there is a need for independent and comprehensive research.

Aim of the Study

This paper presents the research protocol (according to the SPIRIT [Standard Protocol Items: Recommendations for Interventional Trials] guideline [20]) for the “Smart Diaper research and implementation project” to evaluate the effectiveness, cost-effectiveness, and implementation process of SCC for people with PIMD living in a long-term care facility. Thorough research on the effects, added value, and costs will

help the funding bodies and policy makers of long-term care facilities to make an informed decision about whether to implement smart continence products for people with PIMD.

Besides the societal and economic values of such a study, this research is unique from an academic perspective. Literature reviews have shown that the number of studies on the effectiveness of (technological) interventions for people with PIMD is very limited. Maes et al [21] revealed a total of 16 intervention studies between 1995 and 2006, and Dupont et al [22] showed a total of 39 studies (including several follow-up studies based on the same initial study, thus containing the same group of respondents) between 2006 and 2018. The reported sample size for most studies was relatively small; only 5 studies reported a sample size of >10 participants, and the largest study included 44 participants with PIMD. Likewise, economic evaluations of interventions for people with PIMD are rare [23]. Therefore, this first well-powered cluster randomized trial (CRT) aims to evaluate the effectiveness, cost-effectiveness, and implementation process of SCC for people with PIMD.

Research Questions

This study will compare SCC with RCC provided to people with PIMD living in a long-term care facility in the Netherlands. This study consists of 3 parts, each with its focus and research questions. Textbox 1 lists the 3 parts and corresponding research questions.

Textbox 1. The 3 parts of this study and corresponding research questions.

Effectiveness study

1. What is the effect of smart continence care (SCC) for people with profound intellectual and multiple disabilities (PIMD) on the number of leakages compared with regular continence care (RCC)?
2. What is the effect of SCC on the number of changes of incontinence material compared with RCC?
3. What is the effect of SCC on the quality of life of people with PIMD compared with RCC?
4. What is the effect of SCC on the work perception of caregivers with regard to continence care compared with RCC?

Economic evaluation

1. What is the cost-effectiveness of SCC compared with RCC provided to people with PIMD from a societal perspective?
2. What is the cost utility of SCC compared with RCC provided to people with PIMD?

Process evaluation

1. What are the experiences of the participating long-term care providers with respect to the implementation of SCC?

Methods

Study Design

This study design can be best described as a staggered-entry CRT. A total of 6 long-term care providers for people with disabilities are divided into 3 pairs. This allocation is done in consultation with the long-term care providers, depending on their readiness for the research and implementation of SCC. Within these pairs, the long-term care providers are randomized into the SCC or RCC conditions using random.org (1:1 ratio). The research started at the end of 2021 for the first pair, and the second and third pairs started during the first and second halves of 2022, respectively. The long-term care providers randomized into the RCC condition will implement SCC once data collection is completed (Table 1). Considering the complexity of successfully implementing health care technologies [24], time and effort are required to realize the full potential of SCC. With this design, a small team of researchers and implementation consultants can consecutively support all long-term care providers with the implementation of SCC, as it allows lessons learned to spill over to the second and third pairs. The intervention does not allow for blinding within the trial. Furthermore, the study has a mixed methods design to answer the research questions, using quantitative as well as qualitative data.

Table 1. Timeline within the staggered-entry cluster randomized trial.

	T0 (week 0)	Start SCC[a]	T1 (week 6)	T2 (week 12)	Start SCC	T3 (9 months)
Couple 1 Q3-Q4 2021 and Q2 2022						
Long-term care provider A	✓	✓	✓	✓		✓
Long-term care provider B	✓		✓	✓	✓	__[b]
Couple 2 Q1-Q2 2022 and Q4 2022						
Long-term care provider C	✓	✓	✓	✓		✓
Long-term care provider D	✓		✓	✓	✓	__[b]
Couple 3 Q3-Q4 2022						
Long-term care provider E	✓	✓	✓	✓		N/A[c]
Long-term care provider F	✓		✓	✓	✓	N/A[c]

[a]SCC: smart continence care.

[b]Will be based on data collected at T2.

[c]N/A: not applicable. This measurement cannot be completed in the allotted time frame.

Ethics Approval

This study has been reviewed and approved by the Medical Ethics Committee of Radboudumc (NL72751.091.20). The trial has been registered at ClinicalTrials.gov (NCT05481840). Any modification to the study protocol will be checked with the funding body (outside of the annual progress update) and, if necessary, with the Medical Ethics Committee. The legal representatives of the participants will provide their written consent for the person with PIMD to participate in the research. Caregivers consent to participating and completing the web-based questionnaire by reading the information before the start and continuing to answer the questionnaire. The World Health Organization trial registration data set is presented in Multimedia Appendix 1.

Sampling

Power

The power calculations for the study are based on the observed effect sizes in previous studies that used the same outcome measure. Bouman et al [18] and Nap et al [19] reported 73% and 62% reductions in the number of leakages, respectively. As these studies were fairly small, this study will be powered to detect a rather conservative reduction of 40%. By using 3 measurements (T0, T1, and T2) per participant across 6 clusters (each long-term care provider being one cluster), with an assumed intraclass correlation coefficient (ICC) of 0.01, an α value of .05, and a design effect of 1.05, the study will be adequately powered (80%) to detect an incidence rate ratio (IRR) of 0.60 (1-0.40) if 80 (50%) participants per arm are included (N=160). In addition, the power calculation is cross-checked hereto using a simulation procedure from the R package simstudy [25], in which each unique combination of ICCs (0.01, 0.05, and 0.10), IRRs (0.5, 0.6, 0.7, and 0.8), the number of clusters (6, 8, and 10), and the number of participants per cluster (8, 12, 16, 20, and 24) is used to generate 100 simulated data sets in which ρ=0.75 between consecutive time points. Each data set is subsequently analyzed using a generalized linear mixed model with a Poisson link function (R package lme4 [26]). The respective power of each combination of parameters is subsequently inferred from the fraction of the resulting *P* values <.05 of the treatment indicator (SCC vs RCC). This simulation shows that our study will be well powered (80%) to detect a 20% reduction (IRR=0.8) in the number of leakages when 6 clusters with 24 participants each are included, irrespective of the ICC. We aim to include 6 long-term care providers containing 27 participants each, thus resulting in 160 participants overall.

Selecting Long-term Care Providers

A total of 6 Dutch long-term care providers for people with disabilities were recruited before the grant proposal.

They should meet the following conditions:

- Provide residential care to people with PIMD and be able to provide at least 27 participants for the study
- Have an intention to implement SCC people with PIMD sustainably
- Have an IT infrastructure to support the use of SCC
- Show commitment to implementation and participation in the research by doing the following:
  - Signing an intention agreement at the level of management, middle management, and caregivers
  - Releasing funding for the purchase of the product
  - Providing human resources for implementation and training
  - Providing a project leader to coordinate the project

Long-term care providers will receive a financial contribution for the research activities, up to a maximum amount of €10,000 (US $9816.50, currency rate as per October 19, 2022), when different targets are met (such as enrolling 27 participants and completing data collection) to promote full participation in the Smart Diaper research and implementation project.

Participant Selection

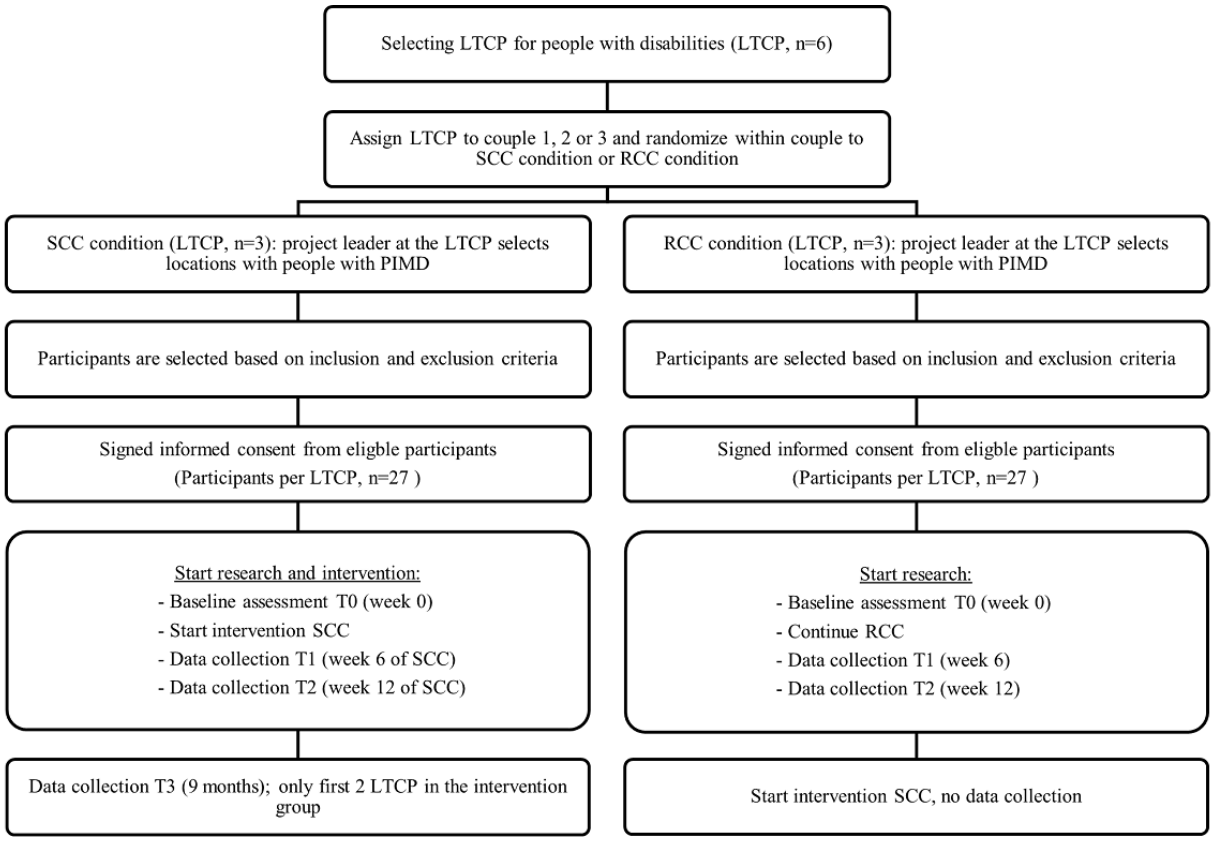
A long-term care provider for disabled people often has multiple locations (eg, “houses” or “residential groups”) where people

with disabilities live. Most of these locations have permanent teams of caregivers. When selecting locations with people with PIMD, favorable conditions for implementation will be checked, such as willingness to implement SCC; low staff turnover; and whether other priorities could jeopardize the research and implementation, such as other (research) projects, renovation, or relocation. This is important because research and implementation will require commitment, resources, and time. The locations of each long-term care provider are recruited after the randomization. Information on the study sites will be available upon request from the corresponding author.

After locations are selected, individual participants will be eligible for inclusion in the study if they are aged >18 years, have PIMD, use incontinence products, and are not able to communicate the need for a change of the incontinence material, and their legal representatives will give informed consent for them to participate in the study. Participants who use a permanent catheter or show behavior that may result in a risk for the patient when using SCC (such as pica disorder) are excluded from the study. There are 2 possible soft exclusion criteria in which participants should be carefully considered: release of feces ≥3 times per 24 hours, as this may interfere with the technology detecting urine and a behavior that can hinder the successful implementation of SCC, such as, but not limited to, removing the incontinence material, clip, or clothing. Caregivers will be encouraged to make a thoughtful decision in this situation regarding whether it is meaningful to try SCC for these people and how these potential impediments can be mitigated.

The use of SCC will set no limitations for concomitant care, such as the use of tranquilizers, diuretics, or laxatives. The caregivers propose participants at their locations based on the inclusion and exclusion criteria. The researchers, the product specialist of the supplier, behavioral therapist, and other experts within the long-term care provider are available for any consultation if there are any doubts about inclusion. People can be included even if they check 1 or 2 boxes of the soft exclusion criteria, as caregivers might see the added value of implementing SCC for such people. If people are eligible, their legal representatives receive an informational letter about the study and are asked to sign an informed consent form. The legal representatives are also offered to participate in the research. If they opt in by signing a second informed consent form, they will receive questionnaires about the person with PIMD. Figure 1 summarizes the recruitment and selection process.

Figure 1. Flowchart of randomization, study inclusion, and measurements. LTCP: long-term care provider; PIMD: profound intellectual and multiple disabilities; RCC: regular continence care; SCC: smart continence care.



Intervention

Overview

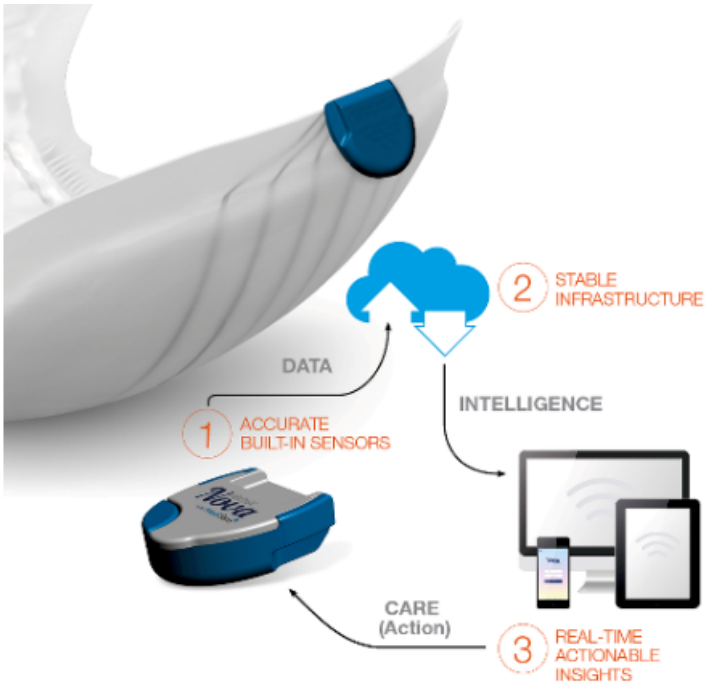
In this study, SCC for people with PIMD will be provided by implementing Abena Nova with MediSens, produced by the Abena Group in collaboration with MediSens Wireless Inc [17]. This product was selected because it had higher market readiness than other products and was commonly used in Dutch pilots at the time of the grant application.

RCC consists of changing incontinence products, providing skin care if needed, and other hygienic activities, such as changing bed sheets and showering the person if a leakage has

occurred. Most of the time, continence care is provided by following a fixed schedule, such as standard changes in the morning, around noon, and before going to bed (routines might vary among care teams). Leakage, specific behavior, or feces can cause deviations. Some people receive continence care during the night at fixed moments or when monitoring technology picks up noises during the night, indicating the need for care or continence care. In the RCC condition, the caregivers continue these regular routines.

Abena Nova (Figure 2) consists of incontinence material with integrated sensors and a detachable and reusable clip. When the sensors become moist, the clip transmits this information to the receiver near the person with PIMD. The receiver sends this information to the cloud, and this information is displayed in an app called Wetsens (available on Android and iOS) and a web portal. When an adjustable threshold level for saturation is reached, the app sends a notification to inform the caregivers. Reaching the first threshold level triggers the notification "change desired" and displays an orange sign; then, caregivers have approximately 60 minutes to change the product. If the next threshold level is reached, a red sign is shown with the notification "risk of leakage." Each receiver and app can monitor multiple users simultaneously, and each user can be monitored on several mobile devices at once. The sensor registers only urine. Feces is not detected and could even interfere with the registration of urine by blocking the sensors [27].

Figure 2. Schematic representation of the Abena Nova (reprinted with approval of Abena).



To provide SCC, caregivers need to be trained in using the technology and different incontinence materials. The supplier offers a 30-minute e-learning program and highly recommends that caregivers take this e-learning. Next, the team will have a live instruction (approximately 1 hour) from the supplier's product specialist to discuss and practice using Abena Nova, such as how to attach the clip and use the app. It will be emphasized that perfectly fitting products (not only in size but also in applying it correctly) and reacting to notifications are essential to prevent leakages and provide SCC correctly.

For each participant, different teams providing continence care for 24 hours will be identified (residential care team, day care team, and night care team). Each team will have at least one ambassador who supports and motivates the team to provide SCC. This ambassador will receive additional training on using the web-based Wetsens portal. During the use of SCC, several meetings will be organized between the different ambassadors and product specialist of the supplier to discuss the individual participants and the results of SCC. If needed, alterations in SCC can be made to optimize the effectiveness, such as the size and absorption capacity of the material or the threshold level for notification. In addition, these meetings and the possibility of discussing the experiences will contribute to the adherence of caregivers to SCC.

Besides learning how to use the technology, caregivers will also need to change their working routines. Instead of having fixed schedules, notifications about "full incontinence products" should trigger continence care. Note that as feces is not detected by Abena Nova, normal schedule or observations apply for providing continence care in these cases. Altering work routines is difficult and time-consuming. Supporting and motivating the team will be needed and can be done by the product specialist of the supplier, ambassador, and project leader. The type and amount of support for each team might differ. Customization of the support for a team is recommended to increase adherence to SCC.

There are valid reasons for caregivers to discontinue SCC in individuals with PIMD, such as skin irritation or nonacceptance by the person with PIMD. Caregivers are free to make this choice by following what is best for the person with PIMD. The number of such discontinuations and their reasons are collected, as they hold valuable insights into the suitability of SCC. Data

will still be collected for these persons according to the intention-to-treat principle.

Implementing SCC

Long-term care providers will receive implementation support through a practical step-by-step guideline (based on interviews with the supplier, users of SCC, the expertise of the research and implementation team [OS and VJCvC], scientific implementation protocol "Replicating Effective Programs" [28], and insights described in the work of Wensing and Grol [29] and implementation workbook by ZonMw [30]). This guideline is developed by the research team and will be updated during this project (Table 2). In this way, best practices and valuable insights into fostering or inhibiting factors for implementation can be transferred to the next organization. Meetings will be organized between the 6 project leaders of the participating organizations to exchange their best practices and difficulties. In addition, the project leaders will have weekly to monthly consultation sessions with members of the research team (VJCvC and OS). These moments of contact and the use of the guideline will be flexible according to the needs of the long-term care provider. This flexible approach to implementation is considered the most appropriate strategy for implementation and research projects in health care [31].

Table 2. A summary of implementation guidelines for the long-term care providers implementing smart continence care.

Phase	Examples of activities and focus
What to arrange beforehand	• Involving relevant stakeholders (such as management, IT and facilities department, and internal health care services) in setting up the project team • Assigning resources (time and finance) to the project • Recruiting locations where people with profound intellectual and multiple disabilities live to implement smart continence care • Indicating different care teams (24/7) involved in continence care for the people living at these locations • Discussing vision on continence care with stakeholders • Technical preparations (checking hardware, software, and support of IT department) • Signing contract with the supplier
Preparing the teams and location	• Making timeline per location and care team (training, technical installation, start smart continence care, and evaluations) • Selecting people with profound intellectual and multiple disabilities who will receive smart continence care • Completing training activities for caregivers to use smart continence care • Technical preparations
Using smart continence care	• On-site support for the care teams • Continuous monitoring by the project leader on how the implementation (use of smart continence care) and changing work routines proceed; intervene if necessary
Decision-making on continuation and further uptake	• End evaluation of the first use of smart continence care: Is it a success? When is it a success? What is needed to continue the uptake of smart continence care within long-term care facility? • Decision-making with relevant stakeholders and plan of action for next steps • Evaluating smart continence care with the different care teams involved, discussing specific cases, and using the Wetsens portal

Preparations Before the Research

We conducted a pilot study to test one of the research instruments, the continence diary, and learn about the implementation process. A total of 2 people with physical disability and moderate intellectual disability living at a long-term care facility used Abena Nova for 1 week. Three care teams were involved: the residential care, day care, and night care teams. The caregivers of the 2 participants were instructed on the use of SCC, research, and pilot's goal. A think-out-loud session was conducted with 2 caregivers to discuss all research instruments and check their feasibility. A total of 2 caregivers and a project leader evaluated the implementation process and continence diary. This resulted in valuable insights for the practical step-by-step guideline and an improved continence diary by adding a clear-written instruction and better formulation of the questions.

Measures

Overview

To assess the (cost)-effectiveness of SCC, outcome assessments will be performed at baseline (T0) and after 6 weeks (T1), 12 weeks (T2), and 9 months (T3). T3 only applies to the first 2 long-term care providers in the intervention group, as only these 2 care providers are assessed within the allotted time frame. Table 3 shows an overview of the questionnaire for each time point. Most data will be collected using paper and pencil, as this is easiest for caregivers. Research assistants will be trained for data entry, and the researchers will perform regular quality checks. Pseudonymized data will be stored at a secure site with limited access and separated from personal data such as names. Qualitative research will complement the effectiveness measures to evaluate the implementation. All data collection procedures and a data management plan (in Dutch) are available upon request from the corresponding author.

Table 3. Overview of the questionnaires over time.

	T0 (week 0)	Start SCC[a]	T1 (week 6)	T2 (week 12)	Start SCC	T3 (9 months)
About the person with PIMD[b]						
Continence diary	✓		✓	✓		✓
Resource measurement questionnaire	✓		✓	✓		✓
EQ-5D-5L proxy 1[c]	✓			✓		✓
MIPQ[d]	✓			✓		
QOL-PMD[e]	✓			✓		
Goal Attainment Scale[f]				✓		
General questionnaire	✓		✓	✓		✓
About the caregiver						
Work perception questionnaire—continence care	✓			✓		

[a]SCC: smart continence care, for the long-term care providers assigned to the SCC condition.

[b]PIMD: profound intellectual and multiple disabilities.

[c]The caregiver (the proxy) is asked to rate the patient's health-related quality of life in their (the proxy's) opinion.

[d]MIPQ: Mood Interest and Pleasure Questionnaire.

[e]QOL-PMD: Quality of Life of Persons With Profound Multiple Disabilities.

[f]Only applicable for the long-term care providers assigned to the SCC condition.

This study is an open-label trial, as it is not possible to blind the application of SCC to caregivers, participants, and families. Open-label trials are common among trials that investigate devices and other nonpharmaceutical interventions [32]. An independent outcome assessor unfamiliar with the treatment allocation will reduce the bias in the outcome assessment [33]. For this study, a statistician (WdH) will perform a blind assessment of the primary outcome measure.

Effectiveness Study

Primary Outcome

The number of leakages is registered in a "continence diary" for each participant for an entire week. Each caregiver providing continence care will enter the continence care provided per participant for an entire week in the printed diary. The primary outcome variable, whether leakage has occurred, will be registered by ticking a box. The diary will also hold information about the content of the incontinence material (ticking boxes for urine and feces separately). The data indicate the number of leakages per person per week at each time point. The change in the number of leakages over time within the intervention group will be compared with that in the group continuing their RCC.

Secondary Outcomes

Continence Care

Every instance of continence care is registered within the continence diary, providing information about the number of changes per participant per week. Shifts in the number of changes of incontinence material over time within one study arm will be compared with those in the other study arm. These registrations will include information about the reason for a change (eg, fixed schedule, notification generated by the sensor technology, behavior, leakage, or feces). Furthermore, the time spent on continence care and additional information on extra activities, such as skin care, washing the person, or changing bedsheets or clothing, will be registered.

Quality of Life

The number of instruments used to measure the quality of life of people with PIMD is limited. To select an instrument, it is important that there have been psychometric evaluations of the instrument within the target populations [34,35] and that the questionnaire be available in Dutch [36]. Two questionnaires developed explicitly for people with PIMD will be used to measure the effect on the multidimensional construct of quality of life [37-39] by comparing the difference in the scores of T2 to T0 between the 2 study arms. The "Mood, Interest, and Pleasure Questionnaire" is an indicator of subjective well-being [40]. This questionnaire consists of 22 items resulting in 3 subscales. The items are statements about the observed behavior of people with PIMD for the last 2 weeks. The proxies of the people with PIMD indicate their observations by scoring between 0 and 4 (0=never and 4=always occurred). The score is calculated by taking the sum of the corrected scores per subscale. A high score indicates high subjective well-being.

The questionnaire "Quality of Life of Persons With Profound Multiple Disabilities" [12] measures the objective quality of life and consists of 55 items resulting in 6 subscales. Each statement is scored between 0 and 2 (0=disagree, 1=partly agree, and 2=fully agree). The subscale score and total score are expressed as a percentage, between 0% and 100%. A score of 100% represents highly objective quality of life. Proxies can provide written clarifications to elaborate on their answers.

The proxies for both questionnaires are caregiver(s) of the person with PIMD and the legal representative (if opted in). Caregivers are allowed to consult with other colleagues when

answering the questionnaires. Complementary interviews with caregivers will be held to explore how SCC influences the quality of life of persons with PIMD.

Setting Goals

During T0 and T2, an open question asks caregivers to describe the goal of providing SCC for the participant. In addition, the questionnaire at T0 asks the caregivers to elaborate on when this goal is met. The Goal Attainment Scale [41] depicts the extent to which this goal is met at T2 in the intervention groups. A total of 5 answer options are available to the respondents, ranging from "goal is not met, there has been a decline" to "the change exceeds the expectations, or more than just the goal is met."

Perception of Work Related to Providing Continence Care

To measure a possible change in work perception, a web-based questionnaire is distributed among caregivers providing continence care to the participants. The web-based questionnaire is composed of and inspired by various questionnaires measuring different constructs related to the perception of work. First, the experienced burden of providing continence care is measured by 4 statements about work pressure (5-point Likert scale), scoring the physical and mental burden of continence care (scale: 0-10; 0=no burden and 10=very high burden). These items are inspired by Karasek [42] and Daems and Kunen [43]. Second, the construct of autonomy is measured by 4 items on a 5-point Likert scale specified for continence care, inspired by the Maastrichtse Autonomie Lijst (MAL) [44]. The overall satisfaction with continence care is measured by 1 item, which is scored between 0 and 10 (0=very low satisfaction and 10=very high satisfaction), and the participants are asked to explain the score. Work engagement is measured using the 9-item Utrecht Engagement Scale (UBES; a 7-point scale indicating frequencies) [45].

The web-based questionnaire at T2 contains 8 additional statements about SCC, which can be scored on a 5-point Likert scale (from totally disagree to totally agree). The RCC group selects the answer that best represents their opinion on the expectations of SCC. The SCC group selects the answer that best represents their actual opinion of SCC after using it for 12 weeks. Two additional open questions will explore the expected or experienced positive and negative effects of SCC.

Complementary in-depth interviews with caregivers will be held to explore their experiences with the implementation of SCC and its effect on their work routines. The interviews will be guided by a topic list available upon request from the corresponding author.

Economic Evaluation

Overview

The economic evaluation will use a trial-based approach and will be performed from a societal perspective, as recommended by the Dutch guidelines for cost calculations in health care [46]. Besides the societal perspective, it is relevant to adopt the perspective of the long-term care providers, as they themselves make the primary decision regarding whether to implement SCC. The trial-based economic evaluations will include both a cost-effectiveness analysis (CEA) and cost utility analysis (CUA). The time frame of the study is 9 months. Within the RCC group, data will be collected at T0, T1, and T2; there will be no data collection at T3, but the measurement of T2 will serve as a proxy for T3 in the RCC condition. This can be done because the target population is expected to be stable, and having additional measures will cause an unnecessary burden to the caregivers filling in these questionnaires. Besides, this gives long-term care providers randomized in the RCC condition the opportunity to start the implementation of SCC immediately after T2. Within the SCC group, data will be collected at T0, T1, T2, and, for the first 2 intervention groups, at T3. This follow-up measurement will provide data about whether and to what extent the effect remained and whether medical costs changed for the participants who received SCC. The cost prices will be expressed in euros based on the cost prices in 2022. If necessary, the existing cost prices will be updated to those in 2022 using the consumer price index available from Statistics Netherlands [47]. In this economic evaluation, discounting is irrelevant, as the follow-up period is less than a year.

Estimation of Costs

The cost within health care and cost for participants and their families will be taken into account (Table 4 presents an overview). To identify relevant cost aspects, we have adopted an iterative process, similar but more condensed, as described by Thorn et al [48]. A search performed in the DIRUM (Database for Instruments of Resource Use Measurements; June 2021) did not provide instruments that could serve as a basis for resource use collection. Therefore, to determine the cost aspects of each category, previous cost studies on SCC [18,19,49] and field observations provide an initial list of cost aspects directly related to continence care. This list is finalized by a brainstorming session with different employees within a long-term care facility (people with and without experience in using SCC, such as coordinator night care, physiotherapist, and project leader). These cost aspects together with the resource measurement questionnaire, using a selection of relevant items from the *i*MCQ (*i*MTA Medical Cost Consumption) [50], are used to indicate all possible impacts on health care costs. Table 4 provides a general overview of the cost aspects, which instruments will be used to estimate resource use, and which unit prices will be used to valuate the resource use to calculate the costs. It also includes some cost aspects that are not further investigated because of the overall research costs (time-consuming and complicated to measure and validate) and the expected negligible impact on the total cost [51]. Costs within other sectors, such as productivity loss or absenteeism in a work-related setting, are not relevant to people with PIMD because they are unable to do (voluntary) work owing to their disability.

Table 4. Unit costs and how these are measured and valued.

	Method to measure resource use	How it is valued (source of unit cost)	Remarks and examples
Cost within health care			
Health care costs	Continence diary and resource measurement questionnaire	Dutch reference prices	Staff costs of continence care and all health care resources used, including medication
Related costs	Estimation based on continence diary	Dutch reference prices	Laundry and waste disposal costs
Intervention costs			
Material costs (disposable)	Continence diary	Market price	Incontinence material, gloves, bathing gloves, and skincare
Material costs (reusable)	Long-term care provider and supplier	Market price	Only applicable for the intervention group; clips, receivers, and care phones (optional)
Licensing fee for smart continence care	Number of days per user	Market price	Only applicable for the intervention group
Education and instructions to caregivers on the intervention	Information from the project leader at the long-term care provider	Dutch reference prices	Use Dutch guideline for costing to calculate
Costs of ICT[a] for the implementation and facilitation of the intervention within the long-term care provider	Information from the project leader at long-term care provider	Salary ICT	Use Dutch guideline for costing to calculate
Costs of project managing the implementation and facilitation of the intervention within the long-term care provider	Information from the project leader at long-term care provider	Dutch reference prices	Use Dutch guideline for costing to calculate
Cost for the participants and their families			
Costs of nonvisit because of continence leakage	Expert opinion	Not valued in monetary terms	Expert opinion is needed to estimate the impact
Costs of shorter visits because of leakage	Expert opinion	Not valued in monetary terms	Expert opinion is needed to estimate the impact
Costs of change in leisure activities	General questionnaire and expert opinion	Not valued in monetary terms	Expert opinion is needed to estimate the impact

[a]ICT: information and communication technology.

Estimation of the Effects

For the CEA, the change (T3-T0) in the number of leakages will be used as the outcome measure. Within the RCC group, the number of leakages at T2 will serve as a proxy for T3, still representing the RCC condition. Information regarding this outcome will be collected through the continence diaries.

For the CUA, the quality-adjusted life years (QALYs) will be used as the study outcome. To calculate these QALYs, the proxy 1 version of the EQ-5D-5L will be used because a person with PIMD cannot self-report. This instrument is seen as a valid, reliable, and more discriminating measurement compared with the previous 3-level version (EQ-5D-3L) and is often used in CUAs [52,53]. The primary caregiver acts as the proxy, and if opted in, the legal representative is the second proxy. The questionnaire consists of two parts: the EQ-5D, which is a descriptive system providing a health state, and a visual analog scale. The health state provided by EQ-5D consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each scored on a 5-point scale, giving 3125 possible health states [54]. These health states are valued using the Dutch utility score [52]. The visual analog scale is scored between 0 and 100, with a lower score indicating a lower health-related quality of life.

Process Evaluation

The difficulties and milestones of the implementation process will be discussed during regular meetings between the project leader of the long-term care provider and the implementation specialist and researcher (OS and VJCvC). Field notes and observations of these meetings and other important events (such as training sessions, evaluations, or site visits) will be taken by the researcher (VJCvC). In addition, interviews will be held with project leaders after implementing SCC using a topic list as an interview guideline. The field notes can be used to ask additional questions about certain events. Furthermore, the caregivers will be interviewed about their experiences with implementing and using SCC. Purposive sampling will be used to select caregivers for the interviews, aiming to obtain a wide variety of experiences from different long-term care providers

and contributing to the credibility of the findings [55]. The field observations will guide this purposive sampling. All participants will be asked for their consent to audio record the interviews.

Analysis

Effectiveness Study

Although it is not possible to blind the intervention during the trial, statistical analyses of the primary outcome measure will be performed by a statistician (WdH) unfamiliar with the treatment allocation. The data set will contain dichotomous variables (using condition "A" or "B"), referring to either SCC or RCC. The meaning of this dichotomous variable is randomly assigned using random.org. Primary outcome data will be analyzed using a generalized linear mixed model with a Poisson link function (R version 4.0+, package lme4) containing 3 levels: measurements within participants nested within long-term care providers. Time will be coded into binary dummy variables and added to the model as an interaction with the intervention, allowing for testing the difference between the treatment arms at each time point. Secondary outcome data will be analyzed similarly, albeit with the appropriate link function matching the type of outcome data. While mixed models allow missing data and hence appropriately serve the intention-to-treat principle, completer analyses will also be performed. The results will be described in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines for randomized controlled trials [56,57]. This study will be reported by following the CHEERS (Consolidated Health Economic Evaluation Reporting Standards) 2022 guidelines for reporting economic evaluations in health care [58].

Economic Evaluation

The sample size for the economic evaluation is based on the power analysis performed for the CRT. The primary (base case) analyses will be performed according to the intention-to-treat principle. This means that data from all the participants will be used, regardless of whether they received the intervention. For the analyses, we will use SPSS (version 28) statistical software and Microsoft Excel (Office 365; version 2205). However, if correction for baseline differences is needed, R (version 4.0+, package Ime4) will be used. Missing measurements will be handled using multiple imputation. Before the start of the analyses, a baseline analysis will be performed to examine the comparability of the groups at baseline for both costs and outcomes. If necessary, methods will be applied to control for differences in baseline measurements [59,60].

Owing to the expected skewness of cost data, besides means (and SDs), medians and IQR will be presented. The incremental cost-effectiveness ratios (ICERs) will be calculated for both CEA and CUA. The ICER will be calculated as follows: ICER = (Ci − Cc)/(Ei − Ec), where Ci is the total cost of the new intervention (SCC), Cc is the total cost of the comparator (RCC), Ei is the effect at the 9-month follow-up for SCC, and Ec is the effect at the 12-week follow-up for RCC, which is expected to be a good predictor for the situation after 9 months of not having the intervention. The robustness of the ICER will be checked by nonparametric bootstrapping. Bootstrap simulations will also be conducted to quantify the uncertainty around the ICER, yielding information about the joint distribution of cost and effect differences. Bootstrap replications will be used to calculate 95% CIs around the costs based on the 2.5 and 97.5 percentiles. The bootstrapped cost-effectiveness ratios will be plotted in a cost-effectiveness plane, in which the vertical axis will reflect the difference in costs, and the horizontal axis will reflect the difference in effectiveness. In addition, to demonstrate the robustness of our base-case findings, various sensitivity analyses will be performed, such as subgroup analyses examining the effect at 3 months. In these analyses, assumptions made in the base-case analysis will be varied to investigate their possible influence on the study outcomes, for example, by varying the cost prices and volumes between minimum and maximum.

The choice of treatment depends on the maximum amount of money that the society is prepared to pay for a gain in effectiveness, which is called the ceiling ratio. Therefore, the bootstrapped ICERs will also be depicted in a cost-effectiveness acceptability curve, showing the probability that the intervention is cost-effective, using a range of ceiling ratios. The ceiling ratio for the societal cost per QALY depends on the disease burden. Severe motor and cognitive impairments result in a disease burden of 0.425 (95% uncertainty interval 0.286-0.587) [61]. In the Netherlands, the disease burden is currently estimated to be €50,000 (US $48,847.92, currency rate as per October 19, 2022) per QALY (disease burden of 0.41-0.70) [62].

Process Evaluation

The interviews will be audio recorded and summarized by one of the researchers. The project leaders who participate are offered a member check on this summary to check the researcher's understanding of what is said and meant by the participant [55]. A second researcher will review these summaries by listening to the audio recordings and adding illustrative quotes. Using the software program Atlas.ti (version 9.1), these summaries will be coded through an iterative process. In this process, several researchers will be involved in discussing data analysis and increasing the credibility of the findings.

Results

This project received approval for funding on December 5, 2019, by ZonMw, the Netherlands Organization for Health Research and Development (grant 80-85300-98-19110). The funding period is 36 months. Owing to the COVID-19 pandemic, we received an extension of 6 months.

Data collection from the 160 participants living in one of the 6 long-term care facilities and their caregivers will provide insights into the effectiveness, cost-effectiveness, and implementation process of SCC compared with RCC. As of June 2022, we enrolled 118 of the 160 participants. The enrollment of participants will continue in Q3 and Q4 of 2022.

Discussion

Expected Findings

We expected that SCC would decrease the number of leakages compared with RCC when used for people with PIMD. A

decreasing number of leakages and the avoidance of unnecessary changes are expected to have a positive effect on the quality of life of people with PIMD. Because disruptive activities such as changing clothing and showering owing to leakages and skin irritation due to long exposure to wet incontinence material are expected to decrease, this will result in less agitated behavior. More personalized continence care is also expected to be cost-effective. Despite the higher cost of the material and cost of implementing SCC, it has the potential to save time for caregivers and decrease the use of products such as skin care products. In addition, the evaluation of the implementation process will provide valuable insights for long-term care providers. One of the insights expected is that facilitating employees with time and resources for implementation is important, as is setting up a project team and the early involvement of relevant stakeholders.

Strengths and Limitations

Although research guidelines argue that to measure the effectiveness of an intervention, the variation between individuals delivering this intervention should be minimized [20], providing continence care to people with PIMD is done by a wide variety of caregivers. Successful implementation of SCC and thus its observed effectiveness depends on the caregivers using it and the degree to which they change their work routines. This research will be conducted in a real-life setting, in which a great variety of other factors might influence the outcomes. Therefore, this pragmatic CRT (effectiveness study) is less controlled than expected from a controlled trial.

Furthermore, caregivers may alter their behavior and compliance with (smart) continence care because they are aware of the ongoing research (Hawthorne effect). However, we argue that this real-life research will provide more valuable insights into the added value that SCC can bring to long-term care facilities, caregivers, and, most importantly, people with PIMD [63]. Furthermore, including 6 different long-term care providers from across the Netherlands increases generalizability. Adherence to the CONSORT [57] and CHEERS 2022 [58] guidelines increases the quality of data reporting.

To incorporate the voice of the people with PIMD and the effect of the intervention on their quality of life, we must use proxies because the researchers lack the experience to understand the participants' behaviors and translate them into meaningful outcomes. By inviting caregivers and relatives to act as a proxy, we aim to incorporate the experience of people with PIMD in the best possible way. This could be seen as a limitation, as the experiences are never firsthand; however, receiving firsthand answers from people with PIMD is not possible.

Overall, this study protocol presents a unique (cost)-effectiveness research for a population rarely researched in such a way, people with PIMD. To the best of our knowledge, there has not been a large-scale study of this size (N=160) within this population before. This study investigates the effectiveness, cost-effectiveness, and cost utility of SCC compared with RCC. Thorough research on the effects, added value, and costs within this real-life setting will help funding bodies and policy makers at long-term care facilities with important information to make an informed decision about whether to implement smart continence products for people with PIMD. This is relevant because SCC enables person-centered care, which is an important goal, as stated by the Health and Youth Care Inspectorate.

Dissemination Plan

This study will produce several result papers, which will be submitted to scientific journals. Furthermore, this study is part of the dissertation of the first author (VJCvC), meaning that all the results will be available to the public through the expected dissertation. In addition, all long-term care providers and legal representatives, if interested, will receive a public-friendly summary of the results.

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This protocol will result in at least three publications: an effectiveness study, a cost-effectiveness study, and a process evaluation of the implementation. These studies will be submitted to scientific journals. The results will be published in the dissertation by VJCvC at Tilburg University. Legal representatives and participating organizations will receive information about the outcomes of the study. Abena Healthcare can refer to the publications.

Data Availability

The data sets generated during or analyzed during this study are not publicly available because of the vulnerable position of the participants but are available from the corresponding author upon reasonable request.

Authors' Contributions

VJCvC and MFMG drafted the manuscript. VJCvC was involved in finalizing the research instruments and will execute and manage the study under the supervision of MFMG and BB. OS and VJCvC wrote the implementation plan for smart continence care and will oversee its implementation. GAPGvM guided VJCvC on economic evaluation. WdH and FS contributed to the statistical analyses. BB, SMAAE, FS, MFMG, OS, and WdH conceived the study design. All the authors reviewed the manuscript for critical content and approved the final version.

Conflicts of Interest

BB and MFMG work for one of the participating long-term care providers (Siza).

Multimedia Appendix 1
The World Health Organization trial registration data set.
[DOCX File , 22 KB - resprot_v11i11e42555_app1.docx]

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Abbreviations

CEA: cost-effectiveness analysis
CHEERS: Consolidated Health Economic Evaluation Reporting Standards
CONSORT: Consolidated Standards of Reporting Trials
CRT: cluster randomized trial
CUA: cost utility analysis
DIRUM: Database for Instruments of Resource Use Measurements
ICC: intraclass correlation coefficient
ICER: incremental cost-effectiveness ratio
iMCQ: iMTA Medical Cost Consumption
IRR: incidence rate ratio
MAL: Maastrichtse Autonomie Lijst
PIMD: profound intellectual and multiple disabilities
QALY: quality-adjusted life year
RCC: regular continence care
SCC: smart continence care
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
UBES: Utrecht Engagement Scale

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Protocol

Developing an mHealth Intervention to Reduce COVID-19–Associated Psychological Distress Among Health Care Workers in Nigeria: Protocol for a Design and Feasibility Study

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Abstract

Background: Globally, COVID-19–related psychological distress is seriously eroding health care workers' mental health and well-being, especially in low-income countries like Nigeria. The use of mobile health (mHealth) interventions is now increasingly recognized as an innovative approach that may improve mental health and well-being. This project aims to develop an mHealth psychological intervention (mPsyI) to reduce COVID-19–related psychological distress among health care workers in Nigeria.

Objective: Our objective is to present a study protocol to determine the level of COVID-19–related psychological distress among health care workers in Nigeria; explore health care workers' experience of COVID-19–related psychological distress; develop and pilot test mPsyI to reduce this distress; and assess the feasibility of this intervention (such as usability, engagement, and satisfaction).

Methods: A mixed (quantitative and qualitative) methods approach is used in which health care workers will be recruited from 2 tertiary health care facilities in southwest Nigeria. The study is divided into 4 phases based on the study objectives. Phase 1 involves a quantitative survey to assess the type and levels of psychosocial distress. Phase 2 collects qualitative data on psychosocial distress among health care workers. Phase 3 involves development of the mHealth-based psychological intervention, and phase 4 is a mixed methods study to assess the feasibility and acceptability of the intervention.

Results: This study was funded in November 2020 by the Global Effort on COVID-19 Health Research, and collection of preliminary baseline data started in July 2021.

Conclusions: This is the first study to report the development of an mHealth-based intervention to reduce COVID-19–related psychological distress among health care workers in Nigeria. Using a mixed methods design in this study can potentially facilitate the adaptation of an evidence-based treatment method that is culturally sensitive and cost-effective for the management of COVID-19–related psychological distress among health care workers in Nigeria.

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KEYWORDS

COVID-19; psychological distress; Nigeria; health care workers; mental health; well-being; pandemic; mHealth; mobile health; digital health intervention; health intervention; health care; smartphone; mobile phone

Introduction

Globally, medical doctors and nurses have been praised for their dedication in providing care for those affected with SARS-CoV-2, responsible for the ongoing COVID-19 pandemic. The frontline occupied by medical doctors and nurses in the fight against COVID-19 has had a heavy toll on their mental health [1]. A high prevalence of COVID-19–related psychological distress among medical doctors and nurses has been reported in Nigeria [2,3].

Psychological interventions targeting medical doctors and nurses are very important, as they comprise a high-risk group for COVID-19–related psychological distress [4]. Moreover, mobile health (mHealth) interventions are increasingly seen by some experts as a game changer in the context of solutions to mental health and well-being challenges [5,6]. mHealth describes various health care practices and delivery based on apps or software installed on mobile devices, such as smartphones or phablets, client supervising and monitoring devices, and personal digital assistants [7]. The concept of mHealth also pertains to using these devices to synthesize and store data as well as retrieve and exchange information among those connected to the mHealth platform [8]. The provision of medical and public health services through mHealth is dependent primarily on the mobile phone use of SMS text messaging, voice, and multimedia services [9].

In achieving universal health coverage, mHealth can broaden health care services' quality and reach and enhance human resources' capacity [10]. Due to the widespread usage of smartphones, mHealth apps are an increasingly acceptable avenue for implementing interventions for psychological or mental health problems [11]. One significant advantage of the mHealth technology is its capability for periodic sampling and recording the prevailing behaviors and experiences of the users in real time and in natural settings; this is described as ambulatory assessment or experience sampling method [12]. mHealth-based ambulatory assessment can also be applied with psychological or behavior change interventions, a concept described as ecological momentary interventions whereby treatment is provided to subjects in real-time contexts and settings [13]. These treatments can be administered independently or as a supplement to other ongoing treatments. The use of mHealth interventions has been described as a "therapist in the pocket" treatment technique and is extensively perceived to have the capability to transform psychological treatment [14].

Nigeria, the seventh most populous country globally, has an estimated population of 203 million [15] and has the most extensive and fastest-growing mobile phone market on the African continent [16]. Currently, the use of smartphones in Nigeria is approximated at 40 million, and it has been projected to increase to 140 million by the year 2025 [17]. The use of smartphones has been described as universal among Nigerian doctors and nurses [18]. Although a study reported that a significant percentage of Nigerian medical doctors and nurses were not familiar with the term "mHealth," most are aware of the application of mobile phones in health care and delivery [19]. A systematic review that evaluated mHealth interventions targeted at health care workers reported that these interventions focused primarily on patient data collection during hospital visits, facilitation of communication between health care workers and patients, interactions between health care workers, and public health monitoring [20].

A literature search revealed that no study had described an mHealth-based intervention protocol directly targeted at reducing COVID-19 pandemic–related psychological distress among Nigerian health care workers, specifically medical doctors and nurses. Most of the empirical evidence for the use of mHealth interventions to improve the mental health of health care workers are from the high-income countries such as Spain [21,22]. The authors of an mHealth-based intervention to reduce mental health problems among Spanish health care workers during the COVID-19 pandemic indicated that additional mHealth treatments specifically tailored to improving the mental well-being of health care workers are needed [21]. However, this intervention was mostly beneficial to participants who were also receiving medication and psychotherapy and may reflect the short duration of the intervention—2 weeks. A meta-analysis of randomized clinical trials of psychological interventions delivered through mHealth for anxiety [23] and depressive [24] symptoms in a general population sample reported statistically significant reductions in symptom severity among those exposed to the interventions as compared to the control group.

Due to the impact of the COVID-19 pandemic on the mental health and well-being of health care workers, we acquired funding to develop or adapt and evaluate the feasibility (ie, usability, engagement, satisfaction, acceptability, benefits, and challenges) of an mHealth-based psychological intervention (mPsyI) specifically for medical doctors and nurses in Nigeria. This intervention is a subjectively managed and subjectively guided psychoeducation mobile-based treatment app that does not require the support of a therapist to ease the symptoms of

psychological distress (ie, anxiety and depressive symptoms). This paper presents the description of the protocol for a study on developing the mPsyI app, in conformity with the Standard Protocol Item: Recommendations for International Trials (SPIRIT) guidelines [25]. The overall aim of the study is to investigate COVID-19–associated psychosocial distress and evaluate the feasibility of using the mHealth-based intervention in managing this distress among health care workers in Nigeria. The specific objectives are to assess the type and level of psychosocial distress associated with COVID-19 among health workers in Nigeria; explore health care worker's experience of psychosocial distress associated with COVID-19; develop an mHealth-based guided psychological intervention; and assess the feasibility of the intervention.

Methods

Study Setting

The target population comprised doctors and nurses working in the following 2 tertiary hospitals in southwest Nigeria: the Obafemi Awolowo University Teaching Hospital Complex (OAUTHC) in Ile-Ife and the Lagos State University Teaching Hospital (LASUTH) in Lagos. The 2 hospitals were chosen because of ease of access, similar health care delivery structures, and minimal cultural differences. OAUTHC is a Federal Government–owned tertiary hospital with 465 doctors and 887 nurses, and LASUTH is a State Government–owned tertiary hospital with 536 doctors and 987 nurses.

Design

The study will employ a mixed methods (quantitative and qualitative) approach.

Recruitment

At the beginning of study phases 1 and 2 (explained below), electronic advertisements including links to the survey were broadcast on professional social media platforms used by health workers in OAUTHC and LASUTH, Nigeria, such as WhatsApp groups, Facebook, email lists, and departmental noticeboards. The advertisements were rebroadcast 3 times a week for the duration of each study period or until the optimal sample size was attained. These were supplemented by physical advertisements placed on departmental noticeboards in the hospital. Participants could follow links in these advertisements to the participant information sheets for both study phases. The sheets contained the aims and scope of the study, the contact details of the principal investigator for further enquiries, and a web-based form to provide contact details for prospective participants in the qualitative studies (to help research assistants contact participants); consent for the web-based survey was obtained by asking participants to select a button indicating this on the survey.

Sample Size

Phase 1 (quantitative study) comprised 440 nurses and doctors (ie, health care workers), derived using the sample size formula for estimating population proportions using 38.5% as the proportion of health care workers with psychiatric morbidity, based on previous work among Nigerian health care workers [26]. We estimated a minimum sample size of 364 to give a power of 80%, and this was increased by 20% to 440 to allow for incomplete data. Phase 2 (qualitative study) comprised 60 in-depth interviews and 20 key informant interviews and 4 focus group discussions (24 participants). Analyses were carried out alongside data collection to enable us to detect saturation and discontinue subsequent interviews. In phase 4 (mixed methods study), 40 participants will be purposely selected for an in-depth interview.

Procedure

The study was divided into 4 phases as follows: in the first phase, a quantitative survey will be conducted among health care workers to assess the type and levels of psychosocial distress. The second phase involves qualitative data collection (ie, in-depth interviews, key informant interview, and focus group discussions) among health care workers. In the third phase, a modified Delphi panel comprising a group of experts will be conducted to develop the mHealth-based psychological intervention according to an available evidence-based intervention tool kit [6,27], and the fourth phase is a mixed methods study to assess the feasibility and acceptability of the mHealth-based guided psychological intervention.

Phase 1 (Quantitative Survey)

In this phase, doctors and nurses from the 2 hospitals who consented to participate in the study were requested to complete the following measures: The Kessler Psychological Distress Scale [28], the 9-item Patient Health Questionnaire [29], the 7-item Generalized Anxiety Disorder scale [30], the Short Adapted Social Capital Assessment Tool [31], and the Social Connectedness Scale-Revised [32].

These questionnaires were administered physically, and the responses built into electronic forms using REDCap (Version 11.1.2). Only one entry was allowed per participant for the web-based survey. After completing the survey, we asked participants interested in follow-up studies (phase 2) to provide their contact details, which were stored separately from their provided data. To ensure sociocultural relevance, the variables were selected based on previous research among Nigerians, which showed that pandemic-related stress was associated with higher anxiety and depressive symptoms and perceived social support was protective against these adverse mental health outcomes among Nigerians [33].

Phase 2 (Qualitative Study)

The aim was to explore health care workers' experience of COVID-19–associated psychosocial distress and available psychosocial support in their workplace. It comprised 60 in-depth interviews, 20 key informant interviews, and 4 focus group discussions. Previous qualitative studies have recommended a minimum sample size of at least twelve to reach data saturation [34,35]. Through the interviews, we contextualized and understood the experience of psychological distress associated with the COVID-19 pandemic among health care workers; identified protective factors and available psychosocial support at their workplace; and explored the desired features and preferences for an mHealth-based psychological intervention as well as potential barriers to

intervention delivery. The in-depth interviews and key informant interviews were conducted through telephone calls and physical meetings (the recommended social distancing measures by the World Health Organization and appropriate personal protective equipment were used). Interview guides were developed, and all interviews were conducted in English, audio recorded, and transcribed for analyses.

Phase 3 (Intervention Development)

This phase aims to develop gender-related and culturally sensitive aspects of the mHealth guided psychological intervention. Results from phase 1 will provide quantitative data, and phase 2 will provide qualitative data, such as the expression of psychological distress among Nigerian health care workers. Phase 2 will inform the sociocultural adaptation of available evidence-based psychological interventions [6,27]. Specifically, themes that emerge from phase 2 will be used to contextualize the intervention by changing phrases in the intervention in a more culturally appropriate way and using culturally relevant examples to make it more relevant to the lived experiences of Nigerian health care workers. Both male and female Nigerian voices will be used in the oral or spoken draft of the mPsyI intervention.

A modified Delphi approach (carried until saturation is achieved) will be conducted among a panel of experts in psychiatry, clinical psychology, guidance and counselling, nursing, and computer science. An intervention will be identified based on the World Health Organization collection of low-intensity psychological interventions [6,27]. This intervention will be independently scored for feasibility (ie, usability, engagement, satisfaction, acceptability, benefits, and challenges) using a 5-point scale. The experts will later decide on intervention options based on brevity, cost, the best mode of delivery, and the total number of sessions and then produce an initial draft of the mPsyI intervention. The initial oral or spoken draft of the mPsyI will be presented to end users (ie, health care workers with psychological distress) and facilitators (ie, health care workers without significant psychological distress or professional qualifications in mental health) to assess the practical application, usefulness, and feasibility of the proposed intervention and give feedback via questionnaires (ie, the System Usability Scale and the Mobile App Rating Scale, described below) and informal interviews. Both groups will suggest possible improvements and modifications of the intervention, including the language and contents of the intervention package, during discussions. These suggestions will be returned to the Delphi panel, who will then produce an amended draft of the mPsyI intervention tool kits, including manuals, training guidelines, as well as monitoring and evaluation methods.

Phase 4 (Feasibility Assessment)

In this phase, feasibility and pilot test of the mPsyI intervention will be assessed. A total of 8 facilitators (2 doctors and 2 nurses per hospital) will be purposively selected, trained, and supervised by 2 research team members. The facilitators' training will consist of didactic lectures, clinical demonstrations, and role-plays. Training will be standardized across both study centers with the use of video or audiotapes. Before and after the intervention, end users (ie, medical doctors and nurses) will complete measures used in phase 1. Those with a Kessler Psychological Distress Scale score of 5 and above (being the threshold for significant psychological distress) [28] will be recruited. For 6-8 weeks (depending on the total number of sessions), interventions will be delivered to 40 end users (20 from each hospital)—1 session per week. Previous qualitative studies have recommended a minimum sample size of at least twelve to reach data saturation [34,35].

The trained facilitators will provide weekly support to the end users to make sure that the intervention is being used appropriately. At the end of intervention delivery, the end users and facilitators will test the feasibility of the intervention concerning usability, engagement, satisfaction, acceptability, benefits, and challenges. Additionally, the System Usability Scale [36] and the Mobile App Rating Scale [37] will be used quantitatively to assess user's experience in terms of intervention acceptability, engagement, satisfaction, and complexity.

Measures

Before and after the intervention, the Kessler Psychological Distress Scale [28], the 9-item Patient Health Questionnaire [29], and the 7-item Generalized Anxiety Disorder Scale [30] will be used. After administering the intervention, the System Usability Scale [36] will be used to assess the user's experience in terms of engagement, satisfaction, level of motivation, and complexity of the tool; the Mobile App Rating Scale [37] will be used to assess the acceptability of the tool in terms of engagement, functionality, aesthetics, and information quality. A semistructured interview will be conducted on benefits, challenges, and barriers among end users and facilitators within a week of completing the intervention.

Data Management and Storage

In phase 1, data will be collected using web-based surveys, exported into SPSS (version 27; IBM Corp) for analyses and stored on a secure passworded laptop, which will be stored on the university premises. Contact details provided were stored separately on a different secure laptop accessible only to the principal investigator, and they will be destroyed immediately after the study. In phases 2 and 4, the audio recordings will be destroyed immediately after transcription, and deidentified transcripts will be saved on a password-protected computer that only the principal investigator and statistician will access. An external hard drive will be used as backup with data encrypted (using full-disk encryption) and stored using a password, and it will be kept in a locked office. Transcripts will only be shared with other members of the research team.

Statistical Analysis

The recorded interviews will be transcribed verbatim and uploaded into the NVivo 12 for analyses using the framework approach [38]. The framework approach involves 3 interconnected steps that include familiarization with the transcript, deciding initial themes or categories, and summarizing or synthesizing the data [39]. For quantitative data, statistical analyses will be performed using the IBM-SPSS software for Windows (version 27; IBM Corp). Descriptive statistics, frequency distributions, and percentages will be used

for categorical variables. For continuous variables, mean, median, standard deviation, percentiles, and ranges will be used. Between-group percentages will be compared with chi-square tests for observed differences, and the student *t* test will be used to determine differences in scores in different groups. Bivariate relationship will be investigated using Pearson correlation, and multiple regression analyses will be used to examine the relationship between psychological distress and the independent variables. Statistical significance will be based on 2-sided tests and set at $P<.05$.

Ethical Consideration

We obtained ethical approval for the research from the ethics and research committees of OAUTHC (number ERC/2020/10/17) and LASUTH (number LREC/06/10/1528), Nigeria; a favorable ethical opinion was further obtained from the Liverpool School of Tropical Medicine research ethics committee. Informed consent will be obtained from the participants at all phases of the study, and confidentiality will be maintained, as anonymized data will be used for storage and analysis. In testing the mHealth app, only the mental health personnel directly involved in testing the app will have access to data to preserve confidentiality. All identifying information will be excluded before transferring the data to the statisticians for analysis. Participants will also be reassessed midway and at the end of the study to identify those with persistent or increasing distress. Participants with persistent distress in Phase 4 who consent will be referred for more specialized care. Those who do not consent will be provided with contacts they can access for support.

Dissemination of Knowledge

Findings from the quantitative and qualitative studies in the first and second phases of the project will be used to design the intervention in the third phase of the project. The findings from all phases of the project will be summarized and disseminated to the public via television and radio programs; to stakeholders in hospitals, policymakers, as well as the federal and state ministries of health via webinars; and to the scientific community through local and international conferences and publications in open-access journals. All participants will be invited to provide their contact details to receive summaries of the study results at all study phases.

Results

Recruitment for phase 1 took 2 months (July to August 2021). The manuscript of data collected in phase 1 titled “psychological distress and associated factors among Nigerian health care workers during COVID-19 pandemic: a cross-sectional study” is under review in the *International Journal of Public Health*. Data collection for phase 2 occurred over 2 months from August through September 2021. Phase 3 lasted for 3 months between October and December 2022, and phase 4 was carried out over 2 months between January and February 2022. Data analysis and scientific reporting are expected to be completed before the end of 2022.

Discussion

To our knowledge, this is the first study to describe the protocol for the development and evaluation of the feasibility of an mHealth-based intervention to reduce COVID-19 pandemic–related psychological distress among Nigerian medical doctors and nurses. This study hypothesizes that there will be high levels of COVID-19–related psychological distress among health care workers, and the mHealth psychological intervention is a feasible solution for this type of distress among doctors and nurses in Nigeria. Drawing from previous disasters, such as the SARS epidemic and the terrorist attack on September 11, 2001, in the United States, up to 20% of health care workers had stress-related disorders immediately after the events [40]. This is probably because health care workers have to provide care for patients affected by these occurrences, and they also have to navigate their own personal stress and uncertainties [41]. The data obtained in the feasibility study (phase 4) will guide further modifications to the intervention and the potential for a randomized controlled trial later (a potential offshoot of this study). The study will yield insight into the feasibility of providing an mHealth web-based intervention for Nigerian medical doctors and nurses currently experiencing psychological distress due to the COVID-19 pandemic. The results of this study can guide future implementation and promulgation of mHealth-based interventions for other occupational groups in Nigeria. The execution and dissemination of an mHealth evidence-based web-based intervention aimed at improving mental well-being can potentially represent one of the strategies to reduce the mental health gap in low- and middle-income countries, where there is an imbalance between the availability and geographical spread of mental health care specialists and the proportion of those who are experiencing mental health difficulties [5,42].

The exponential increase in the infiltration of internet services and smartphones in low- and middle-income countries can spur the implementation of mHealth-based interventions [43,44]. A plausible advantage of our mHealth intervention is that it might assist in overcoming mental disorder–related stigma, since the end users of this intervention can connect to mental health care services regardless of their location in Nigeria [45]. The longer duration of our intervention may also allow for more time for the manifestation of its therapeutic effects. This mHealth intervention may enhance the quality of life of Nigerian medical doctors and nurses during the ongoing COVID-19 pandemic. Another plausible benefit of this mHealth intervention is the prospect for scalability that will enable it to be available to a greater proportion of Nigerian medical doctors and nurses under real-world conditions. We believe that the availability of our mHealth intervention will encourage Nigerian medical doctors and nurses who are experiencing the ongoing pandemic-related psychological distress to use a platform that does not necessitate their need to seek face-to-face consultation with a psychiatrist or other mental health specialists [5]. Any technological development in the context of primary and public health can potentially positively impact disease control, thereby minimizing complications and treatment costs [46,47]. However, some patients and providers may hesitate to use mHealth interventions

due to low levels of health literacy, low familiarity with mobile apps and technology, or reduced access to mobile and internet facilities.

We are hopeful that our mHealth intervention will encourage a positive help-seeking attitude among Nigerian medical doctors and nurses experiencing COVID-19–related psychological distress.

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Data Availability

The data sets generated during this study are available from the corresponding author on reasonable request.

Authors' Contributions

AA, OA, and O Oginni contributed to the conceptualization, literature review, and design of the study, as well as the discussions and drafting of the manuscript. IO, OI, BM, TO, AMO, O Olibamoyo, CTSF, VOO, and AOA assisted in the literature review, design of the study, discussions, and drafting of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

LASUTH: Lagos State University Teaching Hospital
mHealth: mobile health
OAUTHC: Obafemi Awolowo University Teaching Hospitals Complex
SPIRIT: Standard Protocol Item: Recommendations for International Trials

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Protocol

A Telemedicine Platform for Aphasia: Protocol for a Development and Usability Study

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Abstract

Background: Aphasia is a central disorder of comprehension and expression of language that cannot be attributed to a peripheral sensory deficit or a peripheral motor disorder. The diagnosis and treatment of aphasia are complex. Interventions that facilitate this process can lead to an increase in the number of assisted patients and greater precision in the therapeutic choice by the health professional.

Objective: This paper describes a protocol for a study that aims to implement a computer-based solution (ie, a telemedicine platform) that uses deep learning to classify vocal data from participants with aphasia and to develop serious games to treat aphasia. Additionally, this study aims to evaluate the usability and user experience of the proposed solution.

Methods: Our interactive and smart platform will be developed to provide an alternative option for professionals and their patients with aphasia. We will design 2 serious games for aphasia rehabilitation and a deep learning–driven computational solution to aid diagnosis. A pilot evaluation of usability and user experience will reveal user satisfaction with platform features.

Results: Data collection began in June 2022 and is currently ongoing. Results of system development as well as usability should be published by mid-2023.

Conclusions: This research will contribute to the treatment and diagnosis of aphasia by developing a telemedicine platform based on a co-design process. Therefore, this research will provide an alternative method for health care to patients with aphasia. Additionally, it will guide further studies with the same purpose.

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KEYWORDS

aphasia; serious games; deep learning; telemedicine; diagnosis; treatment; language; machine learning; rehabilitation; smart platform

Introduction

Aphasia is a language disorder caused by damage to 1 or more areas of the brain that control some or all language modalities, including the expression and comprehension of speech, reading, writing, and gestures [1]. Although many people have aphasia because of stroke, other sources of brain damage can cause it (eg, head trauma, brain surgery, epileptic disease, and neurodegenerative syndromes) [2-4]. When caused by neurodegenerative syndromes, aphasia can be diagnosed as primary progressive aphasia and classified as logopenic, semantic, and nonfluent/agrammatic [3]. When caused by stroke, it can be classified as anomic, Broca (motor), Wernicke

(sensory), global, conduction, and transcortical (motor, sensory, and mixed) [4,5]. As the main impairments of aphasia are related to the expression and comprehension of language, aphasia can be divided into 2 large groups: expressive and receptive [6].

The aphasia diagnosis is usually made by a neurologist or speech therapist, based on the clinical and pathological features to characterize the language disorder [7]. Discriminating the different types of aphasia is a complex task since signs such as impaired speech comprehension and/or articulation, inability to repeat, impaired semantics, and difficulty in naming objects are present in various types of aphasia, whether due to neurodegenerative disease or by the interruption of cerebral flow [8]. To make the diagnosis of aphasia simpler and more precise, computational solutions have been developed to classify/detect the types of aphasia. The proposed computational techniques have used classical machine learning [9-13], deep learning (DL) [14,15], and fuzzy logic [16,17]. DL techniques have shown better results in different performance metrics to classify aphasia [14,15].

Once the patient is diagnosed, the treatment of aphasia is a challenge for health care professionals. Patients with expressive aphasia appear to be the easiest to rehabilitate, because these patients can understand the method used in a particular rehabilitation technique or, at least, the instructions for using it. However, there has been little success in receptive aphasia rehabilitation trials [6,18]. Serious games have shown promise in the rehabilitation of diseases of neurological causes, as they can lead to engagement and offer feedback to the patient and therapist on the progress of therapy [19,20]. To the best of our knowledge, few studies have focused on serious games for aphasia rehabilitation [21,22]. In such studies, therapy is only suitable for patients with a good understanding of the task, thus neglecting patients with receptive aphasia. Unlike previous studies, our work will focus on both the development of a platform to aid in the aphasia diagnosis using DL techniques and the application of serious games suitable for patients with receptive and expressive aphasia.

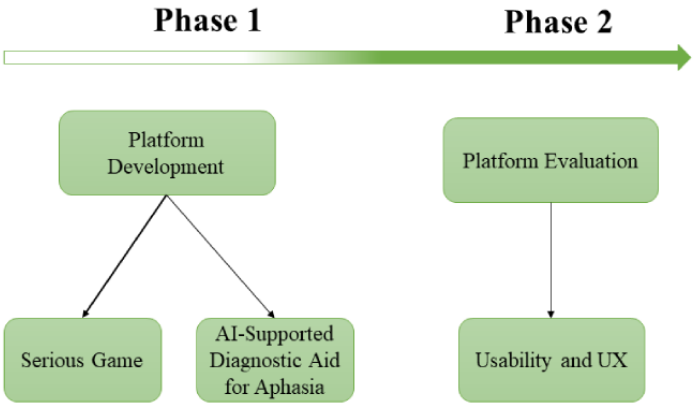
This paper presents a protocol of a study that has 2 objectives: (1) to implement a computer-based solution (ie, a telemedicine platform) that uses DL algorithms to classify aphasia and, following a co-design study, to develop 2 serious games for the treatment of aphasia; and (2) to evaluate the usability and user experience of the developed games.

Methods

Study Design

The study will be divided into 2 phases, as can be seen in Figure 1. The first phase refers to the implementation of a platform to aid in the diagnosis and treatment of patients with aphasia. The second phase refers to a study to evaluate the implemented serious games for aphasia rehabilitation. It will focus on the evaluation of usability and user experience by patients with aphasia and speech therapists.

Figure 1. Flowchart of the study phases. AI: artificial intelligence; UX: user experience.



Phase 1: Platform Development

Literature Search and Questionnaire

A literature search was carried out in June 2022 to identify content related to aphasia rehabilitation using serious games and content related to aphasia classification using computational solutions. This literature search was carried out in the main digital libraries of the medical field, including PubMed and Web of Science. We developed the first version of the game content based on studies [21,22] that used virtual reality tasks with oral expression, articulation, listening comprehension, cognition, articulation, semantics, naming, and repetition. Furthermore, these studies reported on the attractiveness and satisfaction when users are playing a serious game to rehabilitate aphasia. In the studies using computer-based solutions to classify aphasia [14,15], techniques of machine learning and DL have been applied. With these works, we have learned about the best classification techniques and audio features to classify aphasia.

In parallel with the literature search, a questionnaire with 12 open and closed questions that address the clinical needs for the diagnosis and treatment of patients with aphasia was directed to a group of 10 speech therapists with more than 1 year of experience in aphasia rehabilitation. This was a convenience sample, and the recruitment was carried out via social networks. From this questionnaire, we identified that 60% (n=6) of participants reported performing the aphasia diagnostic before starting treatment, and 50% (n=5) used a device to perform this diagnosis. When investigating the difficulties that speech therapists have when performing the diagnosis, the sample reported the lack of resources for rapid testing, standardized

protocol, diversity of symptoms of each aphasic syndrome, and absence of imaging tests and family assistance. As mandatory items for the diagnosis, 80% (n=8) of the participants reported that speech comprehension, object naming, and sentence repetition are relevant characteristics for diagnosis; 70% (n=7) reported speech articulation as relevant characteristic; and 10% (n=1) reported speech expression, lesion size, and underlying disease. For aphasia rehabilitation, 90% (n=9) reported that semantic tasks are essential; 80% (n=8) reported speech articulation and naming tasks as essential; 70% (n=7) reported repetition tasks; and 10% (n=1) reported tasks of cognitive function and socioeconomic impacts.

From the results of the questionnaire and the literature search, we developed content that will be presented to a group of 3 speech therapists, 2 software developers, and 2 neuroscientists to receive feedback. This will enable us to improve the content. The sample is consistent with researchers who accepted being part of the study development process, and the form of recruitment was by invitation.

This group will meet weekly for 1 hour. At this time, a 5-minute video that includes updated content will be presented, and participants will be encouraged to rate the product from 0 to 10, with 0 corresponding to the worst rating and 10 an excellent rating. In addition, participants will be encouraged to justify their rating and suggest improvements to the proposed solution. During all meetings, improvements reported by the group will be enumerated and categorized for later implementation.

Serious Game Design

Aphasia may be divided into 2 major groups: expressive aphasia and receptive aphasia. Each type has characteristics and, therefore, different therapeutic methodologies. By considering such groups, 2 games will be developed.

Game 1: Expressive Aphasia

The objective of this game is to stimulate tasks for expressive aphasia, such as articulation, semantics, naming, repetition, prosody, and emotional tone in utterances. Based on the current literature and discussions with the research team, the initial proposal has already been designed, which is described hereafter.

The game's plot is inspired by a treasure hunt, where the patient will need to open as many chests as possible and collect the treasures in a time interval determined by the therapist. After the set interval runs out, a new game environment will be unlocked, and the user will be able to collect more treasures. To open each chest and collect the treasure, the user must perform a specific task for each environment. The therapist will be assigned the role of deciding which environments the patient should go through. The number of opened chests and collected treasures will not be decisive for the user to move from one environment to another. This rule was defined so that users go through all types of environments defined by the therapist, regardless of their level of language impairment. The more the user collects treasures in each environment, the greater the complexity of the task in that environment will be. The complexity of tasks within each environment will be based on the following 4 elements:

1. Sentence size: This element refers to the number of words to build a sentence. Sentences with 3 to 4 words will correspond to the basic level; 5 to 6 words will correspond to the intermediate level; and more than 6 words will correspond to the advanced level.
2. Number of clauses: This element refers to the number of verbs present in the sentence. Sentences with more than 2 verbs are considered complex. The presence of 1 verb will correspond to the basic level; the presence of 2 verbs will correspond to the intermediate level; and the presence of 3 or more verbs will correspond to the advanced level.
3. Presence of adverbs: An adverb is a word that indicates a circumstance (mode, time, or place). It can modify a verb, an adjective, or another adverb. The presence of adverbs as well as adverbial phrases in the sentence will be indicative of more complex sentences. Adverbs will only be present at the intermediate and advanced levels. At the intermediate level, there will be only 1 adverb, and at the advanced level, there will be 2 or more adverbs.
4. Number of syllables: This element refers to the number of syllables to compose a word. One syllable will correspond to the basic level; 2 syllables will correspond to the intermediate level; and 3 syllables will correspond to the advanced level.

To give feedback on the number of chests that still need to be opened in the environment, a map with the location of the chests and the user will be fixed on the right side, in the lower corner of the screen. In all, there will be a total of 4 environments, each one being designated to a type of task: articulation, semantics, naming, and repetition of sentences. Each environment will have a total of 10 chests to open. The user will be allowed to save the game or pause it without any penalty.

Game 2: Receptive Aphasia

Similar to the previous game, the game proposal was based on the current literature and discussions with the research team and will be described hereafter. We will discuss it with speech therapists, scientists experienced in serious game development, and the development team. After approval, the proposal will be implemented.

The initial proposal of the game's plot is inspired by activities of daily living, where the user must complete some missions that he or she comes across daily, such as entering the elevator and pressing the button to go to the next floor, buying bread at a bakery, or taking out the garbage. The purpose of the game is to work the patient's cognitive skills so that he or she becomes as functional as possible using nonverbal language to complete the missions. The therapist will be able to choose which mission the patient should undertake and the time for the completion of the mission. If the patient is unable to complete the mission in the time set by the therapist, hints with arrows indicating the direction will appear to guide the patient in the mission. After being completed, the mission will be unlocked in case the patient wants to try again without the tips.

A total of 10 missions with different contexts will be implemented. Finally, players will be allowed to save the game or pause it without any penalty.

Tools Used for the Development of the Serious Game's Platform

The games will be developed over a virtual reality platform, as it increases the immersion in the game and the effectiveness of the intervention. In this way, the number of participants for aphasia treatment can be increased. User interaction with the game environment will be performed using 2 options: (1) gaze, with interaction using eye movements; and (2) head movements. These options will add a mouse-like interaction, which is an on-screen pointer that users will be able to move.

For the development of the platform, the *AFRAME* library made in Javascript was selected to create a virtual reality environment. Since no additional framework was used alongside *AFRAME*, the *Parcel* Javascript compiler was used to allow the use of modern Javascript features. Finally, the project will be hosted on the Vercel cloud platform (Vercel, Inc).

Diagnostic Model Development

DL Algorithms and Model Training

At this stage of the research project, we went through a process of developing a model for classifying aphasia. For the development of this model, we will use the DL technique since, according to previous studies, it presents better results to classify aphasia through acoustic data [14,15]. In all, 3 DL algorithms will be used, namely: LeNet, Resnet-34, and SqueezeNet. To acquire data for training the model, vocal data will be collected from patients with aphasia diagnosed by a neurologist or speech therapist and individuals without aphasia whose ages are matched to the aphasia group (see details in Data Set Creation section). The collection of vocal data is made through a collection app developed to record the voices from patients during specific tasks. The app development as well as data collection tasks are described in the following sections. After data acquisition, we will conduct a data preprocessing step. In this step, noise and bad quality audio that may impair the performance of the models will be removed. The extraction of features in DL is an automatic process, where it is not possible to know which features were chosen for training the model. After training the models, an evaluation will be performed using performance metrics derived from the confusion matrix (accuracy, sensitivity, specificity, F_1-score, receiver operating characteristic curve, and area under the curve). The best performing model will be deployed to the platform.

Development of the Data Collection Application

A hybrid mobile app was developed with Ionic (graphics component library), VueJS 3.0 framework, and Capacitor as a native functionality library. The app was written in Javascript, specifically using the *Typescript* superset. The system allows users to manage the participant data (adding, editing, and deleting), as well as collecting audio within a defined protocol for aphasia tracking. The app can be installed via an .apk file or used through the browser. The collection consists of the audio recording of the participants for an indefinite period and an infinite number of times. All files are sent to Dropbox, which is a cloud storage service, for further analysis and discussion.

Data Set Creation

Consent to Participate

Participants will be informed about the purpose of the research, its objectives, and procedures. They will be consulted regarding their acceptance to participate in the study. After clarification, the participants or their guardians will be instructed to sign the Free and Informed Consent Term approved by the Ethics and Research Committee of the Federal University of Piauí, guaranteeing anonymity and freedom of absence from the research, as well as the realization of clarification regarding the same and the right to withdraw from their participation during the study.

Study Participants

The inclusion criteria for participants include providing a signed consent form, agreeing to the study procedures, being available for the study duration, and being aged 40-80 years. For the aphasia group, participants must have a diagnosis of aphasia after stroke given by a specialized health professional, with a post-illness time of 6 months. Regarding the exclusion criteria, patients who do not present a diagnosis and classification of the type of aphasia or who have severe cognitive impairment (Mini-Mental State Examination score less than 22 points) and severe aphasia were excluded. For the control group, participants must be healthy and without a history of language or cognitive disorders.

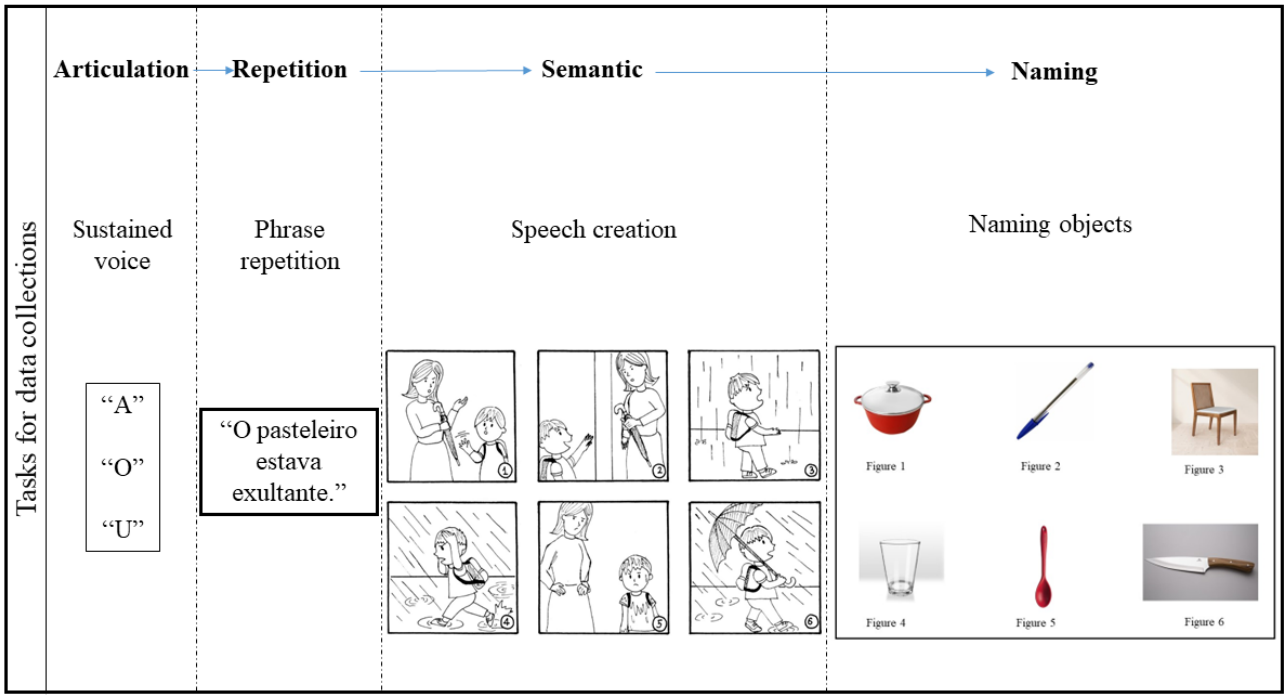
Recruitment

Participants with aphasia will be recruited at the physiotherapy school clinic of the Federal University of Delta do Parnaíba, Parnaíba; at the Dirceu Arcoverde State Hospital, Parnaíba; and at the Neurology Institute Deolindo Couto linked to the Federal University of Rio de Janeiro, Rio de Janeiro, Brazil. Healthy participants will be recruited from advertisements in the cities of Parnaíba and Rio de Janeiro, Brazil. The recruitment and screening of participants will be performed by a trained speech therapist. At this moment, the participant's cognitive level, possible language impairments, and aphasia level will be investigated. As this is a sample group for training a DL model, the sample size will be time-oriented, in which the largest number of individuals will be recruited within 6 months.

Vocal Data Collection

Data will be collected from audio samples from participants with aphasia or healthy participants. Therefore, for this study, participants will be placed in 2 conditions: with aphasia and control (without aphasia). Data collection will be conducted in a noise-free environment through a mobile app for voice capture. The app presents tasks where the participant must sustainably repeat the vowels "a," "o," and "u" and the predefined phrase: "O pasteleiro estava exultante" ("The pastry chef was overjoyed" in Portuguese). These commands are reported in the literature to discriminate against the type of aphasia, since it allows the assessment of speech comprehension and articulation [23]. In addition, figures are presented to the participants, and they will be instructed to name them or develop a speech about the figures (see Figure 2). Those images were taken from the Talkbank database, which are widely used to assess speech and gesture variations in patients with aphasia [24].

Figure 2. Scheme of tasks used for data collection.



Ethics Approval

The study was approved by the Ethics Committee of the Federal University of Piauí (5.134.321) in October 2021.

Phase 2: Usability Study

Platform Schedule

Participants, on a first visit, will receive training on how to use the platform. Speech therapists will be encouraged to customize a different treatment for 2 patients with aphasia, which results in 2 treatments per speech therapist. Patients with aphasia will be encouraged to use the platform for 30 minutes, 3 times a week, for 2 consecutive weeks. The task to be performed will be customized by the speech therapist. After the 2-week period, all participants will be encouraged to complete a usability questionnaire as accurately as possible.

Usability Study Participants

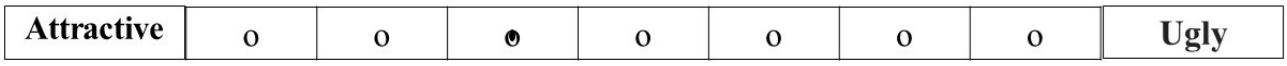
Inclusion criteria for participants include (1) speech therapist with at least 1 year of experience in treating patients with aphasia; and (2) patients with a diagnosis of aphasia after stroke given by a specialized health professional, with a post-illness time of 6 months, and a Mini-Mental State Examination score more than 22 points. All participants must provide a signed consent form, agree to the study procedures, and be available for the study duration. Participants who do not complete the study protocol will be excluded.

Tool to Test the Usability of the Platform

To assess the usability of the computer system, the User Experience Questionnaire (UEQ) will be applied, consisting of 26 items, including 6 factors: Attractiveness, Perspicuity, Efficiency, Reliability, Stimulation, and Novelty. The questionnaire consists of pairs of opposites related to the properties that the product has [25]. The graduations between opposites are represented by circles. By marking one of the circles, the user expresses his or her opinion about a concept. See Figure 3 for an example of a UEQ question.

The user will be asked to mark their answer spontaneously, being instructed not to think too much about the answer. The user will also be asked to always choose an answer even if they are unsure about a couple of terms or the terms do not fit the product as there are no "right" or "wrong" answers—opinion is what counts.

Figure 3. Example of a User Experience Questionnaire question.



UEQ Statistical Analysis

The data analysis will consist primarily of descriptive statistics, and outcomes will be described primarily in percentages or proportions. Data will be analyzed using SPSS statistical software (version 25; IBM Corp). Microsoft Excel (version 16.1) will be used for charts. Participants' responses will be independently analyzed by 2 researchers, and data will be entered twice to minimize typing errors. After analysis by researchers, the consensus among the experts will be evaluated using the Cohen κ coefficient. Statistical significance will be considered at a 2-tailed *P* value of <.05.

Results

Data collection began in June 2022 and is currently ongoing. Results of system development as well as usability should be published by mid-2023.

Discussion

Hypothesis and Significance

We hypothesized that a platform that makes use of DL algorithms will be able to classify aphasia from a set of vocal data and that only this data will be sufficient to classify aphasia. In addition, it is accredited that a platform that offers web-based tasks in the format of serious games will be well evaluated by speech therapists and patients with aphasia who make use of it.

It is expected to provide an alternative that facilitates the diagnosis of aphasia and allows a treatment directed to the type of impairment of the patient with aphasia. Speech therapists assume the role of the prescriber of the treatment and follow-up of the patient. The therapists will be involved from the elaboration of the treatment to the finalization of the process of creation and analysis of the platform. Patients and caregivers are assigned the role of evaluator and system user.

DL techniques, which are applications of artificial intelligence, have recently emerged and are now rigorously applied in the medical field. DL refers to the use of artificial neural networks with multiple hidden layers [26]. The use of DL with vocal data to classify aphasia has been the objective of studies, both to classify the type of aphasia [14] and to estimate severity [15]. Such studies suggest that DL models using vocal data can estimate aphasia in patients with early-stage acute stroke. These findings justify further research to assess the applicability of DL models in different study populations.

Rehabilitation technologies have the potential to increase the intensity and dose of rehabilitation, improve access to rehabilitation, reduce therapists' workload, measure and provide feedback on performance and recovery, and engage and motivate patients [27]. Thus, serious game systems based on virtual reality have become popular in medical rehabilitation and can be used as a new alternative therapy method for language recovery in patients with aphasia [21,22]. Serious games to be proposed will be intended for patients with expressive and receptive aphasia. Therapeutic approaches are aimed at cognitive and expressive speech recovery, which are fundamental in the rehabilitation process of such patients.

Expected Clinical Impacts

The study proposed here will bring clinical, scientific, and socioeconomic impacts as it aims to serve as a diagnostic aid and alternative for the treatment of patients with aphasia within their clinical particularities. It is expected that the use of DL will be promising in the aphasia classification process and thus facilitating the diagnosis and clinical decision. Once classified, the therapist's conduct must be directed to the patient's needs. Here, we propose telerehabilitation as a way to reach a larger audience, in addition to reducing long-term disability, increasing secondary prevention, and allowing follow-up after the acute phase of treatment, thus increasing responses to therapy and encouraging continuity of care. Serious games have been gaining public attention and are becoming an object of interest to researchers, as they can be introduced in various fields of medical practice, since they imply greater patient engagement in therapy [27]. It is hoped that the games to be developed from this proposed study will make patients more enthusiastic and more willing to talk, especially when exposed to virtual reality technology that will provide the creation of interactive worlds in which the patient can experience new therapeutic approaches that would not be accessible in the real world. In addition, with the platform improvement, it is expected that populations that would not possibly receive continued care can have support, thus configuring a socioeconomic impact.

Limitations

The sample sizes used in building the training and testing data sets of DL models in aphasia classification studies may be relatively small. However, our goal will be to capture a sample size that allows the training and testing of DL models with acceptable results in different performance metrics. The collection time will also influence the participant's permanence in the study, which will also be influenced by the availability of those involved. A system usability study does not need a large sample number, and therefore, usability results may not be generalizable and may be specific to the community and environment. However, this study may serve as a basis for others, and new studies with the tool proposed here should be developed to prove its effectiveness.

Conclusions

The expected results of this study will provide a basis for a successful technological development study. The results will produce an appropriate intervention for patients with aphasia and indicate challenges and opportunities for the refinement of study procedures, including methodology for collecting data from patients with aphasia, creating serious games, ways to assess user experience, and using DL to classify vocal samples.

Acknowledgments

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Data Availability

Data sharing not applicable to this paper as no data sets were generated or analyzed during the current study.

Authors' Contributions

All authors contributed to the concept and design of the study. MN, AST, and DF drafted the manuscript, and all authors critically reviewed it. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

DL: deep learning
UEQ: User Experience Questionnaire

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Protocol

Existing eHealth Solutions for Older Adults Living With Neurocognitive Disorders (Mild and Major) or Dementia and Their Informal Caregivers: Protocol for an Environmental Scan

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Abstract

Background: Dementia is one of the main public health priorities for current and future societies worldwide. Over the past years, eHealth solutions have added numerous promising solutions to enhance the health and wellness of people living with dementia-related cognitive problems and their primary caregivers. Previous studies have shown that an environmental scan identifies the knowledge-to-action gap meaningfully. This paper presents the protocol of an environmental scan to monitor the currently available eHealth solutions targeting dementia and other neurocognitive disorders against selected attributes.

Objective: This study aims to identify the characteristics of currently available eHealth solutions recommended for older adults with cognitive problems and their informal caregivers. To inform the recommendations regarding eHealth solutions for these people, it is important to obtain a comprehensive view of currently available technologies and document their outcomes and conditions of success.

Methods: We will perform an environmental scan of available eHealth solutions for older adults with cognitive impairment or dementia and their informal caregivers. Potential solutions will be initially identified from a previous systematic review. We will also conduct targeted searches for gray literature on Google and specialized websites covering the regions of Canada and Europe. Technological tools will be scanned based on a preformatted extraction grid. The relevance and efficiency based on the selected attributes will be assessed.

Results: We will prioritize relevant solutions based on the needs and preferences identified from a qualitative study among older adults with cognitive impairment or dementia and their informal caregivers.

Conclusions: This environmental scan will identify eHealth solutions that are currently available and scientifically appraised for older adults with cognitive impairment or dementia and their informal caregivers. This knowledge will inform the development of a decision support tool to assist older adults and their informal caregivers in their search for adequate eHealth solutions according to their needs and preferences based on trustable information.

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KEYWORDS

dementia; eHealth solutions; mild cognitive impairment (MCI); environmental scan; digital health

Introduction

Dementia is a Public Health Challenge

Neurocognitive disorders (NCDs), both major and minor, were generally termed dementia in many kinds of literature [1]. Hence, in this paper, the term dementia is used generally to represent all these conditions. Dementia is an important public health challenge in current and future societies worldwide. In 2021, the World Health Organization declared dementia a public health priority [2]. Dementia is a syndrome where the decline in cognitive function occurs beyond what might be expected from the usual consequences of organic aging. Alzheimer disease is the most common form of dementia [2,3]. Currently, more than 55 million people live with dementia worldwide, and its incidence is almost 10 million people each year. The prevalence is expected to increase to 70 million by 2030 and 139 million by 2050 [2]. Impacts on well-being also extend to informal caregivers of persons with dementia [4]. Few studies reported higher levels of depression, emotional distress, and physical strain in caregivers of persons with dementia than in caregivers of older adults with physical impairments [5,6].

eHealth for Dementia Care

eHealth is defined as tools or treatments, mostly behavioral-based health interventions, delivered or enhanced through the internet, mobile devices, electronic/digital processes in communication, and related technologies [7]. eHealth implementation in dementia primarily focuses on improving the autonomy of persons with dementia [2]. eHealth assists primary caregivers by providing dementia-related knowledge and assistance to reduce their anxiety and depression, and thus, it can improve the health and well-being of both older people living with dementia and their informal caregivers [4].

Technological initiatives are undertaken at the national and regional level in Europe, Canada, and other countries to help people with dementia and their caregivers [8-10]. Effective eHealth interventions use a “blended” approach, combining remote support with direct coaching and interventions [4]. Some solutions are behavior based, with the primary focus on the self-efficacy of persons with dementia and their informal caregivers, and minimize depression and anxiety in caregivers [8,11,12].

Several literature reviews about eHealth solutions for older adults with dementia show that they are a promising strategy for enhancing the cognitive function of older people [11,13]. eHealth technology helps primary caregivers to assess and apply information related to dementia and offer better care for persons with dementia [14]. Many web-based solutions differ from each other in terms of objectives, features, functions, and specific subpopulations. For instance, the effectiveness of computerized cognitive training to delay the progression of cognitive impairment in people with mild and major NCD and dementia has been demonstrated [11]. Such solutions contain numerous exercises for different cognitive functions for people with mild cognitive impairment (MCI) and dementia, and they are more accessible and cost-effective in comparison to traditional cognitive interventions [11].

A systematic review on the effectiveness of internet-based interventions such as web-based self-management courses for dementia and apps to provide emotional support for family and caregivers shows a positive impact on caregivers’ stress reduction through regular web-based contact with health professionals by offering psychological support and necessary information on persons with dementia [5]. Another recent study emphasized that most of the informal caregivers of persons with dementia are interested in technology-based solutions, as most of them are younger than 65 years old and are familiar with computers in their workplace [15].

At the health care system level, there are various benefits to the implementation of effective eHealth solutions. It improves access to services in remote areas, service efficiency, and costs [4,14,16]. However, more work and effort are essential to fully achieve the potential of eHealth technologies for dementia care [10,14]. Hence, dementia-specific organizations such as the Alzheimer’s Society; local, national, or regional decision makers; and international organizations such as the World Health Organization should support the use of effective eHealth solutions.

One of the major obstacles to the large-scale implementation of effective eHealth solutions is scientific underreporting [5]. Most eHealth solutions are developed and tested over a short period of time, using only pilot evaluation approaches with limited samples or without a formal research/evaluation component [6]. Therefore, effective and user-friendly eHealth solutions that could be implemented on a large scale are difficult to identify. Additionally, variations in cognitive, sensory, and motor skills of persons with dementia in relation to technological advancement make it difficult to successfully assess effectiveness [6]. Research that supports informal caregivers of persons with dementia has shown that less than 3% of evidence-based interventions are effectively implemented into practice [5].

During the pandemic, eHealth was used to provide services such as web-based psychoeducation, self-management, and consultations to persons with dementia and their informal caregivers in many countries. A study from the Netherlands supports this finding. A Dutch survey also stated that video chatting and WhatsApp messaging were highly useful [4]. Similarly, the findings from a Taiwanese study also support the positive effect of telemedicine interventions on home-dwelling persons with dementia or MCI, as the telehealth intervention significantly reduced the participants’ gravity of neuropsychiatric symptoms and their primary caregivers’ stress levels [17]. Therefore, it is reasonable to say that now, more

than ever, there is a need to provide eHealth support to persons with dementia and their informal caregivers [18].

As a part of the PROMISE project, a collaborative research initiative between Quebec (Canada) and Flanders (Belgium), we aim to identify promising eHealth solutions for persons with dementia and their informal caregivers. First, a systematic review of eHealth interventions was conducted for persons with dementia and their caregivers that is published elsewhere to obtain an overview of the existing body of knowledge about eHealth solutions for older adults with mild and major NCD and their informal caregivers [13]. These solutions include computer programs and web platforms to assist in personal organization, medication management, and household activities [18]. In fact, persons with dementia require additional solutions for location and navigation support, as there is a risk of wandering behavior and safety concerns. In addition, solutions offering leisure and reminiscence in persons with dementia were almost completely lacking.

The findings from our previous systematic review do not provide a complete portrayal of the available eHealth solutions for older adults with dementia or mild and major NCD and their informal caregivers. Therefore, we will conduct an environmental scan to gather comprehensive and up-to-date information on potential eHealth solutions that could be recommended to these people. An environmental scan is an efficient and organized means to collect relevant information regarding a new technology, as it is recognized as a good mechanism while expecting a change and improvement. Decision makers often use environmental scans to collect, organize, and analyze data. Moreover, an environmental scan was used to address the self-management of chronic diseases such as NCD [15]. When an environmental scan is properly executed, a series of evidence-based responses can be elicited from this method [12].

Objectives

The purpose of this environmental scan is to identify eHealth solutions for older adults with dementia or mild and major NCD and their informal caregivers and to document their characteristics to inform the implementation of such solutions in Europe and Canada. The specific objectives are to

- inventory eHealth solutions for the targeted populations available in Europe and Canada and
- summarize the characteristics of these eHealth solutions, including their results and outcomes, implementation factors, and conditions of success.

Methods

Ethics Approval

The PROMISE project has been reviewed and approved by the ethics boards of the Centre Intégré de Santé et de Services Sociaux de la Capitale-Nationale (ref: MP-13-2019-1522) and Vrije Universiteit Brussel and Universitair Ziekenhuis Brussel (BUN 143201835242).

Study Design

To achieve these objectives, we will perform an environmental scan. Although environmental scans are gaining popularity in the health sector and in research as a methodological approach to examine a specific health issue, there is no gold standard for this method [19]. The environmental scan is considered an effective assessment and data collection tool to analyze multifaceted issues, explore a policy, and critique articles. An environmental scan identifies the knowledge-to-action gap meaningfully [20]. Several studies have described the usefulness of environmental scans for assessing community needs for program and policy development [19].

As the environmental scan is adopted as an assessment tool in various contexts, it does not have a consistent definition. However, a working definition with details is essential to achieve the desired outcome [19]. It includes several steps from development to dissemination [20]. First, a team member should take the coordinator role. Second, stating the environmental scan purpose helps to keep it focused with a clear scope, and then imposing a timeframe helps to speed up the process. Brainstorming to determine all relevant resources and topics is essential. As the environmental scan progresses, it is important to involve identified stakeholders as needed. Critical analysis and synthesis of results help to make a summary report. Finally, the results and conclusions are shared with key stakeholders [20]. A similar methodology was followed to identify the extent and breadth of existing literature on older people's perspectives on digital engagement and summarize the barriers and facilitators for technological nonuse, initial adoption, and sustained digital technology engagement [13].

Search Strategy and Timeline

To complement the eHealth technologies identified previously in the systematic review [13], we will perform comprehensive bibliographic searches to identify recent eHealth solutions for older people with mild and major NCD or dementia and their informal caregivers. The initial data searches done by Dequanter et al [13] will be updated by two research assistants (AJ and SD) by gathering all available eHealth solutions in their respective jurisdictions (Canada and Europe) through databases and web searches. Identified solutions will then be reviewed by experienced investigators (MPG, MS, and RB).

The search strategy will include combinations of relevant keywords and their declinations, as presented in Textbox 1, and will be run in Google and search engines of websites.

Textbox 1. List of terms for the search strategies.

Terms dealing with the targeted population

- Elderly, older people, caregiver, family caregiver, family caregiving, informal care, informal caregivers, aged, care partners

Medical Subject Headings (MeSH) terms

- Mild cognitive impairment, mild neurocognitive disorder, dementia, Alzheimer's disease, neurodegenerative disorder, neurocognitive disorder, memory support, memory assist, memory help, cognition support
- Cognitive decline
- Cognitive disorder
- Cognitive dysfunction
- Cognitive impairment
- Frontotemporal
- Lewy Body
- Neurocognitive decline
- Neurocognitive dysfunction
- Neurocognitive impairment
- Vascular dementia

Terms dealing with eHealth solutions

- Information and communication technology services, eHealth, medical informatics, health informatics, mobile health, mHealth, telemedicine, telehealth, telecare, mobile devices, mobile applications, self-help applications, self-help devices, self-management applications, handheld computers, tablets, mobile phones, smartphones, personal digital assistant, mobile technology, health care robotics, assistive technology
- Intelligent systems, networked technology, telemonitoring, ambient-assisted living, active and assisted living, e-learning, activities of daily living, technologies, and virtual reality

Additional terms

- Prevention, prevent, adoption, use, nonuse, acceptance, community dwelling, community-based, nursing homes, day care centers, gerontechnology, psychoeducation, prescription

Data Sources

We will also conduct targeted searches on relevant websites, including local, national, and regional organizations; private and public sector; and funding agencies. Three main sources will be searched for eHealth solutions for older adults with minor and major MCI or dementia:

1. General search: Academic sources will include Google Scholar, PubMed, and the Cochrane Library. The relevant keywords will be searched via Google and social networks (eg, Twitter and Instagram). We will consult the 10 first pages of results.
2. Targeted searches: The same search will be performed for each of the organizations listed in Textbox 2.
3. Expert consultation: For all ongoing eHealth projects in the field of dementia identified through websites and conference proceedings, we will contact the project lead if needed to complement the information.

Textbox 2. List of relevant organizations for the environmental scan.

Government agencies

- Canadian Frailty Network, Public Health Agency of Canada, AgeWell, European Commission projects funded through the EU, Canadian Consortium on Neurodegeneration in Aging

Public and private organizations

- Digital Alzheimer Center of the Vrije Universiteit, Medical Center Amsterdam, Cordis Europa, Digital single market, Canadian institutes of health research, Active and Assistive Living programs, H2020 programs, Alzheimer Europe

Foundations

- Advocacy organizations patients/users (Dementia Alliance International, etc)

Nongovernmental organizations

- Research centers (Centre for Aging Brain innovations, etc)

Practitioners and public health-related organizations

- Industries
- Rural Dementia Action Research, Canadian Medical Association

Patient and caregivers' associations

- Alzheimer Society Canada, Alzheimer Disease International, Women's Brain Health Initiative

Other relevant sites

- Canadian Geriatrics Society, Canadian Academy of Geriatric Psychiatry

Inclusion and Exclusion Criteria

The eHealth solutions must meet the following criteria: has the purpose to support or improve health and well-being in the daily life of the targeted population such as apps providing information about health or services, mental exercises and games, virtual assessments, and so forth; are produced within the last 5 years (so as of January 2018 up to the date of the search in 2022) in Europe and Canada; and must be available in these regions. We will include relevant solutions by any public or private entity, provided free of charge, or requiring some payment.

The eHealth solutions that are not currently available or for which we cannot confirm availability will be excluded. We will also discard any solution based on phone calls or one-way signals (ie, panic button), as they are not considered eHealth. Solutions that are not available in English, French, or Dutch will also be excluded.

Data Extraction

We will use an extraction grid to document the characteristics of the technological solutions, based on the main attributes identified through the qualitative component of the larger research project. These attributes include the solution name, geographic availability, scientific evidence of impacts and evidence details, purpose, software technology, target population, domain, features, availability, a summary of the invention, targeted population (digital literacy level, cognitive/physical limitations, and ease of use), battery autonomy, design, compatibility, affordability, relevancy, URL, status/remarks, primary author, or company contact information (email and phone number). We will pilot the extraction grid on a sample of 5 solutions. One author (AJ) will then do the extraction for all identified technologies, and another author (MS or MPG) will check for accuracy.

Analysis

We will gather detailed information based on the selected attributes and list all the available eHealth solutions for the targeted populations in Europe and Canada. This will provide data for the first objective. The next task is to analyze each technology based on the selected attributes, synthesize quantitative and qualitative data, and triangulate the results to understand implementation factors and conditions of success. We will use a narrative approach with charts and figures to summarize the results according to the key characteristics of the technological solutions. Classifying eHealth solutions based on their main function reveals their importance for patients and informal caregivers, along with their documented advantages, implications, and potential drawbacks. We will then prioritize the identified solutions according to the specific needs, expectations, and concerns of older adults with mild and major NCD or dementia and their informal caregivers. This prioritization will be informed by the qualitative component of the PROMISE project that consisted of consultations with older people with minor and major MCI and dyads of persons with dementia and their informal caregivers, and health and social care professionals [13]. These findings indicate that the most important attributes of eHealth solutions are perceived benefits (eg, well-being, autonomy, and self-confidence), risks (eg, burden and loss of autonomy), acceptability, feasibility, and costs.

Results

The results of the environmental scan will be shared with all stakeholders who participate in this project. We will summarize the best available scientific evidence on each selected eHealth intervention in a brief plain language report for diffusion to a large audience. In Quebec, the team members will contribute to knowledge translation and mobilization through their involvement in important networks such as the Quebec Learning Health System Support Unit [21]. Quebec researchers will work closely with knowledge users and decision makers to raise awareness about the potential of eHealth for people with mild and major NCD or dementia, their informal caregivers, and health and social care providers. This can be achieved through ongoing collaborations with health and social care organizations, patient and informal caregiver associations, and national networks. In Flanders, the Flanders Expertise Centre on Dementia will offer active participation and facilitate contacts in their network of informal caregivers, persons with dementia, and relevant stakeholders. The Flanders Expertise Centre on Dementia will facilitate the implementation of the project's results and support tools in their communication and training tools, and share them through their national and international network to promote uptake of the project's output and sustain long-term effects and make them further transferrable by reaching the key stakeholders in daily care practice.

Discussion

Anticipated Findings

This environmental scan will provide timely knowledge about promising eHealth solutions for older adults with mild and major cognitive impairment or dementia and their caregivers. eHealth technology has changed the way people live in and out of their homes, and this revolution continues to make profound changes in better cognitive functions, activities of daily living, and safety [10,11]. Environmental scanning is an assessment method commonly used in business, quality improvement projects, and strategic planning projects and now is gaining popularity in the health sector and in research [18]. Although traditional public health principles differ from an environmental scan, it can lead to evidence-based findings [20]. For instance, the Centers for Disease Control and Prevention used an environmental scan to gather relevant information and share its results [19]. In this study, we expect to obtain pieces of evidence that support the best eHealth technologies.

One of the main limitations of the environmental scan method is its lack of consistent definition. The steps we follow in this study cannot be generalized in other circumstances. For example, in an organization, the environmental scan can be used to identify barriers and facilitators [19]. In the field of research, an environmental scan can be done for a scoping review [20], but in our study, it is done to gather evidence to support the development of a decision support tool. Based on the results of this environmental scan of eHealth solutions, the next phase of the project consists of developing a web-based decision support tool for persons with dementia and their informal caregivers. The purpose of the tool will be to facilitate informed decision-making regarding the choice of eHealth solutions that could be used for different purposes, such as dementia prevention, information and education, management and care, and support. In some studies, an environmental scan is the primary methodological approach. However, in other studies, an environmental scan is represented as one of the multiple methods used [19]. In this study, the environmental scan is considered in this way.

Conclusion

There is an exponential number of initiatives undertaken to provide a better quality of life for older adults with minor and major NCD or dementia and their primary caregivers by using eHealth technologies. However, there is still much work to be done in optimizing research designs and methods. This environmental scan will provide insights into the characteristics of eHealth solutions that are beneficial for persons with dementia and their informal caregivers. Significant conceptual and methodological gaps will be identified. Evidence gathered through this environmental scan can support decision-making and assist health care organizations to respond, adapt, and build on potential challenges and opportunities.

Data Availability

All data from this environmental scan will be made available through an online repository.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the Québec-Flanders Bilateral Research Cooperation Program - The Research Foundation Flanders - Fonds de recherche du Québec (FRQ).
[PDF File (Adobe PDF File), 590 KB - resprot_v11i11e41015_app1.pdf]

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Abbreviations

MCI: mild cognitive impairment
NCD: neurocognitive disorders

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Protocol

Digital Pattern Recognition for the Identification of Various Hypospadias Parameters via an Artificial Neural Network: Protocol for the Development and Validation of a System and Mobile App

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Abstract

Background: Hypospadias remains the most prevalent congenital abnormality in boys worldwide. However, the limited infrastructure and number of pediatric urologists capable of diagnosing and managing the condition hinder the management of hypospadias in Indonesia. The use of artificial intelligence and image recognition is thought to be beneficial in improving the management of hypospadias cases in Indonesia.

Objective: We aim to develop and validate a digital pattern recognition system and a mobile app based on an artificial neural network to determine various parameters of hypospadias.

Methods: Hypospadias and normal penis images from an age-matched database will be used to train the artificial neural network. Images of 3 aspects of the penis (ventral, dorsal, and lateral aspects, which include the glans, shaft, and scrotum) will be taken from each participant. The images will be labeled with the following hypospadias parameters: hypospadias status, meatal location, meatal shape, the quality of the urethral plate, glans diameter, and glans shape. The data will be uploaded to train the image recognition model. Intrarater and interrater analyses will be performed, using the test images provided to the algorithm.

Results: Our study is at the protocol development stage. A preliminary study regarding the system's development and feasibility will start in December 2022. The results of our study are expected to be available by the end of 2023.

Conclusions: A digital pattern recognition system using an artificial neural network will be developed and designed to improve the diagnosis and management of patients with hypospadias, especially those residing in regions with limited infrastructure and health personnel.

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KEYWORDS

artificial intelligence; digital recognition; hypospadias; machine learning

Introduction

Hypospadias is the most prevalent congenital anomaly of the penis, with an estimated incidence of 0.4 to 8.2 cases per 1000 live births [1]. However, most of the parents and families of those with hypospadias experience anxiety and uncertainty regarding the information about hypospadias [2]. Moreover, there remains some confusion in the diagnosis of hypospadias even among clinicians [3]. The confusion among both clinicians and parents delays the diagnosis and treatment of hypospadias, exacerbating the symptoms and lowering the quality of life of those affected [2].

Hypospadias is a multidimensional problem that requires a multidisciplinary approach. Due to the possibility of it being one of the symptoms of disorders of sexual development, various types of specialistic care are required for the most optimal outcome [4]. However, there are shortages of multidisciplinary teams that are capable of performing the diagnosis and surgery needed, especially in low-income countries such as Indonesia [4].

The diagnosis of hypospadias is usually based on clinical observation. However, the accurate diagnosis of hypospadias may prove to be difficult, as its phenotypes widely vary. Different diagnoses for the same phenotypes may result in variable surgical outcomes, even among experienced surgeons who perform the same procedure [5]. Although a few scoring systems exist for standardizing the clinical diagnosis of hypospadias, the lack of complete agreement among clinicians remains an issue [6,7]. There are a few established scoring systems for diagnosing the severity of hypospadias, such as the Glans, Meatus, Shaft (GMS) score; Meatus, Chordee, Glans, Urethral Plate Quality (MCGU) score; and Hypospadias Objective Penile Evaluation score [6,8,9]. Merriman et al [7] showed that complete agreement for a scoring system among clinicians could only be achieved in 78%-85% of their cases. Therefore, some studies utilized photos and videos to help diagnose hypospadias [10,11].

Various studies have been done to address this problem. One such study used standardized photographs, which were taken by using a professional camera, for measurements of various parameters of hypospadias [12]. Another used digital photographs taken by clinicians for media communication in hypospadias care [13], and one study even utilized parents' video cameras for postoperative follow-up examinations [14]. However, there has been no study utilizing artificial intelligence, image recognition, and parents' mobile cameras to help diagnose hypospadias.

This protocol was designed to develop a system and a mobile app with artificial intelligence and image recognition capabilities, which are thought to be beneficial in improving the diagnosis and management of hypospadias cases, especially in low-income countries such as Indonesia.

Methods

Study Design

Ours is an observational study that will use a prospective cohort design for the development of a digital pattern recognition system for the identification of various hypospadias parameters via an artificial neural network (ANN). The digital pattern recognition system will be applied to digital images that are taken by the parents or guardians. Afterward, the system will be applied to a mobile app. The population for our study will be children with suspected hypospadias who are admitted or referred to hospitals in Indonesia.

Ethics Approval

The approval for the protocol of our study was granted by the Medical Research Ethics Committee, Universitas Indonesia, in April 2022 (ethical clearance number: KET-413/UN2.F1/ETIK/PPM.00.02/2022).

Consent to Participate and Consent for Publication

The consent for the capture and publication of the images needed in the study will be obtained from the parents of patients with hypospadias as a part of standard care. The images will be used as a clinical reference. Consent will be requested after the parents and their children receive an explanation from the researcher.

The photographs for the study will be taken by the parents or guardians of the participants, using their mobile cameras. The photographs will then be securely uploaded via the internet to our encrypted database, without any identifiers. Photographs with an identifier, such as a face, will be marked as invalid and will be deleted from our database. The photographs will only be seen by the parents and the researcher. The photographs chosen as examples for the publication will also be randomized according to the parameters needed for the publication.

This protocol was prepared according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist for reporting a protocol study [15].

Eligibility Criteria and Recruitment Procedures

The inclusion criteria for participants in the hypospadias (case) group are as follows: children aged <18 years and (2) children with suspected hypospadias. Those for the control group are (1) children aged <18 years and (2) children without suspected hypospadias.

The exclusion criteria for the hypospadias (case) group are (1) a history of hypospadias repair and (2) the refusal to participate in the study. The exclusion criterion for the control group is the refusal to participate in the study.

The drop-out criterion is death during the follow-up period.

The participants of our study will be recruited by using the consecutive sampling method. Parents of patients who are eligible to participate as study participants during the study duration will be given an explanation about the study process and be asked whether they want their children to participate in the study.

Clinical Outcomes: Hypospadias Parameters

The clinical outcomes measured in our study will be expressed as hypospadias parameters. The hypospadias parameters in our study will be defined as diagnostic features that define the severity of hypospadias [6,7]. These parameters are known to define the prognosis of the surgical management of patients [6]. It is expected that the system will be able to recognize these diagnostic features after sufficient training. The hypospadias parameters and their categorizations in the study will be (1) hypospadias status (hypospadias or nonhypospadias), (2) meatal location (glanular, coronal, distal shaft, proximal shaft, or penoscrotal), (3) meatal shape (normal or abnormal), (4) the quality of the urethral plate (intact or divided), (5) glans diameter in millimeters, and (6) glans shape (normal or abnormal).

The clinical outcomes will be measured preoperatively and 1 month postoperatively.

Model Development, Training, and Testing

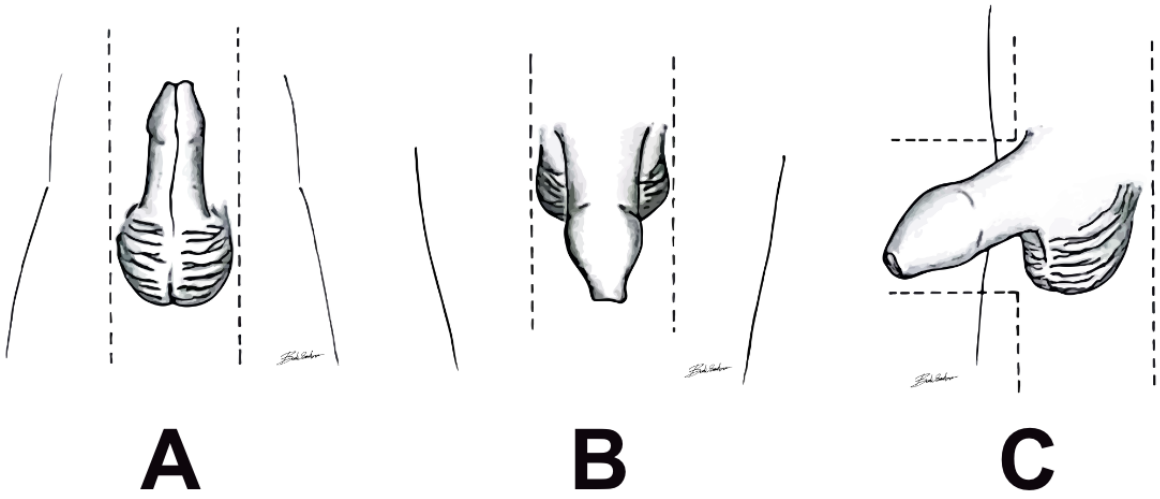
Hypospadias and normal penis images from an age-matched database will be used to train the ANN. Images of 3 aspects of the penis (ventral, dorsal, and lateral aspects, which include the glans, shaft, and scrotum) will be taken from each participant. The images will be labeled with the following hypospadias parameters: hypospadias status, meatal location, meatal shape, the quality of the urethral plate, glans diameter, and glans shape. The data will be uploaded to train the ANN.

In our study, a customized ANN based on a deep learning architecture will be used to develop an image recognition model for determining various hypospadias parameters. The software will be trained to recognize various hypospadias parameters via label boxes as a part of the preprocessing phase. The labels will be filled after consensus among 3 pediatric urologists.

Following the training period, the evaluation of the ANN will be done by comparing the results of the ANN and the three pediatric urologists' evaluations for a single image. Typically, the interrater reliability test for hypospadias is done by comparing scores measured via scoring criteria, such as the GMS score or the MCGU score [6,7]. The results obtained by the ANN will also be converted according to the scoring criteria. The agreement among raters will be assessed by using the intraclass correlation coefficient as the gold standard.

The photographs used for the study will be taken by using the same standard methodology and be of the same quality, using the parents' or clinicians' phones (ie, via a mobile app). An example drawing and guiding lines will be presented before a photograph is taken (Figure 1).

Figure 1. Example drawings that will be presented before a photograph is taken. (A) Ventral view. (B) Dorsal view. (C) Lateral view.



Data Analysis

The sample size was estimated for a prespecified power of 90%, while the α value was set at <.05. The clinical characteristics of the participants and all hypospadias parameters will be presented descriptively. Intrarater and interrater analyses among pediatric urologists will be performed, using the Fleiss κ statistical analysis. The κ score between the ANN results and pediatric urologists' examination results will be calculated by using SPSS for Macintosh, version 25.0 (IBM Corporation). The data will be deemed statistically significant if the *P* value is <.05. In addition, accuracy, precision, recall, and F_1 score values will be computed to measure the performance of the recognition model.

Results

The development of the system and a mobile app started in September 2022, and the recruitment of participants is planned to start in December 2022. The study results are expected to be available by the end of 2023.

Discussion

It is expected that after being trained on images of patients with hypospadias and age-matched controls, the image recognition model will be able to differentiate between a normal penis and a hypospadias penis, determine meatal location and shape, and measure glans size and quality. The parameters identified by

the model will prove to be useful in determining the prognosis of patients with hypospadias.

The diagnosis of hypospadias remains a challenge even among clinicians worldwide [1]. Even among experts, there are many debatable aspects of hypospadias, such as the diagnosis method, the assessment of severity, the classification of hypospadias, and hypospadias treatment [16].

There are some studies that have already used a similar approach to that of our study. Previously, Han et al [10] studied the validity and reliability of guardian-conducted voiding videos for postoperative evaluation following hypospadias surgery. In their study, it was shown that the videos taken by the guardians were acceptable and beneficial for home-based postoperative assessment. However, the videos taken during the assessment were compared to web-based observations by pediatric urologists. Therefore, the applicability of the test was limited by the number of pediatric urologists available and time constraints.

Fernandez et al [11] studied the application of digital pattern recognition and artificial intelligence for the classification of hypospadias. After being trained with 1169 images of hypospadias cases, their model was reported to have about 90% accuracy, surpassing the interrater analysis results among expert pediatric urologists. However, the hypospadias images were taken by the clinicians before surgery, limiting the applicability of the model.

Herein, we present a protocol for the assessment of hypospadias by using digital pattern recognition for the identification of various hypospadias parameters. Using a customized ANN with a deep learning architecture, we will train an accurate model with data from a limited number of participants. We hope that the model will facilitate the diagnosis of hypospadias and ease the burden of hypospadias management among clinicians. However, a previous study showed that there are challenges in encouraging clinicians to use mobile apps in the clinical setting, such as convincing clinicians that an app will be useful [17]. Therefore, we chose to include the parents and guardians of patients with hypospadias due to the limited number of pediatric urologists in low-income countries—an approach that was previously validated by Türk et al [14] for postoperative follow-up assessments among children with hypospadias.

The use of mobile health apps among adults has been previously studied, and it has been deemed a feasible option for dealing with various health issues in Indonesia. Agustina et al [18] previously developed a mobile app for obesity management in Indonesia, especially in urban areas. Even in rural areas, the use of mobile apps has proven to be beneficial for the follow-up assessment of patients [19]. We also hope that our app will be beneficial even in the rural areas of low-income countries.

One of the limitations of our study is the sheer number of images needed to train the model. Based on a previous study, more than 900 images of patients with hypospadias are required to have a system with over 90% accuracy [11]. However, there are only a limited number of health centers with a sufficient number of patients with hypospadias. Therefore, breakthroughs in ANN development and extreme learning techniques are necessary for health centers with a limited number of patients with hypospadias.

Another limitation of our study is the unpredictability of the digital images, which will be taken by the parents or guardians of the patients. Due to the variability in digital camera quality among mobile phones, the quality of the digital images may vary, creating another hurdle for the digital pattern recognition system.

With the advancement of information and communication technology, the advancement of health information technology is expected. Hypospadias, as a prevalent congenital abnormality with recognizable anatomical features, may serve as an example for the use of artificial intelligence in health.

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Data Availability

The data sets that will be generated and analyzed during the study will be available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-review reports from the Kementrian Riset Dan Teknologi / Badan Riset Dan Inovasi Nasional Deputi Bidang Penguatan Riset Dan Pengembangan (Ministry of Research and Technology / National Research and Innovation Agency - Deputy for Strengthening Research and Development) (Jakarta, Indonesia).

[PDF File (Adobe PDF File), 429 KB - resprot_v11i11e42853_app1.pdf]

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Abbreviations

ANN: artificial neural network
GMS: Glans, Meatus, Shaft
MCGU: Meatus, Chordee, Glans, Urethral Plate Quality
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

An Intensive Ambulatory Care Program for Adolescents With Eating Disorders Combining In-Person and Web-Based Care: Protocol for a Single-Site Naturalistic Trial

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Abstract

Background: The incidence of eating disorders (EDs) among adolescents has significantly increased since the beginning of the COVID-19 pandemic. Hybrid care, which combines web-based and in-person modalities, is a promising approach for adolescents with EDs but remains understudied in this population.

Objective: We aimed to implement a novel hybrid (web-based and in-person) intensive ambulatory care program for youth and evaluate its feasibility, acceptability, and preliminary effectiveness.

Methods: We will use a naturalistic pretest-posttest design to evaluate our proposed pilot Intensive Ambulatory Care Program (IACP). This novel type of day hospital care follows evidence-based principles and uses a family-centered, educational, and motivational approach. It will be tailored to the psychological needs of each participant and will be delivered in a hybrid format. A total of 100 participants meeting the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) criteria for EDs, aged 12-18 years, will be recruited over the 2-year trial period. We will examine recruitment, retention, and adhesion-to-protocol rates; participant and family satisfaction; and preliminary effectiveness using quantitative self-report questionnaires.

Results: Rolling recruitment will take place from winter 2022 to fall 2023, during which time we expect to recruit approximately 80% (100/120) of eligible participants, retain at least 75% (75/100) of enrolled participants and have at least 70% (70/100) of enrolled participants complete at least one therapeutic session per week and all pre- and postintervention questionnaires. Data collection will occur concurrently. We base our recruitment and retention estimates on previous literature and consider that the highly flexible design of the IACP and the fact that no extra work will be required of individuals in the program to participate in the study, will lead to high levels of feasibility. We anticipate that participants and their families will be satisfied with both the program and hybrid delivery format. We expect that participation in the IACP will be associated with a medium effect size reduction in ED psychopathology from baseline to end of treatment. The data analysis and manuscript writing are expected to be completed by the summer of 2024.

Conclusions: Given the high clinical burden associated with EDs, this study has the potential to fill an important research gap by testing the implementation of a novel hybrid mode of intervention. If feasible, acceptable, and effective, the IACP could lead to important improvements in health care services for adolescents with EDs.

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KEYWORDS

eating disorders; adolescents; ambulatory care; web-based care; telemedicine

Introduction

Burden of Eating Disorders

Eating disorders (EDs) are a group of serious and complex mental illnesses characterized by disturbed beliefs about body weight, shape, and image, in addition to maladaptive eating behaviors, including restriction, purging, and other methods of excessive compensation for caloric intake [1]. Although EDs can affect individuals of all ages, they often occur during adolescence [2-4]. Illness severity varies widely, and symptoms are highly heterogeneous. The negative consequences of these diseases include poor quality of life, impaired psychosocial functioning [5], psychiatric comorbidities [6], multisystemic medical complications, and mortality [7]. The treatment of EDs also varies widely. Hospitalization is generally reserved for patients at high medical or psychological risk who are unresponsive to other treatments, while ambulatory care is used for patients with less severe forms of illness [1].

Day Treatment Programs for EDs

Day treatment programs provide patients with care on multiple days or hours per week, at an intensity that falls between hospitalization and ambulatory care [8]. This is important for patients with moderate to severe illness who either do not require hospitalization or who can benefit from step-down care after an inpatient hospitalization. The literature supports the use of day treatment programs, considering the limited benefits of extended hospitalization when compared with short hospitalization followed by prompt transition to ambulatory care [9]. The latter option may also reduce health care costs [10] and allow for a more rapid return to school and social functioning without affecting clinical outcomes [9]. Therapeutic approaches used in day programs vary but can be categorized as either family-focused [11-13] or nonfamily-focused [14-16] with most of the latter combining several modalities, including cognitive behavioral therapy, dialectical behavioral therapy, behavioral therapy, cognitive remediation therapy, and acceptance and commitment therapy, among others [8]. Short-term hospitalization followed by day program treatment for adolescents with AN is noninferior in terms of weight outcomes, 1-year rates of readmission, and ED symptoms when compared with continued inpatient treatment [17]. Similarly, several uncontrolled trials [18,19] and a systematic scoping review of the literature [8] suggest that day programs alone are effective in promoting weight gain for those who are underweight, decreasing ED and comorbid psychopathology, and improving psychosocial functioning and quality of life among individuals with moderate to severe ED symptoms.

Considering the high rates of comorbid mental health symptoms among youth with EDs [20], there is a need for integrated treatment strategies targeting both ED symptoms and psychiatric comorbidities. Day treatment programs may offer a unique opportunity to combine multiple treatment modalities because of their intermediate level of intensity and increased scheduling flexibility compared with inpatient treatment. In many cases, day treatment may also allow for the continuation of school and work-related activities. One example of this integrated approach, which included the addition of a self-esteem and social skills therapy group to a multidisciplinary ED day treatment program, effectively improved outcomes, such as happiness, satisfaction, and self-concept related to weight, shape, and others [21]. Day treatment programs may also be particularly amenable to personalized treatment plans given their flexibility, and some interventions that have used data-driven approaches to elaborate personalized plans have been found to be preliminarily feasible and acceptable [22,23].

Web-Based Day Treatment Programs for EDs

The provision of day treatment remotely using technology has the potential to increase access to treatment by addressing barriers such as precautions for infection control (in the context of current or future pandemics) and geographic distance from urban centers (where in-person day treatment programs are typically delivered). However, the evaluation of web-based day treatment programs for youth with EDs has been identified as a research gap [24]. Limited evidence from a naturalistic study conducted during the COVID-19 pandemic to evaluate the experiences of youth transitioning from an in-person to a web-based day treatment program, suggests that this approach is acceptable for youth [25]. A recent scoping review [24] also found that therapy delivered via videoconference, including family-based treatment, cognitive behavioral therapy, and relapse prevention using the Maudsley Model of Anorexia Nervosa Treatment for Adults, may be effective in the ambulatory setting, although evidence was drawn from uncontrolled case reports, pilot trials, and feasibility trials.

In light of the increased need for services for adolescents with EDs [26-30] and the limited amount of empirical evidence for integrated treatment strategies combining in-person and web-based care for the treatment of pediatric EDs and comorbid psychopathologies, we are implementing and evaluating a pilot Intensive Ambulatory Care Program (IACP), a novel type of day treatment program. Our program will be tailored to the psychological needs of each participant and delivered in a hybrid format, both web-based and in-person. We describe the proposed intervention and methodology of a naturalistic study that will be used to evaluate its feasibility, acceptability, and preliminary effectiveness.

Objectives and Hypotheses

The primary objective of this study is to describe the feasibility and acceptability of flexible, modular, and hybrid IACP for adolescents with EDs. Secondary aims include describing the

baseline characteristics of the adolescents who enroll in the IACP, describing the preliminary effectiveness of the IACP for adolescents with EDs in an uncontrolled naturalistic setting, and describing the moderating role of age, ED diagnosis (eg, anorexia nervosa vs other ED diagnoses), length of illness, and level of attendance on clinical response to the IACP.

We hypothesize that recruiting and retaining participants in the IACP would be feasible and acceptable. We expect that participants will mostly present restrictive ED symptomatology, which is representative of the patient population seen in the ED clinic where the study will be conducted; participants will present comorbid symptomatology and ED-related behaviors, such as anxiety and depressive symptoms [31,32], high levels of affective reactivity [33] and perfectionism scores [34], poor coping [35] and self-esteem [36] skills, and high levels of social media use [37], as reported in the literature. We expect that participation in the IACP will be associated with a reduction in ED psychopathology, from baseline to the end of treatment, and that patient age, ED diagnosis, length of illness, family connectedness, and the number of hours of therapy attended will act as moderators of the preliminary effectiveness of the intervention. Although there is no consensus on moderators of treatment outcomes in the adolescent population, these moderators were chosen based on limited evidence from several reviews [8,38,39] that have identified individual, clinical, and family-related factors that are related to treatment response.

Methods

Overview

Our team will conduct a naturalistic study of the IACP for youth with EDs that will gather 3 types of data. First, the feasibility of the IACP will be evaluated using recruitment, retention, and adhesion-to-protocol rates. Second, the acceptability of the IACP program and web-based delivery method among youth participants will be measured using youth and parent satisfaction questionnaires. Finally, the preliminary effectiveness of the IACP will be described using quantitative self-report questionnaires pertaining to ED symptomatology, and several moderators of this effect will be investigated. Body mass index (BMI) and quantitative self-report measures of comorbid psychopathology will be used as secondary outcome measures to describe the preliminary effectiveness of the intervention in an uncontrolled naturalistic setting.

Population

Individuals eligible for the study will be between 12 and 18 years of age, have a diagnosed ED according to the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) criteria [40], and will already have received medical treatment in the hospital or ambulatory setting at our specialized ED clinic. This clinic is located in a tertiary pediatric hospital in a large city in the province of Quebec, which serves both a multicultural urban population representative of other large cities in North America in addition to the surrounding suburban and rural populations. Individuals who meet these criteria will be invited to participate in the IACP and the current research. To be eligible for the IACP, individuals must be available to participate in all aspects of the proposed intervention (including pre- and postintervention measures, individual, family, and group sessions, and an intake and feedback meeting with the IACP clinical team).

Individuals will be excluded from the IACP (and the current research study) if they require hospitalization for medical stabilization when evaluated for recruitment. In addition, the intervention will be discontinued and the individual referred to the appropriate service if they become medically unstable during the program (eg, heart rate <45 bpm, body temperature <35.5 °C) or express acute psychiatric distress (eg, active suicidal ideation requiring hospitalization).

Recruitment, Enrollment, and Consent

Clinicians working in ambulatory and hospital settings at our specialized ED clinic will refer patients who are suitable for the IACP. These patients will be screened for eligibility by an IACP clinical coordinator. All patients who meet the criteria for participation in the IACP will receive a brief explanation of the study during the initial screening meeting with the clinical coordinator and will be presented with the opportunity to meet a research assistant to discuss consent if they are interested in participating in the research study. It will be made clear that participation in the research study is optional and that it will not affect any care or services received in the IACP.

The meeting with the research assistant will take place with the eligible participant and at least one parent, either in-person or via the secure Teams videoconferencing platform. The research assistant will verbally explain the objectives of the study, the main procedures involved, and the potential benefits and risks of participation. The participant and their parents will be given time to ask questions and consider participating. If they agree, a consent form (summarizing the verbal explanation of the study) will be presented to them for both parents and participants to sign.

Recruitment will occur on an ongoing basis over the 2-year study period. We expect that approximately 100 patients will be recruited (see the section on power calculation below for more details).

Attrition and Compliance

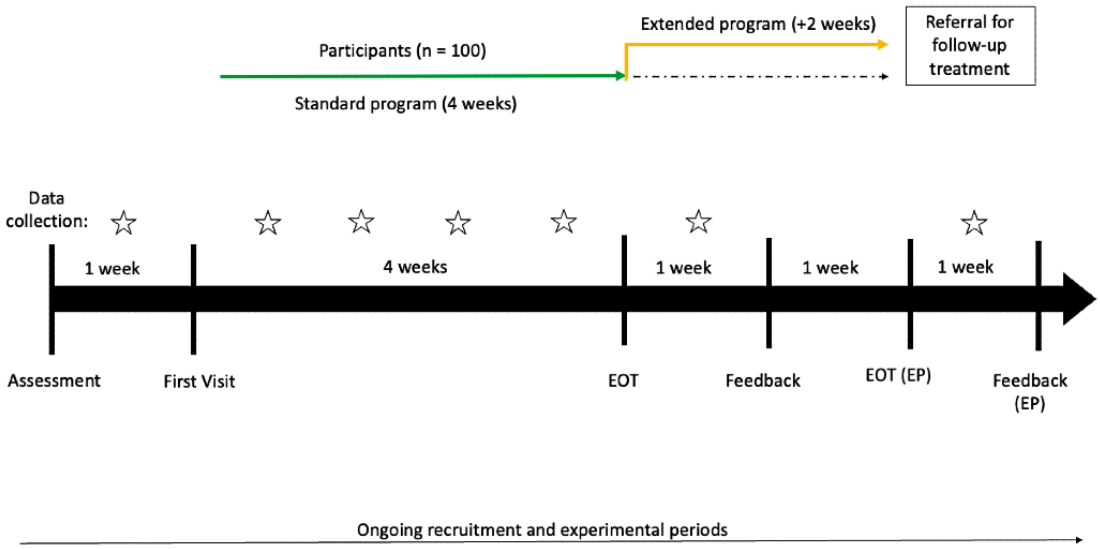
We expect to recruit approximately 80% (100/120) of eligible participants—that is, 80% of all youth enrolled in the IACP—to our study, which is a conservative estimate based on previous literature [41]. Participation in the research study entails no additional commitment from eligible participants, given that all study materials are also an integral part of the IACP. Further, we expect attrition to be less than or equal to 25% (25/100), based on the current literature, which suggests a 7% to 42% dropout rate for adolescents enrolled in day treatment programs for the treatment of EDs [17,42-45], and also considering the flexible, modular, and hybrid nature of our program, which may allow us to improve retention rates.

Participants who attend at least one session per week of treatment in the IACP (and complete both pre- and postintervention materials) will be considered sufficiently exposed to the intervention and, thus, will be included in the data analysis on the preliminary effectiveness of the program.

Study Design

This study will have a natural design. Therefore, all participants who consent to the trial will receive the same individualized treatment modality as part of the IACP. The study will be an uncontrolled, pre- and posttest trial (Figure 1), comparing measures collected at baseline to measures collected at the end of treatment within participants.

Figure 1. Experimental design of the 6- to 8-week IACP for adolescents (12-18 years) with eating disorders. EOT: end of treatment; EP: extended program.



Data Collection

Data will be collected at baseline (clinical and demographic information and preintervention self-report questionnaires), weekly (youth and parent satisfaction questionnaires), and immediately after the end of treatment (postintervention self-report and satisfaction questionnaires), as outlined in Figure 1. The clinical program coordinator will be responsible for collecting all data, deidentifying the data, and sending all deidentified data (including only participants' random study ID) to the research team. Data to be collected include demographic and clinical information at baseline, growth curve charts, BMI pre- and postintervention, self-report standardized outcome questionnaires, acceptability (satisfaction) surveys, and measures of feasibility. All self-report questionnaires and surveys will be completed either on paper (if participants are present on site) or web-based (on a laptop or smartphone) using password-protected interactive PDF format questionnaires that will be sent to the participants using a secure email address.

Demographic and clinical information at baseline, including age, sex, level of education, diagnosis, presenting ED symptoms, duration of illness, ED treatment history (including past hospitalizations), maximum and minimum weight, comorbid symptomatology, and past medical history, will be collected by the clinical program coordinator during the intake visit for the IACP.

BMI will be calculated at baseline and at the end of treatment. Weight (with clothing on but without coats, shoes, boots, or cold weather accessories) and height (without shoes) will be measured during the first and last appointments with the clinical team using an electronic scale and a standard wall measuring scale. BMI will be calculated by dividing body weight in kilograms by the square of the height in meters.

Feasibility data will be collected by the IACP clinical staff throughout the duration of the study and will include recruitment and retention rates, in addition to measures of adherence to the protocol (Table 1).

Table 1. Summary of feasibility measures.

Outcome	Target
Recruitment rate	• 80% (100/120) of eligible participants (ie, of all adolescents participating in the IACP[a]) will enroll in the study and complete the baseline measure.
Retention rate	• ≤25% (25/100) of enrolled participants lost to follow-up.
Adherence to protocol	• At least 70% (70/100) of participants complete at least one therapeutic session per week of treatment in the IACP. • At least 70% (70/100) of participants complete all pre- and postintervention questionnaires. • At least 70% (70/100) of participants complete at least one therapeutic session per week and all pre- and postintervention questionnaires.

[a]IACP: Intensive Ambulatory Care Program.

Intervention

The intervention uses a family-centered, educational, and motivational approach that is based on the biopsychosocial model of EDs as described in Aimé and Bégin [46]. This model theorizes that a combination of sociocultural, environmental, familial, and individual factors, in addition to biological predispositions, converge to contribute to both the development and maintenance of disturbed beliefs and behaviors that characterize EDs. The therapeutic and psychoeducational modules (Table 2) were created based on this theory [46] and on a variety of similar sources such as books by Daniel J Siegel on mindfulness and by Martha M Linehan on impulse control [47], on cognitive behavioral and psychoeducational activities that are carried out in numerous ED treatments (eg, an open letter to my anorexia, metaphors for change, etc), and on original material created in partnership with patients.

Each participant will have an individualized treatment plan combining one or more modules, which will be established based on the initial questionnaire evaluation results and discussions between the clinician, the participant, and their family. Modules on one or more of the following themes will be presented as follows: (1) EDs and related psychopathology; (2) mental health and emotional regulation; (3) stress and anxiety management; and (4) identity, relationships, and life cycle issues in adolescence. Parents will be invited to participate in interventions pertaining to the physical and psychological components of EDs, meal accompaniment, stress, anxiety, hyperactivity management, and family life.

The intake and evaluation process, which will guide the creation of an individual treatment plan, will take place over 1 week. Following this, the intervention will take place over 4 weeks, with the possibility of extending it by 2 weeks, based on a discussion with the clinical team and the participant's individual needs and progress. The intervention will conclude with 1 week of feedback and evaluation. Overall, the programming will last for 6 to 8 weeks.

Table 2. Overview of the 4 therapeutic modules and corresponding activities and interventions offered within the Intensive Ambulatory Care Program.

Module	Activities and interventions
EDs[a] and related psychopathology	• Virtual meal accompaniment • Hyperactivity management • ED recovery and sources of motivation • Perfectionism • Body image
Mental health and emotion regulation	• Recognizing emotions • Emotion regulation • Impulsivity and anger • Suicidal and parasuicidal behaviors
Stress and anxiety management	• Recognizing emotions • Mindfulness • Relaxation techniques • Psychoeducation about stress
Identity, relationships, and lifecycle issues in adolescence	• Changes during adolescence and fear of growing up • Self-esteem and self-affirmation • The influence of social media • Relationships with parents and friends • Communication

[a]ED: eating disorder.

The time commitment for program participants will be variable but will involve a minimum of two to three 60- to 90-minute sessions per week, including meal accompaniment and preparatory activities with the adolescent and at least one parent or guardian. This represents a total of approximately 3 to 4 hours of programing per week. This will be in addition to regular planned outpatient clinical appointments with doctors, psychologists, social workers, etc. which will be considered usual care and which are not part of the IACP.

The modules of the intervention will be delivered using various formats, including in-person and web-based individual meetings, in-person and web-based meetings with parents, web-based synchronous therapy activities (eg, relaxation or mindfulness) administered by clinicians, individual web-based asynchronous therapy activities completed alone by participants with web-based feedback provided by clinicians, web-based viewing of prerecorded informational videos, and participant and family completion of personal logbooks and assignments. Each module has a set format (eg, individual vs group; in-person vs web-based) and was developed by the clinical team based on clinical experience and relevant literature.

Outcome Measures

A set of standardized questionnaires (Table 3) will be administered before the start of the IACP. Many of these will be repeated after the completion of the program (Table 3). The total time required for the administration of all questionnaires will be approximately 55 to 65 minutes at baseline and 40 to 50 minutes at the end of the treatment. The total time dedicated to pre- and postintervention questionnaires may seem long but is justified by their key importance to the development of

individualized treatment plans and the importance of postintervention feedback and debriefing sessions with clinical staff. All questionnaires will be administered in French, given that the language of treatment at the study site is French, and that French is the official and the most spoken language in the province where the study will be held. Language preferences will be discussed at the initial screening meeting with the clinical coordinator, and participants will have the option to request to complete the questionnaires in English at this time.

Table 3. Psychometric properties and characteristics of the included questionnaires.

Questionnaire	Themes covered	Number of questions	Available research on validity[a]	Available research on reliability	Time necessary to complete	Time at which survey is completed (T_0[b]; T_1[c])
Primary outcome (eating disorder symptoms)						
Eating Disorder Examination Questionnaire—Adolescent version	Eating disorder symptoms	36 items	Adolescent (11-18 years old) [48]	Good internal consistency [48]	7-8 min	T_0, T_1
Secondary outcomes (comorbidities and associated behaviors)						
Affective Reactivity Index	Chronic irritability	6 items	Adolescent (3-18 years old) [49,50]	Good internal consistency [49]	1-2 min	T_0, T_1
Child and Adolescent Perfectionism Scale	Trait perfectionism	22 items	Adolescents (10-17 years old) [51]	Good internal consistency [51]	3-4 min	T_0, T_1
Patient Health Questionnaire for Adolescents	Depressive symptoms and suicidality	13 items	Adolescents (grade 8-12) [52]	Good internal consistency [52]	2-3 min	T_0, T_1
Revised Children's Anxiety and Depression Scale	Anxiety and depression	47 items	Adolescents (English version: 8-13 years old [53]; French version: 10-19 years old [54])	Good internal consistency [53]	15 min	T_0, T_1
Generalized Anxiety Disorder 7	Generalized anxiety	7 items	Adolescents (English version: 14-18 years old [55]; French version 18-75 years old [56])	Excellent internal consistency [57]Good test-retest reliability [57]	1-2 min	T_0, T_1
Adolescent Coping Scale (Échelle de coping pour adolescents)	Coping strategies	79 items	Adolescents (English version: 12-18 years old [58]; French version: 14-17 years old [59])	Good internal consistency (French version) [59]	11-13 min	T_0
Self-Esteem Rating Scale, short form	Self-esteem	20 items	Adults (English version: mean 26.8, SD 9.9 years [60]; French version: mean 24, SD 7.4 years [60])	Good internal consistency (French) [60]	3-4 min	T_0, T_1
Eating Disorder Recovery Self-Efficacy Questionnaire-French	Confidence regarding eating disorder recovery	23 items	Adults (English version: mean 26.3, SD 11.1 years [61]; French version: mean 21.8, SD 3.9 years [62])	Excellent internal consistency [61] Good test-retest reliability [62]	5-6 min	T_0, T_1
Dépistage/évaluation du Besoin d'aide—internet[d]	Problematic internet usage	15 items	Adolescents (16-29 years, mean 19.7 years [63])	No data available	3-4 min	T_0
Hyperactivity questionnaire (*Questions pour évaluer le surexercice*)	Excessive exercise habits	3 items	No psychometric data available[e]	No psychometric data available[e]	1-2 min	T_0, T_1
Family Connectedness Questionnaire (*Fonctionnement familial*)	Family functioning	6 items	No psychometric data available[e]	No psychometric data available[e]	1-2 min	T_0, T_1
Total response time	N/A[f]	N/A	N/A	N/A	55-65 min 40-50 min	T_0 T_1

[a]For the purposes of this study, we consider standardized questionnaires to be validated if they have shown favorable psychometric profiles in peer-reviewed studies.

[b]T_0: baseline

[c]T_1: end of treatment

[d]Three additional, nonvalidated questions were added to determine problematic use of the internet to access information about (1) food and calories, (2) exercise and energy expenditure, and (3) dieting and other ways of losing weight.

[e]No psychometric data were available for questionnaires created by members of our research team. However, these questionnaires were either based

on relevant literature or used in other studies. Further details are provided in Multimedia Appendix 1 [25,34,49-92].

[f]N/A: not applicable.

The primary outcome measure for this study is the Eating Disorder Examination Questionnaire for Adolescents (EDE-A) [93], a 36-item self-report questionnaire that evaluates attitudes, feelings, and behaviors related to eating, body image, and weight. It is a close adaptation of the Eating Disorder Examination Questionnaire (EDE-Q) [64], the adult version of this questionnaire, which contains 28 items and is one of the most commonly used ED symptom scales [8,94,95]. The EDE-A was adapted to measure symptoms on a shorter timescale than the EDE-Q (14 days rather than 28 days), which was considered more developmentally appropriate by experts with experience in treating EDs in the adolescent population [93] and is better suited to our study given the short length of our intervention (4-6 weeks, excluding pre- and postintervention meetings). Like the EDE-Q, the EDE-A questionnaire yields a global score in addition to four subscale scores: restraint, eating concern, weight concern, and shape concern. Norms exist for EDE-Q scores in healthy [93] and clinical adolescent populations [48].

No studies have evaluated the internal consistency of the EDE-A specifically, however, the EDE-Q, on which it is based, has good internal consistency, with a Cronbach α of .96 in a sample of female adolescents with anorexia nervosa [48], and between .78 and .93 in the general population [96,97]. Our team produced an adapted version of the questionnaire using a validated translation of the EDE-Q by Turgeon [98] as a guide, given that no validated translations of the EDE-A were available.

The secondary outcomes are outlined in Table 3 and include measures of comorbid ED psychopathology and related behaviors, including anxiety and depression symptoms, irritability, perfectionism, self-esteem, coping skills, social media use, and family connectedness. Further descriptions of the secondary outcome measures, including their psychometric properties, can be found in Multimedia Appendix 1 [25,34,49-92].

Satisfaction questionnaires (acceptability) will consist of self-report surveys completed by the participants both weekly and at the end of the intervention. Weekly surveys will evaluate satisfaction with individual therapeutic activities (eg, meal accompaniment sessions, individual and group sessions) experienced in the IACP using Likert-type questions (eg, Was this activity interesting and useful? Did it help participants understand themselves or find solutions? Did participants feel understood? Were participants satisfied and engaged?) as well as open-ended questions about what participants liked, disliked, and thought were the most important takeaways from each intervention. Postintervention satisfaction surveys for parents and patients will evaluate overall program satisfaction and satisfaction with the web-based mode of intervention, using 10-point Likert-type and open-ended questions.

Power Calculations

Sample size estimations were performed using G*Power 3.1. Sample size estimations were performed for all analyses, and the final targeted sample size was selected so that the analysis requiring the largest number of participants could be adequately powered.

As our proposed treatment is new and the goal of this project is to collect initial data on its effectiveness, formal power analysis cannot be conducted. However, based on the literature on the effectiveness of specialized ED care [13-15,99-104], we expect a medium effect size (f^2=0.15). Recent work in adult patients in a specialized tertiary care ED program also showed that fully web-based care and fully in-person outpatient care both yielded a similar medium effect size [105]. Thus, we expect our hybrid model to yield medium effect sizes. This implies that the sample size required to reach a level of significance of P=.05 with a power of 0.80 is 68 participants. By testing three moderators and with an assumed dropout rate of 25% [17,42,43], we would need to recruit 98 people to test our hypotheses. Therefore, a total of 100 patients will be recruited.

Statistical Analysis

Statistical analyses will be performed using SPSS version 27.0. Feasibility and acceptability will be analyzed by summarizing quantitative data from (1) clinician-reported recruitment rate, retention rate, and adherence to protocol using descriptive statistics; (2) weekly satisfaction surveys of individual and group activities; and (3) postintervention surveys of overall satisfaction and satisfaction with the web-based mode of intervention. Qualitative data from both the weekly and overall satisfaction surveys will be analyzed using conventional content analysis. Patient characteristics at baseline will be summarized using descriptive statistics.

The preliminary effectiveness of the IACP intervention will be examined using general linear mixed models, with changes in global EDE-A scores from baseline to the end of treatment as the primary outcome. Appropriate covariates (eg, number of attended sessions) and random factors (eg, therapist) may be added to the statistical model for exploratory analysis. Similar general linear mixed model analyses will be run for the secondary outcome measures (Table 3), comparing scores from the baseline to the end of treatment. Finally, general linear mixed models will also be used to study the moderating role of the level of attendance and other clinical and psychosocial factors such as age, length of illness, ED diagnosis (anorexia nervosa vs other types of ED), and family connectedness on the primary outcome (change in EDE-A scores from baseline to end of treatment).

Ethics Approval and Participant Safety

The Scientific Committee of the Sainte-Justine University Hospital Center Ethics Committee (FWA00021692), which was designated by the Quebec government (Ministère de la Santé et des Services Sociaux du Quebec) in Montreal, reviewed and approved the study protocol (project ID number: 2022-3925). Concerning the intervention itself, the risks involved are minimal and inherent to participating in therapy, such as being confronted with difficult information regarding one's own mental health, behaviors, attitudes, etc, which can lead to stress or anxiety. However, this is a part of the treatment process and is expected

to lead to positive therapeutic outcomes. The risks related to the evaluation of the intervention are minimal. There will be no inconveniences in terms of travel time and time spent responding to questionnaires other than that required for the participants' normal follow-up in the IACP. If participants disclose worrisome information in the questionnaires, especially those related to suicidal ideation, the clinical program coordinator (a clinical psychologist) will contact them promptly to provide appropriate support. The clinical program coordinator will refer the participants to the necessary services to ensure their safety. The participants will be notified in advance that the clinical program coordinator may disclose this information to their parents or caregivers. Risks related to data and information-sharing with the research team as well as the measures in place to maintain participant confidentiality (deidentification of all data, transfer of data via a secure email account, and data storage on secure hospital servers) will also be discussed with all participants and parents during the intake meeting with the clinical coordinator.

Results

Recruitment for the study and data collection will be conducted on a rolling basis from winter 2022 to fall 2023. The data analysis and manuscript writing are expected to be completed by the summer of 2024.

Discussion

Anticipated Outcomes

We anticipate that our study will demonstrate the feasibility of running an innovative hybrid (web-based and in-person) IACP for adolescents in a specialized ED clinic located in a tertiary care hospital in a large urban center. We also anticipate that the intervention will be acceptable to both participants and their parents. We anticipate that the intervention will lead to a reduction in ED psychopathology, and that greater levels of participation in the IACP will be associated with a greater reduction in symptoms. We anticipate that participants recruited to participate in the study will represent a subset of the youth population with EDs on the more severe end of the disease spectrum (as patients with less severe illnesses would be less likely to be referred to the specialized ED program by their treating physician). Therefore, we anticipate that most study participants will present with severe ED symptoms (as measured by the EDE-A), comorbid symptoms of anxiety and depression, and personality traits predisposing them to perfectionism and low self-esteem, as reported in the literature [106,107].

Future Implications

The IACP could represent a novel mode of treatment in terms of content, therapeutic approach, and mode of delivery, and would present important advantages for accessibility and patient-centered care, given its flexible and hybrid (in-person and web-based) nature. Indeed, the intent is to make the program as accessible as possible by removing barriers such as geographic distance and interference with school and family functioning. If the results of this study show that such an approach is feasible, acceptable, and preliminarily effective, the model can be easily applied at other sites or in a larger population for a few reasons. First, the initial and final assessments used standardized questionnaires with favorable psychometric properties in child and adolescent populations. Second, guidelines for individualized treatment module selection will be created, allowing clinical coordinators to use predefined threshold scores from baseline assessments to elaborate treatment plans. Similarly, guidelines for evaluating whether participants should participate in regular or extended programs will be created.

Strengths and Limitations

Our study protocol has several strengths. First, the outcome measures will be completely integrated into regular clinical evaluations of patients participating in the IACP. As such, participants and their families will not be required to spend any additional time participating in the study. Second, the novel hybrid model of treatment will facilitate the incorporation of sessions into families' schedules and is flexible and adaptable to individuals' living situations, favoring both participation in the IACP and study completion. Third, the treatment program will be individualized and tailored to each participant's needs. This will ensure that participants receive treatment that focuses on the most pressing issues related to their ED. Given the alignment of treatment modules and standardized pre- and postintervention questionnaires, data analysis is likely to capture the most salient changes in symptomatology. Fourth, building on expanding literature, a comprehensive battery of questionnaires and outcomes will allow for meaningful analyses of several contributing factors related to the treatment of EDs in adolescents by making optimal use of several validated questionnaires. Finally, participants with a broad range of ED diagnoses will be included to appropriately represent diverse symptom presentations.

This study has a few limitations. First, being a single-site study, recruitment will be limited to the number of patients receiving care at the study site, which may limit the final sample size and generalizability of our findings. However, it should be noted that the study will be conducted in the largest tertiary pediatric care hospital in Quebec, a Canadian province with a population of 8.5 million inhabitants. Therefore, the results of this study can be generalized to other sites in large North American urban centers. Second, the naturalistic trial design and individualized treatment approach will make it so that some of the analyses and conclusions may be impacted by external confounders (such as changes in primary treatment, seasonality, and external stressors). However, it will allow for a better understanding of the real-world feasibility and acceptability of this type of day treatment program for EDs in adolescents. Third, given the highly flexible and personalized nature of the IACP, it will not be possible to compare the feasibility and preliminary effectiveness of in-person vs web-based treatment modules. However, acceptability data (satisfaction questionnaires) may provide important clues to the participants' appreciation of the in-person and web-based components of the program. Finally, the short duration of follow-up in this project will not allow for long-term assessment of the effectiveness of treatment in reducing ED symptomatology. Future work may include

long-term follow-up of youth participating in the IACP, as well as more detailed analyses on the effectiveness of different components of the program (eg, in-person vs web-based modules).

Conclusions

Given the high incidence of EDs in the adolescent population and the important physical, psychological, and social impacts of these illnesses, research on scalable and adaptable treatment programs is crucial. Evaluating the feasibility, acceptability, and effectiveness of intensive ambulatory treatment delivered in a hybrid model is in line with this objective. Furthermore, the intervention we describe, using a hybrid and family-focused modular approach that adapts treatment to individual participants, has seldom been described in the existing literature. Despite its limitations, the findings of this study will help evaluate and refine our hybrid (in-person and web-based) IACP in real-life practice. It will also allow us to gain a better understanding of which patients could benefit from it the most. It is our hope that our study may help inform and improve the care of patients with EDs, both in our center and in other centers worldwide.

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KN and RD drafted the manuscript. LP designed the study, contributed to the study design, and revised the manuscript for important intellectual content. LB and NC conceptualized the study, supervised KN and RD, and revised the study for important intellectual content. NC obtained the funding for this study. All coauthors have reviewed the final version of the manuscript.

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Data Availability

Data sharing is not applicable to this study, as no data sets were generated or analyzed for the preparation of this manuscript.

Conflicts of Interest

Study sponsors, including the Sainte-Justine University Hospital Center Foundation, Foundation of Stars, and Bell Canada Let's Talk Foundation, were not involved in the conception, review, or approval of the manuscript. They are not involved in conducting the study and will not be involved in the analysis and interpretation of the study data.

Multimedia Appendix 1
Secondary outcome measures assessing comorbidities and eating disorder associated behaviors.
[DOCX File , 34 KB - resprot_v11i11e37420_app1.docx]

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Abbreviations

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ED: eating disorder
EDE-A: Eating Disorder Examination Questionnaire Adolescent version
EDE-Q: Eating Disorder Examination Questionnaire
IACP: Intensive Ambulatory Care Program

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Protocol

Psychotherapeutic and Psychiatric Intervention in Patients With COVID-19 and Their Relatives: Protocol for the DigiCOVID Trial

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Abstract

Background: The COVID-19 pandemic is negatively impacting the mental health of both patients with COVID-19 and the general population. As current guidelines are limiting in-person contacts to reduce the spread of the virus, the development of a digital approach to implement in psychiatric and psychological consultations is needed. In this paper, we present the DigiCOVID protocol, a digital approach to offer remote, personalized psychological and psychiatric support to former or current patients with COVID-19 and their relatives.

Objective: The main goal of this project is to evaluate the feasibility, acceptability, and usability of the DigiCOVID protocol. Furthermore, we also aim to assess the impact of the abovementioned protocol by means of pre-post changes in psychological clinical variables.

Methods: Participants undergo an initial telephonic screening to ensure inclusion criteria are met. Secondly, participants complete a video-assisted neuropsychological IQ test as well as web-based self-reports of health and general well-being. Participants are then assigned to a psychotherapist who offers 8 teletherapy sessions. At the end of the therapy cycle, the web-based questionnaires are administered for a posttreatment evaluation.

Results: As of April 2022, we enrolled a total of 122 participants, of which 94 have completed neuropsychological tests and web-based questionnaires.

Conclusions: Our study aims at testing the feasibility and preliminary efficacy of DigiCOVID, a remote telemedicine protocol for the improvement of psychological and psychiatric health in patients with COVID-19 and their relatives. To date, the approach used seems to be feasible and highly customizable to patients’ needs, and therefore, the DigiCOVID protocol might pave the way for future telepsychiatry-based interventions.

Trial Registration: ClinicalTrials.gov NCT05231018; https://clinicaltrials.gov/ct2/show/NCT05231018?term=NCT05231018&draw=2&rank=1

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KEYWORDS

telepsychiatry; telemedicine; COVID-19; mental health; digital mental health; digital support; clinical outcome; telehealth; psychiatric health; health intervention

Introduction

The COVID-19 pandemic caused by SARS-CoV-2 virus is an unprecedented event both for the general population and health care workers.

Northern Italy has rapidly emerged as one of the epicenters of the first COVID-19 outbreak. The hospital in which our trial was designed and implemented, the Fondazione Istituto di Ricerca e Cura a Carattere Scientifico (IRCCS) Ca' Granda Ospedale Maggiore Policlinico in Milan, was completely reorganized to face new cases in the intensive care unit, paralleled by a large-scale optimization of the entire health care system [1,2].

Current literature is focusing on the connections between COVID-19 and psychiatry, in particular concerning the development of posttraumatic stress disorder and related conditions in patients who contracted the disease [3]. Furthermore, evidence suggests that the pandemic itself might be a potential trigger for various other mental health diseases in the general population, with higher rates of psychological deterioration [4], a probable impact on the development of first episodes of psychosis [5], obsessive compulsive disorder [6], depression [7], anxiety [8], phobic behaviors [9], addictions [10], and general health care workers distress [11,12].

In such a historical moment, it appears of paramount importance to prevent rather than treat psychological distress with every possible means available despite the limitations associated with in-person visits, social distancing, and isolation [13,14]. In fact, current 'shelter-in-place' guidelines and restrictions implemented by the public health system to limit the diffusion of the virus are significantly reducing in-person psychological and psychiatric consultations [15]. On the 24th of March 2020, the Ministry for Technological innovation and Digitalization, the Ministry of Health, the National Institutes of Health, and the World Health Organization together published a formal invitation to use telemedicine technologies more thoroughly in clinical practice [16].

A multitude of digital approaches have been tentatively operationalized worldwide to meet clinical needs, with COVID-19 serving as a catalyst for a change in the way instruments are used daily in health care settings [17]. Telepsychiatry, an innovative approach that consists of remote consultations and evaluations for mental health symptoms, has become a reliable alternative to face-to-face assessments, thus adapting rather than succumbing to COVID-19 [18,19], and assisting those affected by the psychosocial consequences of the pandemic [20].

Aside from patients with COVID-19, the psychological aftermath of this pandemic to a similar degree interests those who have not contracted the virus but have clinical conditions to manage, have lost family members or peers, are unable to enjoy the physical presence of their families, and have been living in restricted conditions for months. This phenomenon is likely due to the general psychological impact of the pandemic event per se and the systemic modifications in family relationships, with high amounts of stress also in healthy relatives [21,22]. Incidence and prevalence of psychological distress have been skyrocketing beyond the possibilities of any mental health system to intervene with in-person services. This segment of the population has profound unmet clinical needs and increasingly requests access to psychiatric services.

In this paper, we aim to describe DigiCOVID, a digital mental health protocol designed to offer remote, personalized support to former or current patients with COVID-19 and their relatives. DigiCOVID includes psychotherapy sessions and psychiatric consultations depending on participants' needs. An observational longitudinal study in patients with COVID-19 and their relatives is being conducted to investigate whether the intervention described above is feasible, usable, and acceptable for the target population. Outcome measures include engagement rates with psychotherapy sessions and psychiatric consultations, overall program completion rates, reported adverse effects, usability ratings, and clinician burden. The secondary objectives aim to (1) evaluate whether DigiCOVID induces changes in self-reports of anxiety, depression, insomnia, trauma, and quality of life and (2) determine whether DigiCOVID impacts patients with COVID-19 and their family members differently.

Methods

Overall Design and Timeline

The study is conducted jointly by the units of pneumology, internal medicine, psychiatry, and the laboratory of brain injury and therapeutic strategies of the Istituto di Ricerche Farmacologiche Mario Negri. Before accessing DigiCOVID, participants are taken through the following steps: first, participants undergo an initial screening to ensure the main inclusion criteria are met. Then, 2 trained neuropsychologists remotely perform neuropsychological tests on patients via Zoom. The tests are aimed at assessing patients' IQ through the Test di Intelligenza Breve (Italian for brief intelligence test) [23] and standard progressive Raven matrices [24]. Suicidality is assessed via the Columbia Suicide Severity Rating Scale [25]. Finally, participants complete a battery of web-based self-reports that include the following: the 12-item General Health Questionnaire [26], the Impact of Event Scale–Revised [27], the 7-item General Anxiety Disorder assessment [28], the Insomnia Severity Index [29], and the 9-item Patient Health Questionnaire [30]. After

completing these assessments, participants are assigned to a trained psychotherapist who offers 8 teletherapy sessions carried out through Zoom.

This model is designed to be applied to patients with COVID-19 during hospitalization, after discharge, as well as during the remission and recovery phases. Similarly, this model is intended to be delivered to people who are dealing with the hospitalization or discharge after COVID-19 of a family member or have lost a family member due to COVID-19. A total of 8 remote, 50-minute, individual psychological sessions are offered weekly using secure videoconferencing software. The severity of the clinical conditions of patients with COVID-19 has largely influenced the sequencing of the intervention.

During all phases of the clinical work, suffering is contextualized both in the light of the recent traumatic experience (eg, bereavement, hospitalization in intensive care, and fear for one's life or that of a relative) and in the light of historical ways of suffering, so that the patient is able to recognize the meaning of the symptoms experienced.

We considered it appropriate to circumscribe the exploration of different psychological targets within each session, given the unpredictable nature of the course of illness and the possible onset of events that radically change the psychological state of patients and family members. What follows is a very schematic summary that refers to the 'ideal' situation, where clinical conditions (of the patient or of the relative of the patient) evolve linearly toward recovery.

Session 1 includes introductions, the exploration of the patient's current experience, identification of the areas of suffering, and a brief recapitulation of the patient's pre–COVID-19 psychological functioning. Session 2 attempts to define shared goals for the therapeutic process and creates an initial diagnostic framework to identify unprocessed or unregulated emotions. Session 3 aims to validate the intrapsychic and interpersonal resources associated with a greater degree of adaptation to the stressful situation, including a flexible personality; positive beliefs about the self; identity roles, acceptance, and commitment skills; work functioning; and a solid network of friends, family, or loved ones. In sessions 4 through 6, areas of clinical concern are addressed, and defense mechanisms are investigated. Session 7 aims to integrate the lived experience in the cohesive narrative of the self. In session 8, internal working models or relational patterns that have emerged during therapy closure are discussed, and psychoeducation on relapse prevention is offered. At the end of the abovementioned cycle, participants repeat the battery of web-based self-reports.

This paper follows the SPIRIT guidelines for the trial's publication, as suggested by the EQUATOR Network. The trial is registered on ClinicalTrials.gov (NCT05231018). Of note, the protocol has been registered as it was designed at the beginning of the project, that is, it did not include relatives but only patients. Given the high number of requests, and because the intervention is customizable to each patient's clinical needs, we have decided to extend our intervention to relatives, thus explaining the differences between the registered protocol and this methodological paper. Regarding the gap between the registration and the trial start, the internal organization of our research unit does not require the registration of trials that do not involve drugs and placebos. Therefore, the trial has been registered on ClinicalTrials.gov to improve the recruitment process.

Study Population

Our population of interest includes patients with COVID-19, either previously or currently hospitalized at the Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, and their relatives, according to our inclusion and exclusion criteria.

Inclusion Criteria

The inclusion criteria for our study are as follows: (1) age 18-80 years; (2) a positive COVID-19 test at the moment of enrolment for participants in the 'patients' group; (3) adequate sensory and motor abilities, without impairments in vision and hearing or handling devices; (4) access to wireless internet technologies; and (5) a good level of Italian in terms of speaking, reading, and writing.

Exclusion Criteria

The exclusion criteria for this study are the following: (1) present or past medical history of schizophrenia, schizoaffective disorder, delusional disorder, bipolar disorder, or current substance abuse, all according to the Diagnostic and Statistical Manual Fifth Edition [31]; (2) a diagnosis of cognitive impairment or dementia (eg, mild cognitive impairment, Alzheimer disease, or Parkinson disease); (3) intellectual disability defined by a total IQ <70 as obtained by the Test di Intelligenza Breve [23] or the standard progressive Raven matrices [24]; (4) severe present medical conditions that could interfere with participation; (5) present or past suicidal ideation or commitment; (6) significant impairment in the use of digital and technological devices, questionnaires and test completions, as well as comprehension, or lack of a compliant behavior in the earliest evaluations; and (7) being enrolled in other clinical trials assessing any psychological or experimental pharmacological treatment.

Recruitment

As of April 2022, 122 participants have been referred to the study. Participation is voluntary, and an extended informed consent form is signed before any evaluation, assessment, or voice and video call. Consent forms are collected remotely for those who have been discharged and are currently in remission and in person for those hospitalized in a COVID-19 ward of either pneumology, internal medicine, or infectious disease departments.

Primary and Secondary Outcome Measures

Primary Outcome Measures

Efforts will be made to assess all participants who have completed the minimum required intervention activities. For DigiCOVID, the minimum required intervention activities include attending psychotherapy sessions at least 4 times. As the main goal of this project is to evaluate the feasibility, acceptability, and usability of DigiCOVID, we will conduct an analysis of the following primary outcome measures in all intention-to-treat (ITT) participants:

- Assessment completion rate—based on our previous studies, we expect ≥80% of participants will complete the battery of web-based self-reports.
- Usability ratings obtained post DigiCOVID via a 7-point Likert scale questionnaire (ie, mean rating of all responses)—this is a brief and embedded poststudy questionnaire on program satisfaction, clarity, and perceived benefits. Participants will rate each sentence on the following 7-point Likert scale: 1=completely agree; 2=mostly agree; 3=somewhat agree; 4=undecided; 5=somewhat disagree; 6=mostly disagree; and 7=completely disagree. Based on our previous studies, we hypothesize exit survey ratings of at least ≥4.5 (SD 1.5) on the 7-point Likert scale items.
- Reported side effects (ie, raw score)—based on our previous findings, we expect 0 adverse events due to program use.
- Overall program completion rate—based on previous findings, we hypothesize full program completion in ≥70% study participants.

Secondary Outcome Measures

The secondary outcome measures will be collected at baseline and immediately after the treatment for all participants. We designed DigiCOVID to improve mental well-being. Therefore, we will measure the impact of the intervention by looking at pre-post changes in the following outcome measures: the 12-item General Health Questionnaire [26] , the Impact of Event Scale–Revised [27], the 7-item General Anxiety Disorder scale [28], the Insomnia Severity Index [29], and the 9-item Patient Health Questionnaire [30]. We expected to observe a significant improvement across all these secondary outcome measures $P<$ in both patients with COVID-19 and their family members. To verify these experimental hypotheses, we will conduct the analysis based on the preintervention (baseline) and postintervention data, using parametric and nonparametric statistical tests. The criterion for statistical significance is $P<.05$. Results with $P<.1$ will be described as trends.

Data Collection

The sources of the research material will consist of data collected through assessment visits and the DigiCOVID app, strictly for research purposes. Participants will be carefully screened for contraindications prior to participation. All intervention data are coded so as not to identify any given participant and be securely stored. Hard copy data from the neuropsychological tests will be stored in a locked file cabinet in a safe location with limited access by authorized personnel or on password-protected computers in locked offices. All data from this trial will be recorded on a secure, web-based software application designed to support data capture for research studies. To achieve robust and unbiased results, data will undergo a rigorous quality control process to ensure consistency in scoring, coding, and accuracy of data entry. Standard data quality procedures will be used, including double scoring, random spot checking of assessments, and electronic data capture. Additionally, 20% of all data folders will undergo a random audit every 3 months. The database will be designed to not allow illegal values in entry. Any outliers will be double-checked with the raw data for accuracy.

Data Analysis

There are 3 a priori defined analysis populations, including a primary analysis population, a secondary analysis population designed to compare effect sizes in populations with no missing data, and a population who completed all study visits. The 3 populations are as follows:

- ITT population: this is the a priori primary analysis population, defined as including all participants who attended at least 4 remote psychotherapy sessions.
- Intention-to-treat fully evaluable (ITT-FE) population: this is a secondary analysis population, defined as including all members of the ITT population who complete a postintervention visit. Note that a participant may complete a specific visit but have missing data for a test, in which case the participant is in the overall ITT-FE population but does not contribute data to the ITT-FE population for that visit (eg, the number of evaluable cases for a specific test on a specific visit may be smaller than the ITT-FE population for that visit because of missing data).
- Intention-to-treat completers (ITT-C) population: this is a secondary analysis population, defined as including all members of the ITT-FE population who complete all intervention sessions. Note that the ITT-C population is a strict subset of the ITT-FE population; a person who completes the treatment but does not complete the postintervention evaluation visit is not a member of the ITT-C population.

We also plan to perform different analyses in order to better describe the demographics of patients and relatives and to test whether there are significant differences in terms of response to our psychotherapy intervention.

Ethics Approval

This study was approved by our local Ethics Committee (IRCCS Ca' Granda Ospedale Maggiore Policlinico) on October 28, 2020 (protocol code 962_2020, 03/11/2020).

Results

This project has been funded by Fondazione Cariplo under Award number 2020-1366, in June 2020. As of April 2022, we enrolled a total of 122 subjects, of which 94 have completed neuropsychological tests and web-based questionnaires; data analyses are currently completed in terms of preliminary results, and we expect results to be published by the end of 2022.

Discussion

Expected Outcomes

This paper describes the methodology adopted to remotely assess and promptly treat psychiatric symptoms in a sample of patients with COVID-19 and their first-degree relatives. This digital approach is showing its innovation potential by helping to manage the psychological burden caused by the pandemic in patients with COVID-19 and their relatives.

We expect, as a prediction of our hypotheses, that the DigiCOVID protocol will result in a feasible approach; such a

claim is clearly a hopeful statement, yet it is based on the quick, efficient, and technological step procedure described earlier. In terms of descriptive statistics, we might observe slight differences in terms of symptoms between patients and relatives (ie, in the posttraumatic scale, which we expect to be higher in patients than in relatives). In conclusion, we also expect the DigiCOVID protocol to be effective for both patients and their relatives in diminishing psychological distress. Future directions might involve the standardization of the DigiCOVID protocol in COVID-19 wards, as part of a complete program for the treatment of patients with COVID-19 and participants who might not have the opportunity to move to see a professional if remote visits are not possible.

To date, we are completing the recruitment, and we are expecting future and conclusive analyses to determine the efficacy and effectiveness of the protocol.

Strengths

This project has several lines of innovation. First, the length of the intervention is in line with services routinely offered by the Italian National Health Service (8-week cycle of psychotherapy sessions), which makes the implementation of this remote approach feasible and acceptable. Second, thanks to the data from the self-reports collected before the intervention start, psychotherapists have the opportunity to rapidly customize treatment goals and spare time usually spent collecting past and current psychiatric history. Third, the remote psychological support offered to first-degree relatives can increase personal resources, positively impact the resources of the family, and reinforce familiar bonds, ultimately producing better psychological prognoses for patients. If proven successful and efficacious, this intervention protocol could be standardized and disseminated at a large scale, helping clinicians remotely treat psychological distress, thereby alleviating at large the mental health consequences of the COVID-19 pandemic.

Limitations

Some limitations have emerged as we operationalized this project. First, we observed a lack of motivation in some patients, likely caused by the remote technology-based approach. Second, even if telepsychiatry has been proven efficacious in assessing patients remotely, psychologists and psychiatrists are asked to adapt their methods of assessment, diagnosis, and treatment to new means of communication. The dissemination of this digital approach at a national level may require additional training for mental health professionals to ensure impact and effectiveness of this promising intervention.

Data Availability

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

Conflicts of Interest

None declared.

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Abbreviations

IRCCS: Istituto di Ricercar e Cura a Carattere Scientifico
ITT-C: intention-to-treat completers
ITT-FE: intention-to-treat fully evaluable
ITT: intention-to-treat

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Protocol

Validation of Prediction Rules for Computed Tomography Use in Children With Blunt Abdominal or Blunt Head Trauma: Protocol for a Prospective Multicenter Observational Cohort Study

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Abstract

Background: Traumatic brain injuries (TBIs) and intra-abdominal injuries (IAIs) are 2 leading causes of traumatic death and disability in children. To avoid missed or delayed diagnoses leading to increased morbidity, computed tomography (CT) is used liberally. However, the overuse of CT leads to inefficient care and radiation-induced malignancies. Therefore, to maximize precision and minimize the overuse of CT, the Pediatric Emergency Care Applied Research Network (PECARN) previously derived clinical prediction rules for identifying children at high risk and very low risk for IAIs undergoing acute intervention and clinically important TBIs after blunt trauma in large cohorts of children who are injured.

Objective: This study aimed to validate the IAI and age-based TBI clinical prediction rules for identifying children at high risk and very low risk for IAIs undergoing acute intervention and clinically important TBIs after blunt trauma.

Methods: This was a prospective 6-center observational study of children aged <18 years with blunt torso or head trauma. Consistent with the original derivation studies, enrolled children underwent routine history and physical examinations, and the treating clinicians completed case report forms prior to knowledge of CT results (if performed). Medical records were reviewed to determine clinical courses and outcomes for all patients, and for those who were discharged from the emergency department, a follow-up survey via a telephone call or SMS text message was performed to identify any patients with missed IAIs or TBIs. The primary outcomes were IAI undergoing acute intervention (therapeutic laparotomy, angiographic embolization, blood transfusion, or intravenous fluid for ≥2 days for pancreatic or gastrointestinal injuries) and clinically important TBI (death from

TBI, neurosurgical procedure, intubation for >24 hours for TBI, or hospital admission of ≥2 nights due to a TBI on CT). Prediction rule accuracy was assessed by measuring rule classification performance, using standard point and 95% CI estimates of the operational characteristics of each prediction rule (sensitivity, specificity, positive and negative predictive values, and diagnostic likelihood ratios).

Results: The project was funded in 2016, and enrollment was completed on September 1, 2021. Data analyses are expected to be completed by December 2022, and the primary study results are expected to be submitted for publication in 2023.

Conclusions: This study will attempt to validate previously derived clinical prediction rules to accurately identify children at high and very low risk for clinically important IAIs and TBIs. Assuming successful validation, widespread implementation is then indicated, which will optimize the care of children who are injured by better aligning CT use with need.

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KEYWORDS

pediatric trauma; intra-abdominal injury; traumatic brain injury; clinical prediction rules; emergency medicine

Introduction

Background

Traumatic brain injuries (TBIs) and intra-abdominal injuries (IAIs) are leading causes of death and disability in children aged >1 year [1]. More than 600,000 children who are injured are evaluated annually for IAI in US emergency departments (EDs), and approximately 25% undergo abdominal computed tomography (CT) imaging [2-4]. However, 90% of children undergoing abdominal CT do not have IAIs [5-7]. In addition, more than 650,000 children with blunt head trauma are evaluated for potential TBIs annually in US EDs; of these children, approximately 50% undergo cranial CT scans [2-4]. Fewer than 10% of imaged children, however, have TBIs on CT, which suggests the inefficient use of this technology [8,9].

For more than 2 decades, CT scanning has been the diagnostic imaging method of choice to detect IAIs and TBIs in children [10,11]. CT is highly accurate in diagnosing IAIs and TBIs, which decreases the level of clinical monitoring required and is an important factor in determining the need for surgical treatment [12,13]. CT scanning also presents risks to children from ionizing radiation [2,4,14-24]. The lifetime attributable risk of a solid cancer from 1 abdominal CT scan is estimated to be as high as 1 per 485 abdominal CT scans for children, whereas the risk of a solid cancer from cranial CT scans in children is estimated to be as high as 1 in 960 [4]. The appropriate use of CT, targeted to the population of children who are injured who would benefit from the test, is an area for quality and safety improvement.

Several professional societies and organizations have called for action to promote the judicious use of imaging in patient care [25], including recommendations to (1) perform only necessary CT examinations, (2) encourage the development and adoption of pediatric CT protocols, and (3) encourage the use of selective strategies for pediatric imaging. Our study addresses these issues directly by proposing to validate, in a large, diverse population, previously derived clinical prediction rules for children with blunt abdominal or head trauma.

Clinical prediction rule development has become an important research area aimed at helping clinicians optimize the decision-making process at the point of patient care [26-28]. ED clinicians support the development of prediction rules for determining the use of radiographic imaging after traumatic injuries [29,30]. Previously, clinical prediction rules to identify children with abdominal or minor head trauma (presenting Glasgow Coma Scale scores of 14-15) at high and very low risk of IAI undergoing acute intervention and clinically important TBI were developed in the Pediatric Emergency Care Applied Research Network (PECARN), with the goal of optimizing CT use [7,9]. However, a critical piece to rule implementation is multicenter validation [26], as the spectrum and evaluation of traumatic injuries varies between centers [31]. In the hierarchy of creation to implementation, prediction rules that have been derived but not validated are the lowest level of evidence (Level 4), and rules that have been broadly validated at multiple sites advance to Level 2 [26]. In this study, we aimed to externally validate these prediction rules and raise the level of evidence so that implementing the rules in clinical practice in all EDs is appropriate and subsequent impact studies can be performed.

Objectives

The objectives of the current study were to (1) validate the previously derived PECARN clinical prediction rule that accurately and precisely identifies children at near zero risk of IAIs undergoing acute intervention; (2) validate the previously derived PECARN clinical prediction rules that accurately and precisely identify children aged <2 years and those aged 2-18 years at near zero risk of clinically important TBIs; and (3) identify factors associated with CT use in children considered very low risk for IAIs or TBIs by the prediction rules. For the validation of both prediction rules, we planned the sample size to have sufficient power to ensure very narrow CIs around point estimates for the sensitivities and negative predictive values (NPVs) of the prediction rules.

Methods

Study Overview

This was a prospective, multicenter observational study of children aged <18 years who presented to the ED with blunt torso trauma or nontrivial blunt head trauma. The study was endorsed by the Clinical Translational Science Award

Emergency Care Translational Research Collaborative and was conducted at 6 of the participating hospitals in the network. The 6 sites are dedicated pediatric EDs with high volumes of pediatric trauma; 4 are in California and 2 in Texas. The goal was to validate previously derived and highly accurate prediction rules for IAI undergoing acute intervention and clinically important TBI in children.

Study Population

Inclusion and Exclusion Criteria

Children aged <18 years with blunt abdominal trauma, head trauma, or both presenting to the participating EDs were enrolled based on the same inclusion and exclusion criteria as the derivation studies. The specific criteria are listed in Textboxes 1 and 2 [7,9]. Patients with both blunt head and abdominal trauma were entered into *both* cohorts, as in both prior PECARN derivation studies [7,9]. In addition, we enrolled all eligible children whether or not CT scans were obtained. Due to ethical concerns, the use of CT scans was not mandated by the study protocol, but all patients were followed to detect outcomes, including SMS text messaging or telephone follow-up of those discharged home from the ED.

Textbox 1. Intra-abdominal injury (IAI) cohort inclusion and exclusion criteria.

Inclusion criteria

1. Aged <18 years
2. Blunt torso trauma resulting from a substantial mechanism of injury defined as [32,33]:
   - Motor vehicle collision >60 mph, ejection, or rollover
   - Automobile versus pedestrian or bicycle with automobile speed >25 mph
   - Falls >20 feet in height
   - Crush injury to the torso
   - Physical assault involving the abdomen
3. Decreased level of consciousness (Glasgow Coma Scale score <15) in association with blunt torso trauma
4. Blunt traumatic event, regardless of the mechanism, with either extremity paralysis or multiple long bone fractures at multiple sites (eg, tibia and humerus fracture)
5. History and physical examination suggestive of IAI following blunt torso trauma of any mechanism (including mechanisms of injury of less severity than mentioned above), including any abdominal imaging (computed tomography or focused assessment with sonography for trauma), chest and pelvis radiographs, or laboratory screening for IAI

Exclusion criteria

1. Penetrating trauma
2. Preexisting neurological disorders seriously confounding physical examination assessment (eg, profound mental retardation or cerebral palsy)
3. Traumatic injury occurring more than 24 hours prior to the time of presentation to the emergency department
4. Transfer of the patient to the participating center from an outside facility with prior abdominal computed tomography imaging
5. Strong suspicion that the injury was the result of child abuse (eg, skeletal survey ordered)
6. Known pregnancy
7. Prisoner

Textbox 2. Traumatic brain injury (TBI) cohort inclusion and exclusion criteria.

Inclusion criteria

1. Aged <18 years
2. Nontrivial minor blunt head trauma (defined by Glasgow Coma Scale [GCS] scores of 14-15 at emergency department presentation)
    - Cranial computed tomography performed following trauma were assumed to have nontrivial minor blunt head trauma for the purposes of inclusion in this cohort.

Exclusion criteria

1. Children with trivial mechanisms of injury defined by falls from ground level, or walking or running into stationary objects, *and* the lack of any signs or symptoms of head trauma or the presence of scalp lacerations or abrasions alone
2. GCS score <14, except for those who had a posttraumatic seizure and the postrecovery GCS score was 14-15
3. Penetrating trauma (eg, gunshot or knife wounds)
4. Preexisting neurological disorders seriously confounding physical examination assessment (eg, substantial mental retardation or cerebral palsy)
5. Preexisting ventriculo-peritoneal or ventriculo-atrial shunts (or similar devices)
6. Traumatic injury occurring more than 24 hours prior to the time of presentation to the emergency department
7. Transfer of the patient to the participating center with prior cranial computed tomography or magnetic resonance imaging
8. Preexisting brain tumor or history of a bleeding disorder (eg, hemophilia and von Willebrand disease)
9. Strong suspicion that the injury was the result of child abuse (eg, skeletal survey ordered)
10. Prisoner

Clinician Survey Inclusion Criteria

A survey of the clinicians providing initial evaluation and care to eligible patients at each participating site was conducted prior to study participation (see below). In this survey, we queried clinicians about perceptions and the frequency of use of prediction rules. As new faculty or fellow clinicians were hired at participating sites, they received the survey prior to study participation.

Study Procedures

ED Data Collection

Children enrolled in the study underwent history and physical examinations per standard clinical care. The emergency clinician providing care (eg, emergency medicine attending physician, pediatric emergency medicine attending clinician, or trauma surgeon) was prompted to complete the standardized case report form (Multimedia Appendix 1) *prior* to knowing the results of diagnostic testing or imaging results (if performed) to avoid observation bias. This clinician then collected and recorded the limited number of variables that constituted each prediction rule (Textbox 3) [7,9]. In addition, clinicians self-reported their unstructured suspicion for the risk of IAI or TBI for all patients and the indications for imaging in those who underwent CT imaging. Only one case report form was completed for each patient.

Textbox 3. Prediction rule variables for intra-abdominal injury and traumatic brain injury.

Intra-abdominal Injury Prediction Rule Variables

- Does the patient complain of abdominal pain?
- Has the patient vomited since the time of injury?
- Is the patient's Glasgow Coma Scale (GCS) score <14?
- Does the patient have absent or decreased breath sounds?
- Does the patient have any thoracic wall trauma? (eg, erythema, abrasions, ecchymosis, subcutaneous air, or laceration)
- Does the patient have any abdominal wall trauma? (eg, seatbelt sign, erythema, abrasions, ecchymosis, subcutaneous air, or laceration)
- Does the patient have abdominal tenderness?

Traumatic Brain Injury Prediction Rule Variables, Aged <2 Years

- Does the patient have a GCS score <15 or altered mental status? (eg, slow to respond, agitation, sleepiness, confusion, or repetitive questioning)
- Does the patient have a nonfrontal scalp hematoma?
- Was there a loss of consciousness ≥5 seconds?
- Does the patient have a palpable skull fracture or is it unclear due to scalp swelling?
- Is the patient acting abnormally per the parent or guardian?
- Was there a severe mechanism of injury? (defined as motor vehicle crash with patient ejection, death of another passenger, or rollover; pedestrian or bicyclist without helmet struck by a motorized vehicle; fall >3 feet; or head struck by a high-impact object [substantially heavy object struck head, baseball, horse kick, etc])

Traumatic Brain Injury Prediction Rule Variables, Aged 2-18 Years

- Does the patient have a GCS score <15 or altered mental status? (eg, slow to respond, agitation, sleepiness, confusion, or repetitive questioning)
- Was there a loss of consciousness?
- Has the patient vomited since the injury?
- Are there clinical signs of basilar skull fracture?
- Does the patient have a severe headache (score of 8 or greater out of 10)?
- Was there a severe mechanism of injury? (defined as motor vehicle crash with patient ejection, death of another passenger, or rollover; pedestrian or bicyclist without helmet struck by a motorized vehicle; fall >5 feet; or head struck by a high-impact object [substantially heavy object struck head, baseball, horse kick, etc])

For the TBI cohort, the rule variables were different for those aged <2 years versus those aged ≥2 years, as per the derivation study [9]. For the IAI cohort, complaints on patient history that required verbal skills (eg, abdominal pain) were recorded as "preverbal" for children aged <3 years. Completed case report forms were entered by the site research coordinator into Research Electronic Data Capture (REDCap; Vanderbilt University), a secure, Health Insurance Portability and Accountability Act (HIPAA)–compliant web application for building databases and managing web-based data for research [34].

Diagnostic imaging was performed at the discretion of the emergency clinician caring for the patient, with instructions to complete the case report form before knowledge of CT imaging results. In the uncommon event that patient instability or other issues precluded recording study data prior to knowledge of the imaging results, the clinician was instructed to complete the case report form once the patient was stabilized. Based on our previous studies and the Glasgow Coma Scale eligibility criteria, we had anticipated that this scenario would occur infrequently. At a random interval and for a limited number of enrollments (approximately 250 enrollments for both the TBI and IAI cohorts, for a total of 500 enrollments), the study team collected whether any CT imaging was reviewed prior to completing study-related ED case report forms.

Diagnostic radiologic imaging examinations were performed according to each site's radiology protocol. Final interpretations of all CT and magnetic resonance imaging scans as well as angiographic studies were made by attending radiologists at each study site. With site principal investigator oversight, research coordinators identified all abdominal and cranial CT scans with any traumatic or nontraumatic abnormalities. The dictated CT scan reports of these abnormal CT scans were entered into the electronic database. Detailed data from these abnormal abdominal or cranial CT scans were then further abstracted by trained abstractors. Dictated reports for all magnetic resonance imaging and angiographic studies, regardless of the presence or absence of any abnormalities, were additionally uploaded into the database. For patients with radiologic reports containing the wording "questionable" or "possible," we relied on the treating clinicians' determinations.

Patient Follow-up Procedures

The guardians of enrolled patients were provided an information sheet about the study. This information sheet notified the guardians of patients discharged from the ED that they would be contacted by telephone or SMS text messaging by the research coordinator from 1 week to 3 months after the initial ED visit. The research coordinator followed scripted survey instructions to document any possible missed IAIs that underwent acute intervention or clinically important TBIs. If an SMS text response was received that indicated the patient had a subsequent visit with a clinician related to the ED visit–associated abdominal or head injury, the research coordinator attempted to reach them by telephone or text to complete the additional questions on the survey.

When unable to contact the patient's guardian after 4 telephone or SMS texting attempts extending to 3 months after the initial ED visit, we proceeded with alternative follow-up measures. We reviewed the patients' medical records to ensure that no patients discharged from the ED and in whom telephone follow-up attempts had failed were subsequently diagnosed with an IAI, a TBI, or died in the weeks after the ED visit. If such an event was discovered, we collected all data involving the missed injury or death and had the etiology of the outcome adjudicated by a 3-member panel blinded to the ED presentation.

For patients who were hospitalized, data from the medical record were collected to determine outcome status. No telephone or SMS text messaging contact was attempted for these patients. We recorded the results of all imaging studies of interest obtained during the hospitalization. Patients were hospitalized at the discretion of the clinician(s) providing initial care, according to the standard practices of each site.

Missed Eligible Patients

Based on our previous experience [7,9], we had anticipated that approximately 80% of eligible patients would be enrolled; however, some eligible patients would inadvertently be missed. These patients were identified by electronic ED patient log review, and basic information about these missed eligible patients was documented on a separate case report form to allow for general comparisons between enrolled and missed patients and potential enrollment bias.

Survey of ED Clinicians

We surveyed the clinicians providing care at each study site prior to and during the enrollment of the study. This survey was performed to evaluate clinicians' assessment of how well clinical predication rules perform, their knowledge of the rules, and how frequently they implemented these rules in practice. In this survey, we also collected basic information on clinician demographics, clinical experience, and current board eligibility or board certification. Responses were collected through an institutional review board (IRB)–approved survey accessed via a unique link in a scripted email notice sent out to each clinician through a REDCap database. Survey results were assigned an identification number unique to each clinician and entered into each case report form the clinician completed. Records linking the identification numbers and the clinician names were maintained by the research coordinator at the respective participating institutions to protect the clinician's privacy and identifying information from the site investigators. In this way, we evaluated clinician characteristics associated with patients who had no PECARN risk factors for IAI undergoing acute intervention or clinically important TBI but who nonetheless underwent CT imaging.

Study Outcomes

IAI Cohort Outcome Measure

Our primary outcome for the IAI cohort was IAI undergoing acute intervention [7]. An IAI was defined as any injury to the spleen, liver, urinary tract (kidney to bladder), pancreas, gastrointestinal tract (stomach to sigmoid colon including the mesentery), gallbladder, adrenal gland, or vascular structure or fascial defect (traumatic abdominal wall hernia). IAI undergoing acute intervention was defined as an IAI with any of the following: (1) therapeutic intervention at laparotomy (ie, necessary abdominal surgery); (2) angiographic embolization of a bleeding abdominal organ or other abdominal vascular structure; (3) blood transfusion for anemia due to intra-abdominal hemorrhage from an IAI; (4) administration of intravenous fluids for ≥2 nights to maintain hydration in patients unable to eat or drink in patients with pancreatic or gastrointestinal injuries; or (5) death due to the IAI.

TBI Cohort Outcome Measure

Our primary outcome for the TBI cohort was clinically important TBI [9]. TBI was defined as any extra-axial hematoma (subdural or epidural); subarachnoid hemorrhage; intraventricular hemorrhage; intraparenchymal hemorrhage or contusion; cerebral contusion, hemorrhage, or hematoma; cerebral edema; traumatic infarction; midline shift; herniation; venous sinus thrombosis; pneumocephalus; skull diastasis; shear injury; subpial hemorrhage; or skull fracture depressed by at least the table width of the skull. Clinically important TBI was defined as a TBI with any of the following: (1) neurosurgery for treatment of the TBI; (2) endotracheal intubation >24 hours for the TBI; (3) hospitalization of ≥2 nights for the head injury in association with TBI on CT; or (4) death due to the TBI.

Statistical Analysis Plan

Statistical Analysis

We conducted separate analyses for the following specific aims: (1) validation of the IAI prediction rule; (2) validation of the 2 age-specific TBI prediction rules; and (3) measurement of interrater agreement of each of the clinical prediction rules. We assessed the accuracy of the rules by measuring the rule classification performance, using standard point and CI estimates of the operational characteristics of each prediction rule (sensitivity, specificity, positive predictive values, NPV, and diagnostic likelihood ratios).

For the IAI cohort, we aimed to validate the previously derived clinical prediction rule that accurately and precisely identifies children at near zero risk of IAIs undergoing acute intervention. The NPV of this rule must be nearly 100%, and sensitivity greater than 95%. For the TBI cohort, we aimed to validate the previously derived age-stratified clinical prediction rule that accurately and precisely identifies children at near zero risk of

clinically important TBIs. The NPV of these rules must be nearly 100%, and sensitivity above 95%.

The statistical analyses and sample size requirements for the prediction rules were similar. Comparisons of specific characteristics (eg, age, sex, rate of IAI undergoing acute intervention, rate of clinically important TBI) of enrollees to nonenrollees were performed to detect potential enrollment biases.

Sample Size Estimates

Considering the consequences of false negative results, we specified that the validation of each prediction rule would need to meet 2 requirements: (1) that the exact 1-sided 95% binomial CI for the NPV lie above 99.5% and (2) that the point estimate of sensitivity was at least 95%. We designed the study to provide at least 80% power for achieving the NPV requirement if the true NPV (as per the derivation studies) was at least 99.8% and to provide at least 90% power to achieve the sensitivity requirement if the true sensitivity (as per the derivation studies) was at least 98%. Exact binomial test power calculations using SAS statistical software (SAS Institute) indicated that a sample of at least 2360 patients with rule negative results provided at least 80% power for the NPV requirement and that a sample of 55 patients with the outcomes of interest provided at least 90% power to satisfy the sensitivity requirement.

In the derivation studies, 25.6% of children with IAIs had IAI undergoing acute intervention (primary outcome) and 54.3% with TBIs on CT had clinically important TBI (primary outcome) [7,9]. Annually, each of the participating sites provide care for approximately 208 eligible patients per year with IAIs, 112 eligible patients aged 2-18 years with TBIs on CT, and 44 eligible patients aged <2 years with TBIs on CT. With these rates and an estimated enrollment rate of 80% of eligible patients, we anticipated enrolling 128 patients with IAIs undergoing acute intervention, 146 patients aged 2-18 years with clinically important TBIs, and 57 patients aged <2 years with clinically important TBIs. Thus, we anticipated meeting the sample size for the study's sensitivity requirements.

Therefore, we ultimately anticipated enrolling more than 20,000 children with blunt head trauma and 7500 children with blunt abdominal trauma. Since at least 20% of children with head trauma also have abdominal trauma [9], we anticipated enrolling nearly 24,000 patients (including patients with isolated head, isolated abdomen, or both head and abdominal trauma) to meet the sensitivity sample sizes required for the validation of both the IAI and TBI prediction rules. Given the above calculations and the expected number of patients with blunt head and abdominal trauma, we estimated approximately 36-39 months of patient enrollment (and budgeted 42 months to ensure meeting sample size requirements). Therefore, with these estimates, the sample would allow a definitive assessment of the validity of the IAI clinical prediction rule and the 2 age-stratified TBI clinical prediction rules.

Based on anticipated enrollment rates to meet the study's sensitivity requirements, 3200 patients enrolled into the IAI study would be negative for the IAI prediction rule (42% of enrolled patients would be negative for the rule based on prior data) [7]. For the TBI age cohorts, we anticipated enrolling 8600 patients aged 2-18 years with negative results for the TBI rule (59% of enrolled patients would be negative for the rule based on prior data) and 3000 patients aged <2 years would be enrolled who are negative for the prediction rule based on prior data [9]. Thus, we would have more than ample patients to meet the NPV sample size requirements.

Interrater Reliability of the Clinical Prediction Rules

The usefulness of ED clinical prediction rules greatly depends on the reliability (reproducibility of findings) of patient history and physical examination variables [27,28], which we had already measured with great precision for the individual predictors in both rules [35,36]. In this study, however, we estimated Cohen κ for each clinical prediction rule as a whole (ie, clinician agreement that the patient is positive or negative for the prediction rule) and used it to assess the null hypothesis that the true κ value was no higher than 0.6. ED clinicians at the participating sites who were not responsible for the care of the patient performed an independent clinical assessment on a convenience sample of eligible patients (within 60 minutes of the first assessment) to fulfill the interrater reliability assessment of the prediction rule. We specified this to be an asymptotic 97.5% 1-sided CI for Cohen κ that lies strictly above 0.6. The clinicians performing this second assessment were unaware of the results of the initial assessment. We specified that a true κ of 0.7 was important to be able to detect with at least 90% power. For the IAI rule, where we anticipated that 55% would be considered rule-positive by each rater, a conservative power calculation using the approach by Cantor [37] indicated that a sample of 680 patients (each assessed by 2 raters) would satisfy the stated requirements (at least 90% power to detect a true κ of 0.7 under 1-sided testing with α=2.5%). Similarly, for the TBI rule, based on our prior study, we anticipated that 42% of the sample would be considered rule-positive, and a sample of 680 patients would satisfy the stated requirements.

Ethics Approval

This study was conducted in compliance with IRB and HIPAA regulations. The University of California Davis IRB served as the central IRB for the study (920170).

Patient Consent and Data Security

The study involved minimal risk to patients, families, and participating clinicians. Since the initial enrollment of patients was conducted under a waiver of informed consent, we ensured the protection of the privacy interests of the patients by only discussing with the patient's treating team when completing the data collection activities in the ED. For those patients where telephone or SMS text message follow-up contact was planned, verbal consent and an information sheet were provided to the guardians in the patient's ED rooms to ensure that their participation in the study remained private. When conducting any follow-up telephone calls or SMS text messaging, we verified that we were speaking to the correct individual before going into the details of the study. For the SMS text message follow-up portion of the study, we used the StudyPages program (Yuzu Labs PBC), which is a HIPAA-compliant, participant recruitment and engagement platform for clinical research that

enables and facilitates secure communication and data transfer between participants and the study team. Clinicians who were eligible for the survey portion of this study were emailed a link to the survey, which allowed them to complete the survey in a location of their choosing, thus protecting their privacy.

Results

The project was funded in 2016. Patient enrollment began on December 28, 2016, and was completed on September 1, 2021. Patient enrollment was extended due to the COVID-19 pandemic. The COVID-19 pandemic resulted in an initial halt to all non–COVID-19 research activities at participating study sites, after which study enrollment resumed until completion. As of September 1, 2021, over 7500 patients were enrolled in the IAI cohort, over 20,000 patients were enrolled in the TBI cohort, and over 4700 patients were enrolled in both. Additionally, over 450 clinicians were enrolled in the clinician survey. Data clean-up and analyses are projected to be completed by December 2022, and the results are expected to be submitted for peer-reviewed publication in 2023.

Discussion

We expect this large, multicenter prospective cohort study to successfully validate previously derived, highly sensitive, and specific prediction rules for the evaluation of children in the ED following blunt abdominal or head trauma. With the completion of this study, and assuming successful validation, these prediction rules can undergo widespread implementation. Clinician use of these rules will improve care and encourage scientifically based clinical decision-making in pediatric trauma care. Potential reductions in the frequency of CT scanning will not only lead to safer care but also substantial cost savings. These validated rules could also increase efficiency in care by decreasing false positive results and costs associated with the care of future malignancies in those inappropriately imaged with CT.

The evaluation and treatment of patients in the ED is prone to inefficiencies and errors. This is in great part due to the clinical uncertainties of rapidly caring for patients who are acutely injured and the limited patient history and clinical data available to clinicians practicing in the ED setting. Clinical prediction rules help ED clinicians reduce the diagnostic and therapeutic uncertainties inherent to that setting [28]. The validation of these rules in a large, diverse population will provide clinicians with the definitive evidence to accurately and safely use CT scans in children at risk of substantial injuries while avoiding unnecessary CT scans [26]. This will decrease both the rates of errors of omission and commission. The validation and implementation of these prediction rules will improve child health outcomes through the support of evidence-driven practice for the evaluation of children who are injured.

The IAI prediction rule has not been previously validated in a prospective study. Several retrospective validations of the IAI rule exist, suggesting a prospective validation is likely to be successful [38-40]. Several prospective studies validating the PECARN TBI rules have been performed [41-46]. These studies that vary widely in sample size have indicated that the TBI rules consistently perform accurately.

The strengths of our study include the large, multicenter cohort from a geographically diverse set of EDs and rigorous methodology applied to the study design. The limitations of our study include that CT scans were not obtained for all children. However, we followed patients after their visits to ascertain any missed injuries. Additionally, we did not include community or rural EDs; however, previous research has shown applicability in these other settings [47,48].

Overall, this prospective cohort study was designed to validate previously derived prediction rules for the evaluation of children in the ED following blunt abdominal or head trauma. With implementation, this will result in improved care delivery for children who are injured. Future studies should focus on impact analyses of the prediction rules once successfully implemented.

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Data Availability

All data obtained during the study will be placed in a database for future use after being stripped of identifiers. Deidentified data will be reposited within the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Data and Specimen Hub, a centralized resource for researchers to store deidentified data and to access data and associated biospecimens from NICHD-supported studies for use in secondary research [49].

Conflicts of Interest

None declared.

Multimedia Appendix 1
Emergency department case report data collection form.

[PDF File (Adobe PDF File), 195 KB - resprot_v11i11e43027_app1.pdf]

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Abbreviations

CT: computed tomography
ED: emergency department
HIPAA: Health Insurance Portability and Accountability Act
IAI: intra-abdominal injury
IRB: institutional review board
NPV: negative predictive value
PECARN: Pediatric Emergency Care Applied Research Network
REDCap: Research Electronic Data Capture
TBI: traumatic brain injury

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Protocol

Combining the HYM (Healthy Young Men's) Cohort Study and the TRUTH (A Trans Youth of Color Study): Protocol for an Expanded Mixed Methods Study Renewal

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Abstract

Background: As we enter the fifth decade of the AIDS epidemic, health researchers and AIDS activists reflect both on the progress that has been made and the importance of continued prevention efforts for those most at risk. As HIV infection rates continue to fluctuate across communities, a trend has emerged with new HIV infections becoming increasingly concentrated—with cascading effects—among people aged <30 years, from marginalized racial and ethnic groups, and who are sexual or gender minorities.

Objective: In this paper, we discuss the renewal of the Healthy Young Men's (HYM) Cohort Study and the addition of a subcohort—TRUTH: A Transgender Youth of Color Study. The overarching aim of our renewed study was to inform new intervention strategies; understand linkage to care; and examine changes over time with respect to minority-related stress and intersectional identities and their relationship with substance use, mental health, and HIV risk. Findings from this study will help to inform the development of new interventions designed to engage African American and Black and Latino young men who have sex with men (YMSM) and transgender and gender minority youth in the HIV prevention and care continua and to reduce risk by addressing pathways of minority-related stress and intersectional stigma.

Methods: Longitudinal study (baseline and follow-up assessments every 6 months for a total of 8 waves of data collection) is ongoing with reconsented cohort from the last iteration of HYM Cohort Study. This study protocol includes self-report survey, collection of urine to assess recent use of illicit drugs, and collection of blood and rectal and throat swabs to test for current sexually transmitted infection and HIV infection. An additional sample of blood and plasma (10 mL for 4 aliquots and 1 pellet) is also collected and stored in the HYM Cohort Study biorepository for future studies. This mixed methods study design includes collection of triangulated analysis of quantitative, qualitative, and biological measures (ie, drug use, sexually transmitted infection and HIV testing, and adherence to antiretroviral therapy among participants who are HIV+) at baseline and every 6 months.

Results: As of February 2022, participants from the past 4 years of the HYM Cohort Study and TRUTH: A Transgender Youth of Color Study Cohort have been reconsented and enrolled into the renewal period of longitudinal data collection, which is projected from summer of 2020 until summer of 2025. Recruitment is ongoing to reach our target enrollment goal of YMSM and transgender minority youth.

Conclusions: The findings from this study are being used to inform the development of new, and adaptation of existing, evidence-based HIV prevention interventions designed to engage populations of transgender and gender minority youth and YMSM in the HIV prevention and care continua.

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KEYWORDS

young men who have sex with men; HIV prevention; intersectionality; gender-nonconforming; multiple stigma

Introduction

Disparities With HIV in the United States

The US Department of Health and Human Services has proposed an end to the HIV epidemic in the United States by 2030; this will require flexible, yet targeted, strategies that successfully segment people based on age, demographic characteristics, and location. As HIV infection rates continue to fluctuate across communities, a trend has emerged with new HIV infections becoming increasingly concentrated—with cascading effects—among people aged <30 years, from marginalized racial and ethnic groups, and who are sexual and gender minorities [1,2].

Young men who have sex with men (YMSM) account for most new HIV infections each year. Recent data highlight that, in 2018, 21% of new HIV diagnoses were in people aged between 13 and 24 years, of whom 92% reported male-to-male sexual contact as their mode of HIV infection [3]. These numbers are even more alarming among YMSM of color. Of all new HIV cases among African American and Black men, 20% occur in those aged 13 to 24 years, and 39% occur in those aged between 25 and 35 years [4]. Furthermore, although overall infection rates decreased among the general Latino population from 2005 to 2014, new infections among Latino YMSM aged between 13 and 24 years increased by 87% [5]. Although the overall incidence of HIV infection has decreased in the United States, disparities among youth, particularly African American and Black and Latino YMSM, persist [6,7].

YMSM and HIV Risk Profiles

The burden of HIV among YMSM is rooted in the interaction of social, economic, and demographic inequities that enhance their risk for HIV. YMSM report more difficulty in accessing health care, anticipated mistreatment from health care providers, and frequent experiences with stigma, which may lead to psychosocial challenges such as increased substance use and involvement in high-risk behaviors [6,8,9]. YMSM of color are especially vulnerable to multiple forms of stigma (eg, discrimination, racism, family rejection, and homophobia) that are influenced by their race, ethnicity, or sexual identity and interact to produce unique HIV risk profiles for individuals [10-12]. For example, African American and Black YMSM report high levels of institutionalized and sexualized racism and discrimination, which puts them at increased risk for internalized homophobia, maladaptive coping, and other mental health issues, which are further associated with illicit drug use and sexual risk taking [13-15]. Among Latino YMSM, who experience great demands to meet traditional gender roles, *machismo* is associated with elevated rates of unprotected sex [16,17].

Stigma also affects YMSM's engagement in and adherence to the HIV prevention continuum—by discouraging them from accessing information, preventing them from getting tested, and hindering their access to breakthrough biomedical interventions [18]. For example, uptake of pre-exposure prophylaxis (PrEP), a daily regimen of 2 oral antiretroviral drugs taken as a single pill that has been proven to be up to 97% effective in reducing the risk of acquiring HIV [19], is lowest among youth despite their demonstrated need [6,20]. Compared with men who have sex with men (MSM) in general, YMSM are less aware of their HIV serostatus, less likely to engage in and adhere to antiretroviral therapies (ARTs), and less likely to use PrEP; uptake is at 9.4% among YMSM and 19.9% for all MSM [21,22].

Furthermore, African American and Latino YMSM are 2 subgroups with the least likelihood of engaging in PrEP [23,24], suggesting that the efficacy of current HIV prevention efforts is reduced in YMSM who are burdened by multiple forms of co-occurring stigma [7,18].

Transgender Minority Youth and Increased Risk for HIV

Compared with YMSM, transgender and nonbinary youth of color, or transgender and gender minority youth (TGMY), experience high levels of multiple forms of stigma (eg, low income, isolation, safety concerns, and discrimination) that place them at great risk for poor mental health, depression, suicidality (ie, ideation, plan, and attempt), physical and psychological violence, substance use, and HIV acquisition [7,25-29].

TGMY have varied gender identities that differ from their sex assigned at birth [30,31], and although the terminology used to describe TGMY communities is constantly evolving, TGMY generally includes youth who identify with a gender different from the sex assigned to them at birth or youth who express their gender identity in a way that diverges from the traditional male-female gender binary, such as genderqueer, gender-fluid, or nonbinary. TGMY communities also include sexual, racial, and ethnic minority youth.

Data around TGMY's HIV risk and health profiles remain limited, especially for young transgender men and nonbinary youth. This lack of information is reflected by few existing resources, which hinders TGMY's ability to negotiate safe sexual interactions with partners and communicate effectively with providers [7,32]. Health care providers also report a lack

of preparation to care for TGMY, and many institutions lack policies and routine practices to support the needs of gender minority patients [33,34]. In addition, in some nonprobability community samples of young transgender women, 25% to 43% of transgender women reported experiencing unstable housing or homelessness [35,36], 67% reported engaging in sex work [35], and 31% reported experiencing sexual violence in the past 12 months [37]. TGMY are 3 times more likely than YMSM to experience workplace discrimination [38], with traumatic experiences and suicidality being more prevalent among nonbinary and gender-nonconforming minority youth [27].

Furthermore, transgender adolescents are more likely to have ever had sex and less likely to have used a condom during their previous sexual experience than their cisgender peers [39]. TGMY are more likely to report first sexual intercourse at or before the age of 13 years, intercourse with ≥4 partners, substance use before sexual activity, and unprotected sex during the previous encounter [40]. Among transgender women and men who seroconverted between 2009 and 2014, 36% of transgender women and 23% of transgender men were aged between 13 and 24 years [26]. Taken together, these findings indicate that TGMY are more at risk for HIV infection than cisgender youth, including YMSM [40], and underlines the need for contextual understanding of the multiple forms of stigma faced by TGMY in relation to their HIV risk [32].

The Healthy Young Men's Cohort Study and TRUTH—A Transgender Youth of Color Study: Opportunities to Turn the Curve of the HIV Epidemic

Given the need to further understand the unique experiences of African American and Black and Latino YMSM and TGMY, we propose to build on existing studies and longitudinally examine how (1) YMSM and TGMY experience various forms of intersectional identities and stigma over time, as they age; (2) stigma and intersectionality drive risk for substance use, sexually transmitted infection (STI), HIV infection, and mental health and psychosocial disorders; and (3) stigma and intersectionality serve as barriers to engagement in the HIV prevention and care continua, with particular attention to PrEP and ART uptake and adherence. By examining these aims, we hope to identify when and for whom to target interventions aimed at specific determinants and mechanisms of health. This paper describes the protocol for the renewal of our Healthy Young Men's (HYM) Cohort Study to continue our research with the HYM and TRUTH: A Transgender Youth of Color Study (TRUTH) Cohorts.

In 2015, Children's Hospital Los Angeles was awarded a grant (U01DA036926) from the National Institute on Drug Abuse (NIDA) to recruit and longitudinally track a cohort of African American and Black and Latino YMSM to better understand how to engage this high-risk population in the HIV prevention and care continuum. With this grant, we launched the HYM Cohort Study and, in 2016, enrolled 448 African American and Black and Latino YMSM and collected 8 waves of data through assessments administered every 6 months from 2016 to 2020. In 2018, we received an administrative supplement to recruit and collect 2 waves of data for a new cohort of transgender, nonbinary, and gender-nonconforming youth. From this, we launched the substudy, TRUTH, which recruited 108 participants via social media and community referrals and collected 3 waves of data through assessments administered every 6 months from 2018 to 2020; study assessments for both HYM and TRUTH included survey data collection, STI and HIV testing, and drug screening every 6 months.

In 2020, our renewal application was awarded. For this next funding cycle (2020-2025), our study will focus on HIV risk and transmission for YMSM and TGMY through the lens of intersecting stigmatized identities, including sexual identity, gender identity, race, ethnicity, immigration status, financial hardship, HIV+ status, mental health, psychiatric disorders, and sex work or transactional sex.

Study Aims

Overview

The overarching aims of this study are to inform new intervention strategies; understand linkage to care; and examine changes over time with respect to minority-related stress and intersectional identities and their relationship with substance use, mental health, and HIV risk. Findings from this study will help to inform the development of new interventions designed to engage African American and Latino YMSM and TGMY in the HIV prevention and care continua and to reduce risk by addressing pathways of minority-related stress and intersectional stigma. The specific aims are the following:

Aim 1

Examine African American and Black and Latino YMSM's engagement in the HIV prevention and care continua and their developmental transitions and trajectories in drug use, STI and HIV infection, health, and psychiatric and mental health comorbidities. We will examine how intersectional stigma (ie, experiences of stigma stemming from multiple intersecting identities) both discourages African American and Black and Latino YMSM from engaging in care and influences their developmental arcs of risk, transmission, and health.

Aim 2

Examine TGMY's engagement in the HIV prevention and care continua and identify shared and unique transitions and trajectories regarding TGMY's use of drugs, STI and HIV infection, health, and psychiatric and mental health comorbidities. Of particular interest is how these processes are informed by experiences of stigma occurring at the intersection of their multiple, marginalized identities.

Aim 3

Serve as a local and national resource for collaborations and dissemination. We will actively participate in and contribute to the NIDA initiative, Collaborating Consortium of Cohorts Producing NIDA Opportunities. We will also partner with key stakeholders (eg, community organizations and policy makers) and collaborate with trainees, early-career faculty, and investigators across the translational spectrum.

Theoretical Model and Conceptual Framework: Theory of Minority Stress and Intersectionality

Results from the first 4 years of data collection suggest a complicated story that is rooted in minority stress, stigma, and intersectionality of identity and stigma [15]. YMSM and TGMY are located at the intersection of multiple identities, each of which has unique forms of stigma; thus, applying concepts of intersectional identity and stigma to observational studies may provide novel insights into facilitators of and barriers to HIV care.

Theory of Minority Stress

This theory has emerged as a framework to explain the relationship between prejudice, discrimination, stigma, and adverse health outcomes (eg, substance use and high-risk behaviors) [41]. Minority stress stems from several social and psychological theoretical orientations and can be described as a relationship between minority and dominant values and the conflict with the social environment experienced by minority group members. This theory posits that sexual and gender minority health disparities in care are caused mostly by stressors induced by hostile, homophobic and transphobic culture, which often results in a lifetime of harassment, maltreatment, discrimination, and victimization, which ultimately affects access and use of care [41].

Minority stress is also associated with depression and traumatic experiences, which are each linked to suicidal ideation and attempt, thus supporting the notion that minority stress is directly and indirectly linked to negative health outcomes through multiple mental health symptom pathways [42]. This literature is consistent with our own study findings demonstrating that racism, homophobia, internalized homophobia, and stigma are all important to understanding risk among TGMY and YMSM [15].

Theory of Intersectionality

This theory serves as an extension to the Theory of Minority Stress by examining how multiple aspects of marginalized or stigmatized identities (eg, race, class, sexual and gender identity, or HIV status) potentially affect health-related behaviors and outcomes. Intersectionality, or intersectional identity, describes the compounded effects that multiple marginalized identities have on individuals [43,44]. It considers the ecological factors that affect experiences of stigma, discrimination, and marginalization [25]—and in the context of HIV, provides an important framework for understanding the disproportionate risk among YMSM and TGMY. Intersectionality posits that multiple stigmatized identities such as gender, race, ethnicity, sexual orientation, and socioeconomic status, among others, do not exist independently, but intersect to reflect individual experiences and should therefore be considered simultaneously [18,43,45].

An intersectional perspective is vital to holistically understand how living with multiple stigmatized identities affects individual behaviors and population health outcomes [46]. Intersectionality is an emerging approach to stigma studies that can be used to better understand the experiences of vulnerable groups with multiple stigmatized identities while providing guidance on intervention strategies that can reduce stigma, increase resilience, and improve health [47]. Furthermore, it creates a framework for examining the juncture of multiple stigmatized identities that fall within or across several categories: (1) ≥1 coexisting health conditions such as HIV, drug use, or mental health disorders; (2) demographic sociostructural characteristics, such as race, ethnicity, sexual orientation, gender identity, homelessness, and immigration status; and (3) behaviors and experiences such as drug use and sex work.

Methods

Ethics Approval

This study has been reviewed and approved by the institutional review board (IRB) at Children's Hospital Los Angeles (CHLA-14-00279). Participants were initially recruited from the previous iterations of HYM and TRUTH studies [48]; they were screened for eligibility to continue in the study, and if eligible, they were invited to participate in the study as further described in the following sections. All participants provided written informed consent during a web-based reconsenting visit and were informed that continuing participation in the study is voluntary and that they could exit at any time.

Study Design

We will use a longitudinal design with data collection occurring every 6 months to examine changes over time with respect to intersectional identities and relationship with HIV and STIs, drug use, and mental health risk. Data collection will include a quantitative survey; qualitative interviews; and collection of biological specimens for rapid HIV tests and STI tests (ie, rectal and throat swabs), urine for recent substance use, blood for syphilis testing, and blood samples for later analysis. HYM and TRUTH Cohort Study will continue to conduct triangulated analysis of quantitative, qualitative, and biological measures (ie, drug use, HIV and STI testing, and adherence to ART for participants who are HIV+) at baseline and every 6 months for a total of 8 waves of data collection scheduled to occur from fall of 2021 to summer of 2025. Furthermore, qualitative substudies will be integrated into the study using the time line follow-back approach on an as-needed basis to further contextualize our quantitative findings.

Study Participants

In 2016, we recruited a cohort of 448 (n=397, 88.6% HIV– and n=51, 11.4% HIV+) YMSM into the HYM Cohort Study; the sample comprised African American and Black and Latino YMSM who are HIV+ or at high risk for HIV acquisition; 58.9% (264/448) self-identified as Latino, 20.9% (94/448) as African American, and 20.1% (90/448) as multiracial. Mean age at recruitment was 22.3 (SD 2.02) years. We will continue data collection with this existing cohort. To do this, we contacted participants, informed them of the study renewal, and invited them to reconsent via an IRB-approved web-based video conferencing.

Similarly, data collection will continue with the current TRUTH cohort (N=105) using the approach described previously. In addition, we will recruit 250 new TGMY (eg, approximately n=100, 40% transgender women; n=100, 40% transgender men;

and n=50, 20% gender-nonconforming and nonbinary youth) to allow for additional data collection and analysis with this understudied community. We are particularly interested in recruiting participants who are substance users (especially methamphetamines and opioids) or living with HIV. Eligibility criteria for additional study recruitment of the HYM and TRUTH Study Cohorts are as follows: (1) aged between 20 and 26 years; (2) self-identify as Black or African American, Latino or Latinx, or a mixed-race individual; (3) self-identify as a cisgender man, transgender individual, or nonbinary individual; (4) lived in the Los Angeles metropolitan area; and (5) have had sex with a penis in the past 12 months.

YMSM and TGMY will be excluded from the study if they (1) do not meet the inclusion criteria, (2) appear to be under the influence of drugs or alcohol during their study visit (research staff is trained to identify objective signs of intoxication), (3) are not able to commit to the study through completion, or (4) are not fluent in English or Spanish as determined during screening and informed consent process.

Recruitment

Recruitment resumed in October 2021. We continue to recruit participants via referrals from community partners and through social media platforms such as Facebook, Instagram, and Grindr [48].

Tracking and Retention

This study will continue using the tracking and retention procedures previously used, including incentivized monthly check-ins with participants to identify changes in contact information [48]. Participants receive US $5 per month for reaching out to study staff and alerting them to any changes in contact information. Periodic newsletters are sent to participants to remind them about study-related events, and social events maintain participant engagement throughout the study.

Community Advisory Board and Youth Community Advisory Board

Community Advisory Boards (CABs) continue to be critical partners in our study conducted with YMSM and TGMY. We will continue to convene a CAB and Youth CAB (YCAB) to inform all aspects of the HYM and TRUTH Cohort Study. CAB and YCAB members include policy makers, HIV prevention and care service providers, advocates, and members of our target population (eg, racially and ethnically diverse YMSM and TGMY). Our CAB and YCAB have been invaluable in helping us to develop or refine our data collection instruments, methods, sample selection and retention efforts; identify resources for participants; interpret study findings; and disseminate findings to local organizations and policy makers. Going forward, we have adapted our CAB and YCAB to include great representation for our study population of YMSM and TGMY; we have confirmed a total of 18 CAB members, who meet quarterly.

Assessment Measures

Overview

We use a core set of measures for the HYM and TRUTH assessments. Surveys require approximately 90 minutes to complete and are self-administered using a secure web-based platform to protect participants' privacy and reduce response bias, particularly for sensitive questions about sexual behaviors and substance use. Participants who wish to take the survey remotely meet with one of our research associates (RAs) via secure videoconference. During remote survey sessions, participants are allowed to mute their microphone and camera, whereas the RA remains on standby for any participant questions. Participants who come to the office for in-person surveys are brought to a private conference room to ensure privacy and are informed that their RA is on standby to provide immediate support and clarification of questions.

In our latest survey, the separate HYM and TRUTH surveys were combined to yield a single survey with a set of core items that would be presented to all participants. Skip logic was programmed such that specific questions (eg, forms of health care and experiences of discrimination) are presented only to relevant participants. For example, questions regarding experiences with HIV-related care are only asked to participants who have been diagnosed and are living with HIV. Experiences of transgender-related access to health care, discrimination and coping are only presented to participants who identify as transgender or gender expansive (ie, TRUTH Study Cohort participants), whereas questions assessing discrimination and coping pertaining to gay or bisexual men or MSM will only be administered to participants enrolled in HYM Cohort Study. For the 2020 to 2025 cohort, we have retained core measures from the original survey and have included new measures described in the following sections. The HYM+TRUTH survey was significantly modified to reflect the new aims of the renewed study.

Discrimination, Stigma, and Identity

Experiences of discrimination and stigma are assessed generally and in relation to either or both race or ethnicity and sexual or gender identity. General discrimination is assessed using the *Everyday Discrimination Scale*, which asks participants about different experiences and whether they attribute those experiences to aspects of their identity including ancestry or national origins, gender, race, age, religion, height, weight, appearance, sexual orientation, education, or income level [49]. The *LGBT People of Color Microaggressions Scale* assesses multiple minority stress [10]. *The Intersectional Discrimination Index* measures anticipated, day-to-day, and directly enacted stigmatizing experiences attributed to how participants describe themselves and how others may describe them [50]. The *Conflicts in Allegiances Scale* assesses how cultural identity, race, or ethnicity interacts with sexual or gender identity [51]. Experiences of homophobia and racism are assessed using subscales of the *Homophobia, Racism and Poverty Scale* [52]. HIV-related stigma is measured using a revised and brief measure of stigma toward youth who are HIV+ [53]. Anticipated stigma is assessed using the *Heightened Vigilance Scale* [54]. In addition, we measure multiple internalized stigmas including

internalized racism [55], transphobia [56], and homonegativity [57,58]. Finally, we measure positive identity including community connectedness [59]; positive racial and ethnic identity [60]; positive lesbian, gay, bisexual, and transgender identity [61]; and gender expression [62].

Behavioral and Mental Health

We measure several constructs that are possible mediators or moderators—and known correlates—of sexual health and HIV. Impulsivity is captured using the *Barratt Impulsiveness Scale Short-Form* [63]. We assess emotion regulation [64] and partner violence [65]. Coping is assessed using the *Brief COPE* [66], subscales of the *Racism-Related Coping Scale* [67], and coping items related to sexual and gender identity [68]. Finally, social support is measured using both the original *Multidimensional Scale of Perceived Social Support* and an adapted version that enquires about lesbian, gay, bisexual, transgender, and queer and racial and ethnic community support [69]. Furthermore, TRUTH-specific assessments include measures of use of hormones and silicone and items regarding support from family and peers for TGMY identity.

Biorepository

We will continue to maintain a biorepository with blood samples and rectal swabs, which are collected annually from our participants who are HIV– and every 6 months from participants who are HIV+. Specimen collection includes 10 mL EDTA anticoagulated whole blood samples and 2 rectal swabs. Blood specimens are processed to harvest plasma and a cellular pellet. Plasma is then divided into 4 separate aliquots and stored frozen at −80 °C. A red blood cell, buffy coat pellet is harvested and stored for future nucleic acid extraction. This cellular material will be made available to investigators for future studies. All specimens are stored in a secure, password-protected database; their position in storage is noted (eg, rack, box, and position), and they are deidentified from all study participant information. Regarding substance use, we will collect urine samples at each visit to test for the metabolites of methamphetamines, cocaine, ecstasy, marijuana, and opiates using the Integrated E-Z Split Key Cup II-5 Panel (Innovation Laboratories), which can detect drugs from 1 to 4 days after use, except for chronic marijuana use, which can be detected for up to 30 days.

STI Status

Participants will self-collect rectal and pharyngeal specimens for *Neisseria gonorrhea* and *Chlamydia trachomatis* nucleic acid amplification testing (Hologic) at a Clinical Laboratory Improvement Amendments–compliant clinical laboratory. This will occur in our field offices or at a partnering test site. Participants who test positive will be referred to a HIV and STI clinic and treated (along with their recent partners) according to the Center for Disease Control and Prevention and Los Angeles County guidelines. Syphilis testing will be performed using whole blood collected via venipuncture (or fingerstick) using rapid plasma regain and treponemal antibody testing. Specimens will be coded with participants' unique code and securely sent to the Public Health Laboratories for testing and processing. Those with syphilis infection will be referred and treated at one of our partner clinical sites according to the Center for Disease Control and Prevention and Los Angeles County guidelines. STI status will be assessed at each of the 6-month assessments.

HIV Status

HIV status will be assessed at each of the 6-month assessments, and it will be done using the Integrase Strand Transfer Inhibitors HIV-1 and HIV-2 antibody test (Biolytical Laboratories). This will be completed by field staff who have been trained in HIV testing procedures and counseling. We have integrated HIV testing and linkage to care for those who test positive, given the importance of ensuring that youth who are HIV+ are linked with care. Participants who test positive for HIV will be offered information about local resources and referred to clinical care sites for confirmatory testing, further diagnostic evaluation, and care.

Studies on Stress-Related Biomarkers

We have been conducting studies to understand the relationship between stress and stressful life events, drug use, and HIV risk. Before February 2022, we have administered the Strain and Adversity Inventory (STRAIN) to 66.9% (300/448) of our cohort participants. STRAIN is an instrument recommended by the National Institute of Mental Health Research Domain Criteria that efficiently and reliably assesses a person's cumulative exposure to stress over the life course. We hypothesize that stress, including racism and discrimination, will be significant predictors of drug use and HIV risk in our cohort. We will continue these analyses and examine the relationship between STRAIN scores and stress-related biomarkers, including biomarkers of inflammation, genome-wide transcriptional profiling, and biological aging.

Time Line Follow-Back Method Assessment

We will use an adapted time line follow-back method assessment to better understand YMSM's and TGMY's experiences in the HIV care continuum. This method uses memory aids such as calendars and *anchor days* to assist respondents in creating a daily diary for specific behaviors or events [70]. This technique has been found to have acceptable reliability and validity when measuring constructs such as substance use and sexual behavior and similar coefficients to data obtained from more conventional assessments such as single-item survey questions. This technique will be used to complete substudies that will be used to contextualize specific experiences including (1) heavy substance use (to understand social cues or other triggers for this use), (2) inconsistent use of care and challenges in accessing health services (to address structural barriers to care), (3) HIV testing (to identify why YMSM and TGMY are not testing as recommended), (4) dropping out of care, and (5) challenges in adhering to ART medications and achieving viral suppression.

Pandemic Impact Scale

In addition, a subset of our existing cohort was administered the Pandemic Impact Scale [71], which provides a holistic assessment of the impact of the pandemic on participants' lives, including work and employment, education and training, home life, social activities, economic stability, emotional health and well-being, physical health problems, physical distance and quarantine, infection history, and positive changes owing to the

pandemic. Findings from the Pandemic Impact Scale will be reported in a separate paper outlining the impact that the COVID-19 pandemic has had on our overall study participants.

Data Analysis

Univariate statistics will be used to examine and chart the characteristics of the cohorts and subgroups within them (eg, race and ethnicity subgroups and gender identity subgroups), including demographics, STI and HIV incidence by pathogen and anatomical site, substance use from self-report and urine samples, use of HIV testing and prevention services, health care use and engagement, use of biomedical HIV prevention (eg, PrEP) for those who are HIV–, and adherence to ART for those who are HIV+. Bivariate analysis will be used to examine relations among variables of interest. For constructs assessed using multiple items, factor analysis will be used to confirm the scales, and summary scale scores will be created. Psychometric analysis of the developed measures will be performed; exploratory analyses will be used immediately after alteration or creation to explore redundancy or inadequacy of items; and confirmatory analysis will be used at later waves to examine validity, reliability, and stability of the composite scores.

In addition, Latent Class Analysis provides a parsimonious way to identify specific behaviors characterized by particular patterns of responses and to link subgroup membership to predictors and outcomes. We will use Latent Class Analysis to examine the following: (1) patterns of co-occurring substance use, HIV, STI, and mental health comorbidities; characteristics of engagement in care; and how pattern membership changes over time; (2) patterns of multiple intersecting identities and changes over time; (3) patterns of multidimensional interconnected experiences of stigma and changes over time; (4) how associations among HIV and STIs, substance use, mental health, and engagement in care are informed by intersectionality; and (5) differences between African American and Black and Latino YMSM and TGMY in complex intersectionality processes.

Data Management

All data and biological samples collected for this study will remain confidential; all participants' personal information will be coded using a combination of numbers and letters such that the data collected cannot be linked back to the study participants. All personal identifiable information will be removed from self-reported assessments and biological specimens, and any findings in future scientific journals or conferences will be reported in aggregate form and only after the data have been deidentified. All participant data will be deidentified from participant information. All self-reported and collected data will remain in a password-protected database, and all biological specimens will be entered into a secure, password-protected database and be accessible only to the study staff.

Results

Funding for the renewal project began in June 2020, and IRB approval to increase enrollment was obtained on July 9, 2021. As of February 2022, participants from the past 4 years of the HYM Cohort Study and TRUTH Study Cohort have been reconsented and enrolled into the renewal period of longitudinal data collection, which is projected from summer of 2020 to summer of 2025. Recruitment is ongoing to reach our target enrollment goal of 700 YMSM and TGMY. As of September 30, 2022, in total, 68.4% (479/700) participants have been enrolled or reconsented into the renewal project. Assessments will be conducted every 6 months until the end of this project period, in July 2025.

Discussion

Principal Findings

This paper describes the renewal of a longitudinal study with efforts to combine 2 different cohorts of YMSM and TGMY into a unified cohort, with distinct study measures adapted for each. We discuss the renewal period and the adoption of new measures to assess psychosocial characteristics that align with our current study aim—adopting a framework of intersectionality to develop effective interventions for YMSM and TGMY, who may experience multiple forms of stigma owing to their multiple minority identities.

As we broach the fifth decade of the AIDS epidemic in the United States, health researchers and AIDS activists reflect on both the progress that has been made in reducing the incidence of AIDS and the importance of continued prevention efforts. Although significant advances have been made in reducing the incidence of new infections, recent studies have demonstrated that some groups continue to have elevated exposure to HIV transmission risk. YMSM and TGMY are such groups, and more traditional risk reduction efforts do not appear to be effectively reaching this population. One of the reasons why more traditional HIV prevention efforts have failed among these young people is that such efforts often fail to incorporate broad familial, social, cultural, and community factors that influence their lives. Very few proven interventions are available that have been targeted for these groups. The importance of this study rests on its potential to generate appropriate and meaningful HIV prevention efforts targeting YMSM of color and TGMY and to integrate current understanding of a range of psychosocial factors and their influence on HIV risk and protective behaviors, particularly drug use and sexual practices.

Conclusions

We will work to ensure that our cohort serves as a national resource for collaborations and dissemination (aim 3). Our cohorts provide unique opportunities for researchers and interventionists to assess and test how we can reach our national goals with 2 key populations: African American and Black and Latino YMSM and TGMY. In particular, the proposed mixed methods study may offer important insights into the broad array of interpersonal, social, and cultural relationships in young people's lives that underlie their involvement in drug use and HIV risk and protective behavior. This study will provide important information that can be used to develop gender-specific and age-appropriate substance use and HIV prevention and harm reduction efforts.

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Data Availability

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

Conflicts of Interest

None declared.

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Abbreviations

ART: antiretroviral therapy
CAB: Community Advisory Board
HYM: healthy young men
IRB: institutional review board
MSM: men who have sex with men
NIDA: National Institute on Drug Abuse
PrEP: pre-exposure prophylaxis
RA: research associate
STI: sexually transmitted infection
STRAIN: Strain and Adversity Inventory
TGMY: transgender and gender minority youth
TRUTH: TRUTH: A Transgender Youth of Color Study
YCAB: Youth Community Advisory Board
YMSM: young men who have sex with men

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Protocol

Factors Associated With Syphilis Transmission and Acquisition Among Men Who Have Sex With Men: Protocol for a Multisite Egocentric Network Study

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Abstract

Background: In the United States, the rates of primary and secondary syphilis have increased more rapidly among men who have sex with men (MSM) than among any other subpopulation. Rising syphilis rates among MSM reflect changes in both individual behaviors and the role of sexual networks (eg, persons linked directly or indirectly by sexual contact) in the spread of the infection. Decades of research examined how sexual networks influence sexually transmitted infections (STIs) among MSM; however, few longitudinal data sources focusing on syphilis have collected network characteristics. The Centers for Disease Control and Prevention, in collaboration with 3 sites, enrolled a prospective cohort of MSM in 3 US cities to longitudinally study sexual behaviors and STIs, including HIV, for up to 24 months.

Objective: The Network Epidemiology of Syphilis Transmission (NEST) study aimed to collect data on the factors related to syphilis transmission and acquisition among MSM.

Methods: The NEST study was a prospective cohort study that enrolled 748 MSM in Baltimore, Maryland; Chicago, Illinois; and Columbus, Ohio. NEST recruitment used a combination of convenience sampling, venue-based recruitment, and respondent-driven sampling approaches. At quarterly visits, participants completed a behavioral questionnaire and were tested for syphilis, HIV, gonorrhea, and chlamydia. The participants also provided a list of their sexual partners and described their 3 most recent partners in greater detail.

Results: The NEST participants were enrolled in the study from July 2018 to December 2021. At baseline, the mean age of the participants was 31.5 (SD 9.1) years. More than half (396/727. 54.5%) of the participants were non-Hispanic Black, 29.8% (217/727) were non-Hispanic White, and 8.8% (64/727) were Hispanic or Latino. Multiple recruitment strategies across the 3 study locations, including respondent-driven sampling, clinic referrals, flyers, and social media advertisements, strengthened NEST participation. Upon the completion of follow-up visits in March 2022, the mean number of visits per participant was 5.1 (SD 3.2; range 1-9) in Baltimore, 2.2 (SD 1.6; range 1-8) in Chicago, and 7.2 (SD 2.9; range 1-9) in Columbus. Using a community-based participatory research approach, site-specific staff were able to draw upon collaborations with local communities to address stigma concerning STIs, particularly syphilis, among potential NEST participants. Community-led efforts also provided a forum for staff to describe the NEST study objectives and plans for research dissemination to the target audience. Strategies to bolster data collection during the COVID-19 pandemic included telehealth visits (all sites) and adaptation to self-collection of STI specimens (Baltimore only).

Conclusions: Data from NEST will be used to address important questions regarding individual and partnership-based sexual risk behaviors among MSM, with the goal of informing interventions to prevent syphilis in high-burden areas.

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KEYWORDS

sexually transmitted infection; HIV risk; men who have sex with men; sexual network; syphilis; mobile phone

Introduction

Background

Syphilis is a sexually transmitted infection (STI) caused by the bacterium *Treponema pallidum*. In the primary stage, syphilis spreads by direct contact with a syphilitic sore (ie, chancre), which can progress in the secondary stage to include symptoms such as skin rashes and mucous membrane lesions. In 2020, a total of 41,655 primary and secondary (P&S) syphilis cases were reported in the United States, and 81% of these cases were among men [1]. P&S syphilis rates have increased steadily among gay, bisexual, same-gender-loving, and other men who have sex with men (MSM) aged ≥15 years from 20.6 per 100,000 in 2000 to 272.8 per 100,000 in 2015 [2,3]. Both national and state-specific P&S syphilis rates are higher among MSM than among men who have sex with women only (309 per 100,000 compared with 2.9 per 100,000 in 2015) [4]. In 2020, MSM accounted for 43% of reported P&S syphilis cases, and nearly half of MSM with P&S syphilis in 2020 were also living with HIV [5]. HIV and syphilis are often linked because syphilis can cause inflammatory genital ulcers and lesions, which can increase the risk of HIV transmission [6-9].

Several network factors have been implicated in the rise of syphilis cases among MSM, including increase in condomless anal sex and multiple or concurrent (ie, overlapping) sexual partners [10-13]. MSM are more likely to report having concurrent sexual partnerships than heterosexual individuals [14]. Concurrent partnerships can create larger, more connected sexual networks that can amplify the spread of STIs [15-19]. Biomedical HIV interventions such as pre-exposure prophylaxis (PrEP) to prevent HIV infection and antiretroviral therapy for persons living with HIV can also affect STI risk within networks. The selection of partners who use these modalities can affect condom use and serosorting behaviors (ie, limiting partners to same HIV status) both within and across partnerships [20-22]. Racial homophily (ie, same race or ethnicity partners) is another network factor that can affect syphilis case rates, particularly within MSM networks where syphilis and HIV are concentrated [23-28]. The influence of racial homophily on syphilis rates within sexual networks among MSM can be exacerbated by social and environmental factors, such as racism, segregation, poverty and income inequality, education, stigma, discrimination, and access to health care [29-31].

Although research has examined individual and network-related factors contributing to rising syphilis case rates among MSM [32-35], most studies are cross-sectional and cannot account for how individual STI or HIV risk may vary as partnerships change. For example, specific cycles of the National HIV Behavioral Surveillance that focus on MSM sexual behaviors confine questions on sexual partnerships to a 12-month retrospective reference period [36]. Similarly, case reports from disease intervention specialists from local health departments are limited to patients who test positive for STI or HIV, and partner-level information is typically collected only when the partner can be located for STI testing or treatment [37]. Individuals' risk of syphilis acquisition and transmission may change over time depending on the behaviors enacted during specific sexual encounters, such as the introduction of new sex partners. Similarly, the context of these new and continuing relationships may affect sexual behavior (eg, condom use and types of sex [oral or anal]). To fill gaps in what is currently known about syphilis epidemiology among MSM, the Centers for Disease Control and Prevention (CDC) partnered with 3 sites to conduct the Network Epidemiology of Syphilis Transmission (NEST) study.

This Study

NEST was a prospective, longitudinal cohort study aimed to identify drivers of change in syphilis epidemiology and account for network factors affecting syphilis transmission dynamics among MSM. NEST included MSM from the Mid-Atlantic (Baltimore City, Maryland) and Midwestern (Chicago, Illinois, and Columbus, Ohio) regions of the United States. Each of these geographic areas has rates of syphilis among MSM that are higher than the national rate [1,38-41]. In addition, the associated counties were among those identified as *hotspots*,

where >50% of the total new HIV diagnoses occurred from 2016 to 2017 [42]. This paper details the NEST research protocol, the impact of the novel COVID-19 pandemic on NEST data collection, and the successes and challenges in collecting sexual health information among MSM in these geographic areas.

Methods

Study Design

NEST was designed and implemented by Johns Hopkins University in partnership with the Baltimore City Health Department, University of Illinois at Chicago (in partnership with Howard Brown Health), and Ohio State University. NEST study participants completed a structured questionnaire about their sexual and health behaviors over time and provided biological samples at each study visit to test for syphilis, HIV, gonorrhea, and chlamydia. The NEST self-administered survey took approximately 60-90 minutes to complete. During the course of the study, participants received US $40-75 for participating in the survey and diagnostic STI testing and US $10-25 for referring each eligible person that was part of their social or sexual network.

Consent to Participate

The participants provided written informed consent before enrolling. The study staff conducted surveillance activities in adherence to ethical principles and standards by respecting and protecting the privacy, confidentiality, and autonomy of the participants to the maximum extent possible.

Ethics Approval

This study obtained oversight from the CDC institutional review board (IRB) and approval from local institutional IRBs at Johns Hopkins University, the University of Illinois at Chicago, and Ohio State University.

Participant Selection and Recruitment

Data collection for NEST was conducted from July 2018 to March 2022. Participants were followed for up to 24 months with quarterly study visits. Participants were recruited with assistance from local health departments, health clinics, and community-based organizations using multiple recruitment strategies, including convenience sampling, venue-based recruitment, and respondent-driven sampling (RDS) techniques. The recruitment strategies and target populations for NEST were tailored according to the local epidemiology of syphilis among MSM at each study site. The study's inclusion criteria and tailored recruitment strategies are presented in Textbox 1.

Textbox 1. Inclusion criteria and tailored recruitment strategies.

Inclusion criteria

- Assigned male sex at birth
- Currently identifies as male
- Aged ≥18 years
- Had oral or anal sex with a man in the 6 months before baseline interview
- Lived within the study area
- Able to complete the survey in English
- Provided written informed consent

Tailored recruitment strategies (implementation varied across study sites)

- Aged ≤45 years
- Diagnosed with a new, untreated, or recent syphilis infection (6 months before the baseline interview, regardless of treatment)

Formative Research Phase

During the formative research phase of the study (ie, 1 year before study enrollment), NEST investigators focused on developing research methods that were transparent and culturally appropriate and that collected information that could be readily applied to local interventions. A community-engaged participatory approach that included community advisory boards (CABs) and focus groups was used to build trust between researchers and participants and to identify ways in which study participation would benefit the broader community [43,44]. In Baltimore, the CAB consisted of 6 to 7 Black MSM who met monthly throughout the study period. Examples of CAB activities included codeveloping new survey questions, providing feedback on community dissemination materials, and designing a substudy within NEST. In addition, based on needs identified via qualitative data gathered during the formative period, Baltimore strengthened the capacity of community members hired as project staff through education, training, and employment and routinely shared interim findings with NEST participants, relevant community-based organizations, and partnering clinical and nonclinical sites [43].

Questionnaires

Individual-Level Measures

Participants were asked about sociodemographic and health-related information in self-administered surveys. The sociodemographic characteristics included age, race and ethnicity, sexual orientation, education, employment status, and relationship status (refer to individual characteristics in Textbox 2). To describe health care–seeking behavior and prior STIs,

participants were asked about their health insurance status, where they usually received STI-related health care, HIV status, syphilis diagnoses (lifetime and in the past 12 months), prior gonorrhea and chlamydia diagnoses (including anatomical site), PrEP knowledge, PrEP prescription and use, and frequency of STI or HIV testing (refer to the health care access and use section in Textbox 2). In addition, participants were asked about individual-level sexual behaviors, including the number of sex partners in the past 3 months, types of sex, drug or alcohol use during sex, experience of exchange sex, and group sex (refer to individual sexual behavior [in the past 3 months] in Textbox 2). The types of sex (giving or receiving) that participants were asked about included anal sex, oral sex (ie, oral-genital), rimming (ie, oral-anal), and vaginal sex. Specific information on these topics, as well as other sex partner characteristics, was collected about the 3 most recent partners in the past 3 months, including those partners' HIV status and use of PrEP (refer to sexual behavior with 3 most recent sex partners [in the past 3 months] and partner characteristics [in the past 3 months] in Textbox 2). The interview concluded with questions about syphilis symptoms (refer to syphilis symptoms in Textbox 2), substance use (refer to substance use in Textbox 2), and PrEP attitudes and practices (refer to HIV PrEP in Textbox 2).

Textbox 2. Survey domains in the Network Epidemiology of Syphilis Transmission study.

Individual characteristics

- Age
- Race or ethnicity
- Sexual orientation
- Sexual role (eg, “top” [insertive partner], “bottom” [receptive partner], or “versatile” [either insertive or receptive partner])
- Education or employment status
- Relationship status
- Experience with homelessness, food insecurity, and prison or jail

Health care access and use

- Current health insurance
- Type of health insurance
- Time since last saw a physician, nurse, or health care provider
- Inability to afford medical care
- Sexually transmitted infection (STI) testing in the past 12 months
- Regular place for STI-related health care
- HIV testing (ever or in the past 12 months)
- Last HIV test result
- Self-reported history of syphilis, gonorrhea, and chlamydia diagnoses
- HIV pre-exposure prophylaxis (PrEP) knowledge, prescription, and use
- HIV postexposure prophylaxis use

Individual sexual behavior (in the past 3 months)

- Number of sex partners
- Types of sex (oral-genital, anal, oral-anal, or vaginal)
- Drug or alcohol use before or during sex
- Exchanging sex for money, drugs, shelter, or something else
- Group sex

Sexual behavior with 3 most recent sex partners (in the past 3 months)

- Types of sex (oral-genital, anal, oral-anal, or vaginal)
- Frequency of sex and date of sex
- Condom use at last sex (oral-genital, anal, oral-anal, or vaginal)
- Exchanging sex for money, drugs, shelter, or something else
- Sex partner had concurrent (ie, overlapping) sex partners

Partner characteristics (in the past 3 months)

- Name or nickname
- Sex assigned at birth
- Gender identity (ie, personal sense of one’s own gender)
- Age and race or ethnicity
- Sexual relationship (main or casual)
- Where they first met
- Partners’ HIV status
- Partners’ antiretroviral status

- Partners' PrEP use

Syphilis symptoms

- Signs and symptoms related to syphilis

Substance use

- Injection drug use
- Noninjection drug use
- Alcohol use

HIV PrEP

- HIV PrEP knowledge, attitudes, and practices

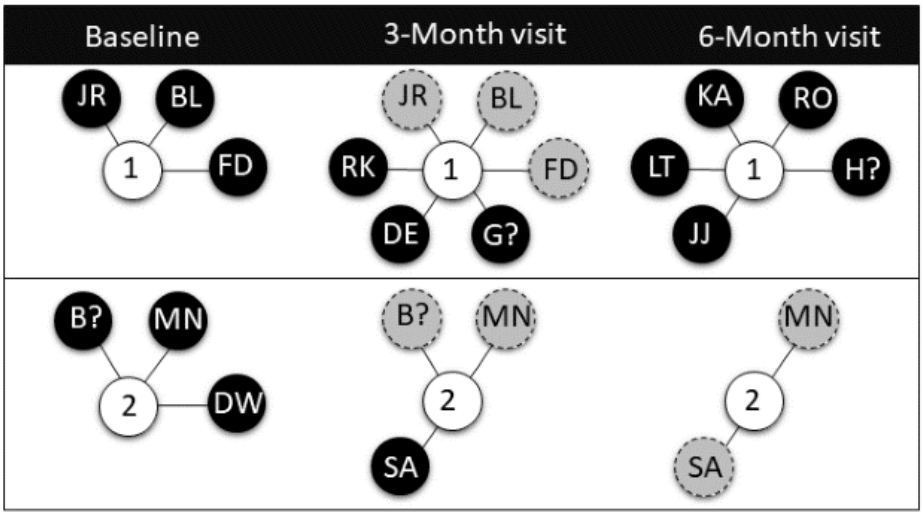
Sexual Network Data Collection

In the interviewer-led portion of the interview, participants were asked to recount all sexual partnerships in the past 3 months, provide basic demographic information about these partners, and provide detailed characteristics for the 3 most recent sex partners. Participants were asked to provide the first and last name, first name and last initial, or a nickname for each partner so that partners could be consistently identified at quarterly visits.

All partners named at the baseline visit were considered a new sex partner. For each partner named by the participant at subsequent visits, the interviewer checked the cumulative list of previously named partners to determine whether this partner was named for the first time or was named at a previous visit (eg, "You have not told me about [new partner name] before. Is that correct?"). After the participant free-listed the names of their partners from the past 3 months (ie, without interviewer prompting), the interviewer would confirm whether any partners not renamed from the previous visit were still current sex partners (eg, "At the last visit you told me about [old partner name]. Have you had sex with this partner in the last 3 months?").

Figure 1 illustrates a hypothetical sociogram (ie, graphical representation of interpersonal relationships) for 2 participants at the baseline and 3-month and 6-month study visits. This figure presents an example of the complexity of sexual relationships that can exist among study participants [45]. Participants 1 and 2 both reported the initials of 3 sex partners at their baseline study visit. Participant 1 reported retaining all 3 baseline partners ("JR," "BL," and "FD") in addition to acquiring 3 new partners ("RK," "DE," and "G?") at the 3-month visit. The question mark indicates names or identifiers that may not be known. At the 6-month visit, participant 1 reported 5 new partners ("KA," "RO," "H?," "JJ," and "LT"), with no previous partners retained. At the 3-month visit, participant 2 reported retaining 2 baseline partners ("B?" and "MN") and acquiring 1 new partner ("SA") at the 3-month visit. At the 6-month visit, participant 2 reported retaining 2 partners ("SA" and "MN") with no new partners.

Figure 1. Hypothetical sociogram of 2 Network Epidemiology of Syphilis Transmission study participants at the baseline and 3-month and 6-month study visits (black circles represent named partners, gray circles represent renamed partners; the letters within circles represent initials provided by participants; the question marks represent names or identifiers that may not be known).



Biological Samples Collection

Overview

Consenting participants provided biological samples for STI or HIV screening at baseline and at each quarterly visit. Positive STI or HIV results were reported to the local health department according to the state and local reporting requirements. Participants with positive test results were referred to the health department or the provider of their choice for treatment.

HIV Sample

Trained HIV counselors collected blood samples for rapid HIV testing (eg, INSTI antibody test) or fourth-generation enzyme immunoassay. Confirmatory testing (eg, polymerase chain reaction for HIV-1) was conducted on all individuals who tested positive for HIV.

Syphilis

Trained phlebotomists collected 2 blood samples: one sample for testing at a local clinic where results were returned to participants and a second sample for additional testing at the CDC for evaluation of syphilis diagnostic algorithms and longitudinal monitoring of serum antibody titers in incident and repeat syphilis infections. A sequential combination of nontreponemal tests (most often the rapid plasma reagin) and treponemal tests (eg, fluorescent treponemal antibody test absorption test, among others) was used locally to screen samples for *T. pallidum*.

Gonorrhea and Chlamydia

Urethral, anorectal, and oropharyngeal swabs were either self-collected or collected by the clinical staff, depending on the local protocol. Nucleic acid amplification tests were performed locally to test samples for the genetic material of *Neisseria gonorrhoeae* and *Chlamydia trachomatis*.

Ecological Momentary Assessment

A subsample of NEST participants agreed to participate in the collection of supplemental data with an ecological momentary assessment (EMA). EMA was a smartphone app comprising short questions to capture the occurrence of specific sexual behaviors in real time. Participants used their own smartphone, or were provided with a smartphone, to respond to brief surveys each day for a 2-week period. In Baltimore, the EMA was augmented with geolocation data (eg, a GPS data point) that was collected while the phone was turned on with a cell phone service [46]. Survey questions included the number of people with whom the participant had oral or anal sex in the past 24 hours, where the participant met sex partners, where sex took place, use of mobile geosocial networking apps to meet sex partners (eg, Grindr, Manhunt, among others), and drug or alcohol use. Data from Baltimore on EMA participation indicated that those who participated were willing to complete the brief surveys and answer the questions when prompted [46].

Data Management

Each study site maintained a centralized data management system for NEST data using their own software (eg, REDCap [Research Electronic Data Capture], Vanderbilt University; Qualtrics, Qualtrics XM) [47,48]. The NEST study participants were assigned a unique study ID number for all study documents and biospecimens. At each study visit, interviewers entered a unique identifier for all sex partners in the past 3 months in the data entry form that corresponded with the participants' study records. The study record was retained throughout the study if the partner was mentioned at subsequent visits. To maintain confidentiality, personally identifiable information was removed from the data before transmission to the CDC's Division of Sexually Transmitted Disease Prevention (DSTDP).

To ensure consistency across study sites, NEST staff from the DSTDP's Surveillance and Data Science Branch provided a data dictionary that contained the questions and variable text, variable names, field limits, skip logic, consistency checks, response values, and formats. Data managers within each site worked with DSTDP to transmit data in a standardized format via a secure application on a quarterly schedule. The CDC's DSTDP NEST staff was responsible for the accuracy, quality, completeness, and internal consistency of the NEST data.

Adaptations to Data Collection During the COVID-19 Pandemic

Beginning in March 2020, the COVID-19 pandemic introduced challenges for NEST study operations as well as partnering state and local public health programs, including closures of clinics, universities, and health departments. During the early months of the pandemic, NEST study sites rapidly transitioned from in-person visits to remote-only visits, in which interviews were conducted via telephone or on the web. During the early months of the pandemic, study staff in Baltimore and Columbus were often successful in scheduling follow-up calls with participants while shelter-in-place orders were in effect. Participants who were already familiar with the questions asked during visits often came prepared by bringing a list of their sexual partners. However, telehealth approaches did not work as effectively in Chicago, where challenges included the limited ability to locate or reach participants who did not have reliable internet or mobile phone services or who experienced housing instability.

The COVID-19 pandemic presented challenges for in-person clinical visits in all 3 NEST sites. In both Chicago and Columbus, STI testing for chlamydia, gonorrhea, HIV, and syphilis was halted in March 2020 for approximately 8 months. Baltimore had the opportunity to provide 2 innovative methods for STI specimen self-collection (ie, not under medical supervision) to its participants. Baltimore participants were offered mail-in testing of self-collected samples through (1) an existing web-based outreach program ("I Want the Kit" [IWTK] [49]) and (2) Molecular Testing Labs (MTL), a provider of diagnostic testing. Historically, IWTK has had a high level of acceptability among its users [50]. Through a specific arrangement with IWTK, chlamydia, gonorrhea, and HIV testing was offered to participants in Baltimore from June 2020 onward. Approximately 200 Baltimore NEST participants enrolled in the participating clinics were sent IWTK collection kits, and of these, 81.5% (163/200) returned the kits for testing.

From January 2021 onward, Baltimore began using MTL for chlamydia, gonorrhea, HIV, and syphilis testing. Syphilis testing was performed using a dried blood spot treponemal test kit. Participants were asked to self-collect 5 to 10 drops of blood

from a fingerstick on a blood collection card. Approximately 71 participants in Baltimore with no prior positive nontreponemal test were sent collection kits from MTL and 66% (47/71) sent the kits back to MTL for syphilis antibody testing.

For STI tests collected through IWTK and MTL, positive results were reported to the Baltimore City Health Department where disease investigation specialists notified and referred participants for treatment via standard health department protocol. The availability of STI test results outside of an in-person visit was important for timely access to treatment during a time of reduced clinic operations. Some Baltimore participants experienced challenges using STI specimen self-collection methods, including United States Postal Service delays in kit deliveries, lags in the receipt of testing results, and delays in remuneration after receiving results. Furthermore, some participants who self-collected fingerstick blood for syphilis testing via MTL reported challenges with the procedure, such as difficulty puncturing fingers and problems following the instructions for blood sample self-collection, which could lead to reduced specimen quality. Despite the potential barriers, the high uptake of these STI self-collection strategies among NEST participants in Baltimore adds to the existing studies on the feasibility and acceptability of such programs among MSM in other jurisdictions [51].

Planned Analyses

CDC and NEST-affiliated researchers are using network analysis approaches to understand how individual-level behaviors and network-level factors affect the acquisition of syphilis and other STIs. These methodological approaches include estimating and simulating sexual network models with respect to the longitudinal fluctuations in partnerships and STI transmission dynamics. Other analyses will explore factors associated with partnership characteristics, partnership duration and turnover, and STI incidence among participants. We will also explore longitudinal changes in sexual behavior during the COVID-19 pandemic.

Results

NEST enrollment began on July 20, 2018 and concluded on December 17, 2021; a total of 748 MSM (444/748, 59.3%, in Baltimore; 63/748, 8.4%, in Chicago; and 241/748, 32.2%, in Columbus) were enrolled. Enrollment ended in March 2020 for Baltimore and Columbus and in December 2021 for Chicago. The mean age of the participants was 31.5 (SD 9.1) years (Table 1), and it ranged from 18-45 years in Baltimore, 21-56 years in Chicago, and 18-77 years in Columbus. The average number of visits per participant was 5.1 (SD 3.2; range 1-9) in Baltimore, 2.2 (SD 1.6; range 1-8) in Chicago, and 7.2 (SD 2.9; range 1-9) in Columbus. Overall, more than half (396/727, 54.4%) of the participants were non-Hispanic Black, 29.8% (217/727) were non-Hispanic White, and 8.8% (64/727) were Hispanic or Latino. Approximately 64.9% (485/747) of the participants had some college education or a bachelor's degree. Most (558/747, 74.7%) participants identified as gay and 19.5% (146/747) identified as bisexual. Most (586/704, 83.2%) participants had private or public health insurance and 67.5% (504/747) were currently employed. When asked about the previous 6 months, 21.2% (158/746) of the participants reported experiencing homelessness (ie, no regular place to stay for at least one night), and 43.2% (323/745) of the participants experienced food insecurity. Approximately 7.6% (57/747) of the participants reported prison or jail experience in the past 12 months.

The demographic characteristics of NEST participants at baseline from Baltimore, Chicago, and Columbus describe a racially or ethnically diverse group of MSM, most of whom had at least some college education, full- or part-time employment, and health insurance. Most of the MSM participants identified as gay, but 24.5% (183/747) of the participants reported other sexual identities (ie, bisexual or "something else"). Potential differences in sexual behaviors by sexual orientation may have implications for corresponding STI risk [52]. Participants' experiences of recent housing instability or food insecurity are examples of social determinants of health that could contribute to disparities in STI diagnoses among MSM [53,54].

Table 1. Baseline characteristics of men who have sex with men participating in the Network Epidemiology of Syphilis Transmission study (N=748).

Characteristics	Values[a]
Age (years), mean (SD)	31.5 (9.1)
Hispanic origin or race (n=727), n (%)	
Hispanic or Latino	64 (8.8)
Non-Hispanic Black	396 (54.5)
Non-Hispanic White	217 (29.8)
Non-Hispanic other or multiple race	50 (6.9)
Education (n=747), n (%)	
Less than high school	54 (7.2)
High school or general equivalency diploma	208 (27.8)
Some college	239 (32)
Bachelor's degree or higher	246 (32.9)
Sexual orientation (n=747), n (%)	
Gay	558 (74.7)
Straight	6 (0.8)
Bisexual	146 (19.5)
Something else	37 (5)
Current health insurance status[b] (n=704), n (%)	
Insured	586 (83.2)
Uninsured	118 (16.8)
Employment status[c] (n=747), n (%)	
Employed	504 (67.4)
Not employed	243 (32.5)
Past 6 months, n (%)	
Homelessness[d] (n=746)	
Yes	158 (21.2)
No	588 (78.8)
Food insecurity (n=745)	
Yes	323 (43.3)
No	422 (56.6)
Past 12 months, n (%)	
Prison or jail experience (n=747)	
Yes	57 (7.6)
No	690 (92.3)

[a]Percentages may not add to 100% due to rounding.

[b]Insurance status included public or private insurance.

[c]Employed: full-time work, part-time work, self-employed, or studying; not employed: unemployed, retired, stay-at-home parent, or unable to work.

[d]Homeless was defined as "living on the street, in a shelter, in a single room occupancy (SRO) hotel, with friends, in a car, or you have not had a regular place to stay for at least one night."

Discussion

Significance of the Study

The NEST study is unique in its assessment of individual- and partner-level characteristics in MSM networks using quarterly behavioral surveys and repeated STI or HIV testing. The detailed list of sexual partners and partner characteristics collected at each interview provides important information about relationship dynamics and concurrency that could be an indication of the participants' connection to a larger sexual network. Public health surveillance data in Baltimore, Chicago, and Columbus have documented rising syphilis rates among MSM [38-41]. In addition to individual-level factors that could affect syphilis case rates, syphilis factors at the network level include injection drug use and party drug use [55] and the use of geospatial network applications to meet sex partners on the web [55-57]. The results of this study may identify local drivers of syphilis transmission that can assist health departments in targeting limited resources (eg, disease intervention specialist interviews) and developing tailored syphilis screening programs among populations of interest. Additional analyses described in the Planned Analyses section are underway with analyses and dissemination of results expected to continue through 2024.

Lessons Learned

Here, we summarize the lessons learned in the hope that future research studies among MSM using a prospective egocentric network study design can use this information to facilitate recruitment and enhance data quality. We focus the discussion specifically on the factors associated with NEST recruitment and sexual network data collection as well as how the study addressed STI stigma, specifically regarding syphilis, among participants.

NEST Recruitment Strategies

Each study site developed recruitment procedures that were guided by consultations with local CABs on the best practices for community engagement. Recruitment procedures included RDS; flyers at relevant locations; targeted community events; partnerships with HIV testing agencies; clinics, hospitals, and community-based organizations; and social media (eg, by placing advertisements on Facebook and dating apps such as Grindr). For RDS, each seed was given coupons to disperse to their sexual or social network peers. RDS was kickstarted at each site during the formative phase of NEST (ie, before pandemic) when in-person meetings could be held to introduce the study to the local community. Approximately 54% (34/63) of the participants in Chicago, 36.9% (164/444) of the participants in Baltimore, and 24.9% (60/241) of the participants in Columbus were recruited through RDS. For Chicago, RDS was the primary method for study recruitment; however, this method proved challenging to implement because the participants' coupons were often not distributed, and many coupon recipients could not be located or were ineligible for the study.

Recruitment methods across sites evolved based on initial enrollment. The RDS recruitment method was adapted over the course of the study in Chicago. Initially, only seeds with a new, untreated diagnosis of syphilis were recruited. To include a larger sample of MSM, eligibility criteria were later expanded to include seeds with a history of syphilis in the last 6 months. In contrast, Baltimore started with broader eligibility criteria, which were narrowed during the study to identify more potential participants with a recent syphilis infection. These eligibility changes were approved by the local IRBs.

Missing and Truncated Sexual Network Data

In addition to the self-administered survey, a central task of NEST data collection was for participants to provide a list of their sexual partners' names, nicknames, or aliases and to describe the demographic (ie, for all partners) and behavioral characteristics (ie, for 3 most recent sex partners) to an interviewer. Whether occurring in person or remotely during the COVID-19 pandemic, this face-to-face activity may have been onerous for some participants who had difficulty recalling such details accurately. Furthermore, participants may not have wanted to disclose behaviors to an interviewer because of social desirability concerns, such as anonymous sexual partners and the sensitive nature of questions about recent sexual behaviors [58].

To enhance data quality, study sites relied heavily on staff training of network elicitation methods and use of the appropriate software. However, as is common with egocentric network studies, there may have been a truncation of partnership data when interviewers asked participants about the characteristics of recent sex partners (eg, last 3 partners in the past 3 months) [59,60]. Participants may have prioritized reporting partners that they knew more about and omitted those for whom they had less information. The biases associated with methods of partner recall in egocentric network studies are important to consider when studying STI or HIV transmission. When designing a sexual network study, investigators can compare the NEST study methods presented here with other methods for partner elicitation [61,62] to determine the best practices for describing network connectivity when relying on participants' retrospective reports.

STI-Related Stigma

STI-related stigma among MSM hinders the disclosure of potential STI exposure and symptoms to health care providers, which may influence timely STI testing and treatment [63,64]. Medical mistrust can also be a barrier for routine sexual health care engagement, particularly among Black MSM given their historical and present experiences with racism in medicine, especially syphilis care [65]. Prior qualitative work has shown that syphilis has a stronger stigma among MSM than HIV [66]. In some sites, potential participants reported reluctance to enroll in NEST because of the study's emphasis on syphilis testing. To address these concerns, site-specific staff used participatory research techniques to build trust with Black MSM and provide a forum for researchers and the community to interact and exchange information about the study [43,66].

Similar efforts to reduce stigma associated with syphilis included the development of forward-facing materials for NEST, such as rebranding the study name for local websites, and using local community members as models for advertisements and flyers

[67]. For example, in Baltimore, the NEST study was named USHINE ("Understanding Sexual Health in Networks") to emphasize the study's broader focus on sexual health issues rather than on syphilis specifically. Study sites are evaluating locally how these recruitment and enrollment materials affected study recruitment and retention to inform future network studies involving MSM.

Dissemination of Study Findings

NEST study sites used a community-based participatory research approach to inform all research activities, including the development of a research dissemination strategy. For example, Baltimore's NEST study, USHINE, worked with CAB members to develop a plan to share results with participants, including share-back events and informational cards given to participants (web-based during COVID-19) after each study visit. The CAB members emphasized ways to share sexual health messages on these study follow-up cards, which included medical information about syphilis, other sexual health factors specific to the community (eg, syphilis rates), local resources, and events of interest. In addition to the study follow-up cards, CAB members encouraged study staff to use social media to communicate the results of the study and to promote local sexual health resources.

Conclusions

NEST data provide a unique opportunity to understand changes in sexual behaviors and sexual networks among MSM participants, particularly as STI case rates and STI or HIV prevention and care activities continue to be affected by COVID-19. The individual- and network-related characteristics of MSM can provide a more complete picture of syphilis acquisition and transmission dynamics within communities. Understanding the potential pathways for syphilis transmission is critical for addressing rising syphilis rates among MSM and developing network-informed behavioral interventions aimed at syphilis control.

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Data Availability

The data sets generated during or analyzed during this study are not publicly available because the data are owned by each of the institutions affiliated with this project in Baltimore, Maryland; Chicago, Illinois; and Columbus, Ohio. Persons interested in analyzing these data should email the site of interest to inquire about data access.

Conflicts of Interest

None declared.

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Abbreviations

CAB: community advisory board
CDC: Centers for Disease Control and Prevention
DSTDP: Division of Sexually Transmitted Disease Prevention
EMA: ecological momentary assessment
IRB: institutional review board
IWTK: I Want the Kit
MSM: men who have sex with men
MTL: Molecular Testing Labs
NEST: Network Epidemiology of Syphilis Transmission
P&S: primary and secondary

PrEP: pre-exposure prophylaxis
RDS: respondent-driven sampling
REDCap: Research Electronic Data Capture
STI: sexually transmitted infection
USHINE: Understanding Sexual Health in Networks

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Protocol

A Trans Youth of Color Study to Measure Health and Wellness: Protocol for a Longitudinal Observation Study

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Abstract

Background: Growing research on transgender youth is accounting for the variety of ways in which young people define their genders and sexualities. Because of this growing representation, more research is needed to understand how intersectional identities and stigma affect risk for HIV acquisition along the HIV care continuum and engagement in mental and physical health care. Little is known about accessibility to HIV-related prevention services of nonbinary and transmasculine youth, and further understanding of the impacts on transfeminine people—those who have historically faced the highest prevalence of HIV positivity—is crucial.

Objective: The overarching aims of the Trans Youth of Color Study are to conduct longitudinal research with a cohort of transgender minority youth (TGMY), explore factors that aid in the prevention of new HIV infection and transmission, and reduce HIV- and AIDS-related disparities by focusing on successful engagement in care. Findings from this research will be used to inform the development of new interventions designed to engage TGMY in the HIV prevention and care continua.

Methods: Longitudinal research (baseline and follow-up assessments every 6 months for 3 waves of data collection) followed a cohort (N=108) of transgender youth of color recruited in Los Angeles, California, United States. Participants were recruited using multiple community-informed strategies, such as from local venues, social media, and participant referral. In addition to self-report surveys, urine was collected to assess recent use of illicit drugs, and blood, rectal, and throat swabs were collected to test for current sexually transmitted infection and HIV infection. Additional blood and plasma samples (10 mL for 4 aliquots and 1 pellet) were collected and stored for future research.

Results: Participants in the Trans Youth of Color Study were recruited between May 25, 2018, and December 7, 2018. Baseline and longitudinal data are being analyzed as of August 2022.

Conclusions: The findings from this research will inform adaptations to existing evidence-based HIV prevention interventions and help to guide new interventions designed to engage TGMY, especially those who are Black, Indigenous, or people of color, in the HIV prevention and care continua.

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KEYWORDS

AIDS virus; HIV; cohort study; gender minority; transgender youth

Introduction

Intersecting Identities Among Transgender Youth

The lesbian, gay, bisexual, transgender, queer, intersex, and asexual (LGBTQIA) community comprises an incredibly diverse community of people from many races, ethnicities, religions, and socioeconomic backgrounds who also share a wide variety of sexual identity– and gender-related experiences. Specifically, transgender individuals seem to experience unique and complex patterns of gender-related experiences throughout the life course [1,2].

Some transgender people may identify with a gender that differs from the sex that they were assigned at birth, and others may identify as being beyond the gender binary, such as nonbinary, genderqueer, gender nonconforming, agender, or other combinations of identities that reflect their personal experience [3].

Data on the prevalence of nonbinary individuals in the transgender community varies across studies, from 52% of 14,320 transgender survey respondents in the United Kingdom to 35% of 27,715 transgender survey respondents in the United States [4,5]. Furthermore, existing data highlight generational differences in nonbinary groups, which illustrate a greater gender-fluid expression among younger individuals [5,6]. However, existing information on these gender minority groups is limited and mostly based on the experiences of White, middle-class populations [7].

Stigma and Health Disparities Among Transgender Youth

Racial and ethnic minorities who also identify as transgender and nonbinary remain particularly underexplored, and this is evident in the lack of available resources designed to help these individuals achieve a higher quality of life [8,9]. Specifically, among these groups, transgender minority youth (TGMY; ie, transgender and nonbinary people of color aged between 16 and 24 years) seem to represent the greatest opportunity to intervene and improve long-term health behaviors; this is due to a combination of environmental factors that put them at increased risk to be victimized by others, experience internalized transphobia, and have trouble in finding affirming resources; for example, TGMY are 3 times more likely than young men who have sex with men (YMSM) to experience workplace discrimination [10], health care providers report a lack of preparation to care for TGMY, and many institutions lack policies and routine practices to support the needs of transgender patients [11,12].

Because of their experiences with multiple identities—for example, gender identity, sexual identity, and racial and ethnic identity—TGMY face more complex patterns of intersectionality, which may lead to greater experience of various forms of stigma (eg, violence, isolation, and harassment). These experiences, in turn, systemically place stress on TGMY, placing them at higher risk for mental health conditions (eg, depression, anxiety, and suicidality); substance use; and sexual health risk, including HIV transmission and acquisition [2,9,13-17].

Regarding sexual health, data show that 14% of transgender women and 3% of transgender men live with HIV compared with <0.5% of the general American population [18,19]; 36% of transgender women and 23% of transgender men who seroconverted during the period from 2009 to 2014 were aged between 13 and 24 years [14]. Perhaps contributing to these disparities, 25% to 43% of TGMY report experiencing unstable housing or homelessness [20,21], 67% report engaging in sex work [20], and 31% report experiences of sexual violence in the past 12 months [22].

A Trans Youth of Color Study

Because of this increased risk for violence and victimization and the necessity to enhance our contextual understanding of multiple forms of stigma faced by TGMY in relation to their increased risk for HIV [8], we applied for an administrative supplement to our existing cohort study [23] to longitudinally observe a cohort of TGMY of color from Los Angeles, California, United States. There has been little research highlighting the developmental health trajectories of transgender and nonbinary youth as well as long-term outcomes for overall well-being. This paper describes the process of designing a longitudinal study to address the gaps in our contextual understanding of TGMY of color and their lived experiences.

Overarching Goal and Specific Aims

The Trans Youth of Color (TRUTH) Study aimed to expand the research of our parent grant, the Healthy Young Men's (HYM) Cohort Study (U01DA036926). As a supplement to this parent project, the TRUTH Study proposed to recruit a sample of 125 African American and Latinx young transgender women and collect 2 waves of data. Herein, we highlight the process of expanding our eligibility criteria and aims through iterative community-informed research. The overarching aim of the project is to better understand the unique challenges and opportunities regarding engaging these young transgender people in primary care and the HIV prevention care continuum.

The specific aims are as follows:

- Aim 1: Conduct qualitative research (focus groups and one-on-one interviews) with transgender youth of color to better understand what linkage, engagement, retention to primary health, pre-exposure prophylaxis (PrEP), and antiretroviral therapy care and adherence mean to them to identify potential strategies for intervention.
- Aim 2: Characterize transgender youth of color on measures of (1) alcohol and illicit drug use; (2) sexual risk behaviors, including sex work; (3) use of HIV testing and prevention services; (4) incidence of HIV and sexually transmitted infections (STIs); (5) use of hormone therapy (physician prescribed or obtained in other ways); (6) insurance status and access to health care services, including primary care and HIV and AIDS treatment services; (7) engagement in,

and use of, health care and HIV and AIDS treatment services; and (8) use of PrEP. We harmonized data collection with the HYM Cohort Study for some measures and administered additional transgender individual–specific measures. This will allow us to compare the responses of transgender youth of color with those of YMSM.

- Aim 3: Identify transgender individual–specific barriers and facilitators to engagement in primary health and HIV-related care, including transgender individuals' coping and adjustment strategies, gender identity, gender-related stigma, self-esteem, empowerment, lack of culturally competent providers, and use of services for transgender individuals.

Theoretical Model and Conceptual Framework

Our HYM Cohort Study found that YMSM of color experience the highest rates of risk factors as framed by syndemic theory, which posits that accumulations of health problems can potentially compound and amplify the negative impact of other health problems [24-26]. For YMSM of color, health issues related to alcohol and substance use, intimate partner violence (IPV), depression, and other health care factors affect wellness; in addition, overlapping stigmas such as racism, discrimination, and homophobia are associated with negative health impacts. Within the HYM Cohort Study sample, 87% of the participants reported experiencing racism, 76% reported experiencing homophobia, and 26% tested positive for ≥1 STIs [27]. These experiences have each been found to be significantly associated with misuse of substances and involvement in sexual practices with higher risk for HIV transmission [28,29].

The proposed analyses will examine syndemic risk factors as predictors of HIV infection among transgender youth of color as well as engagement in care, including HIV prevention, testing, and treatment. The TRUTH Study will focus on areas affecting the health and wellness of transgender youth, such as engagement and retention to primary health care, access to PrEP and antiretroviral therapy, alcohol and substance use, and sexual health behaviors. Through understanding the impacts of intersectional stigma on this cohort, we also hope to observe possible facilitators to care and wellness, such as coping and adjustment, self-esteem, community belongingness, and positive transgender identity.

The purpose of this paper is to describe the protocol for the TRUTH Study: the community-informed method of study design, research methods, and longitudinal recruitment and retention.

Methods

Consent and Ethics Approval

As a supplemental study to our longitudinal HYM Cohort Study, which involves following a cohort of 450 Black or African American, Latinx, and multiracial YMSM in Los Angeles [23], the TRUTH Study has been reviewed and approved by the institutional review board of Children's Hospital of Los Angeles (CHLA-14-00279). Herein, we outline the process of identifying eligible TGMY participants, the process of selecting our final sample criteria, obtaining informed consent, and collecting data from the participants.

As a community-oriented research project, an important component of the informed consent process was meeting participants *where they are at*, meaning conducting field-based, face-to-face consent visits at locations most convenient to participants. All participants provided written informed consent after reviewing consent documents with research field staff. Participants were provided with infographics explaining the consent process (assent process for participants aged <18 years) and the process of participating in the project.

All participants were identified, screened for eligibility, and, if eligible, invited to participate in the study, as described in the following sections. All participants provided written informed consent during a face-to-face consenting visit. A certificate of confidentiality was obtained from the National Institute on Drug Abuse, and a waiver of parental consent was obtained for participants aged 16 to 17 years.

Study Design

Foundational research with the HYM Cohort Study informed the creation and implementation of the TRUTH Study design [23]. Originally, the TRUTH Study proposed to collect two waves of data (baseline and 6-month follow-up assessment). Because of interest in the participant population from our collaborators, scientific committee, and community partners, as well as the demonstrated need for more research on TGMY represented by the TRUTH Study in comparison with other available research, a third wave of data collection was implemented. The cohort consists of 108 TGMY participants. Participants were recruited using multiple community-informed strategies, such as recruitment from public venues, social media, and respondent-driven sampling design described herein.

Modified self-report surveys using scales from the HYM Cohort Study were used to assess social, behavioral, and health concerns specific to TGMY and their intersectional lived experiences. In addition to these measures, data collection also included biological markers for recent illicit substance use via urine analysis, rapid HIV testing, and STI testing. Following our protocol for the original HYM Cohort Study, we collected additional samples of blood (10 mL for 4 aliquots and 1 pellet) and a rectal swab to be stored in a biorepository for future analysis. These samples were collected once during the project [23]. Care was taken to ensure gender-affirming testing environments for the TGMY research participants—specific testing measures used are detailed in the Measures section. The TRUTH Study presents an opportunity for assessing the protective factors that affect social determinants of health, the development and suitability of transgender individual–specific interventions involving evolving biomedical prevention interventions such as PrEP and postexposure prophylaxis, and the impact of affirmation on mental health.

Study Participants

Although we had initially proposed to recruit young Black or African American or Latinx transgender women, our community advisory board (CAB), youth CAB (YCAB), and scientific advisory group strongly encouraged us to broaden our

recruitment strategy to include transgender women, transgender men, and gender nonbinary youth (including gender nonconforming, gender fluid, genderqueer, and gender identities other than cisgender). They also advised us to expand our eligibility to include all Black, Indigenous, and other youth of color. Although much previous research has focused on transgender women and their risk for HIV acquisition because they experience intersectional forms of discrimination, there is growing understanding that research needs to be conducted to understand HIV and STI risk among all transgender people experiencing these overlapping stigmas.

Youth were eligible if they (1) were aged 16 to 24 years; (2) self-identified as transgender, gender nonconforming, or nonbinary; (3) spoke English (because interviews were conducted in English); (4) identified as Black or African American, Latinx, Asian or Pacific Islander, Indigenous, or multiracial; and (5) lived in Los Angeles. Ultimately, we recruited 108 TGMY between May 25, 2018, and December 7, 2018.

Recruitment

Identifying Appropriate Outreach Methods

On the basis of the lessons learned during recruitment for the HYM Cohort Study, the research staff determined that a wide variety of recruitment techniques would be necessary to reach TGMY of color in the Los Angeles area. Conversations with our community partners, including members of our provider CAB and YCAB as well as service providers at local clinics, informed our methods for connecting with potential participants. In total, 281 potential participants were screened for eligibility, of whom 108 (38.4%) consented to participate in the project and completed a baseline assessment.

One of the difficulties that arose when recruiting TGMY was that it was impossible to know someone's gender without asking them. At LGBTQIA youth events, any youth may have met the eligibility criteria; therefore, many participants at these events needed to be screened so that we could know more about their identity and experiences. Although there are spaces dedicated to the LGBTQIA community in Los Angeles, the number of spaces intended exclusively for transgender youth is limited. Although LGBTQIA youth events were identified and attended by study staff members, venue-based outreach programs conducted at several of these events and clinics across our 6-month recruitment timeline only accounted for 19.4% (21/108) of the recruited participants.

Recruitment Using Social Media

Because of the challenges associated with the in-person recruitment of TGMY, as well as the lessons learned from the recruitment of the HYM Cohort Study, our community partners and research team understood that web-based advertising through social media might be an effective method of recruitment. We used paid advertising with images of gender-diverse youth alongside transgender imagery (such as the transgender pride flag and transgender symbol) to recruit participants on Facebook and Instagram. These sites were identified by our YCAB as places that TGMY frequent and feel most comfortable fully expressing themselves. Participants filled out a screener with their name, demographic information, and contact information. If they met the eligibility criteria for the TRUTH Study, a member of the research field team contacted them to verify their eligibility and invite them to participate in the project. This recruitment strategy accounted for 48.1% (52/108) of the total enrolled participants.

Other Recruitment Methods

Participant referrals were recommended by both our CAB and YCAB as an effective strategy for connecting with TGMY, and 24.1% (26/108) of the enrolled participants were recruited using this respondent-driven sampling design. YCAB members and study participants could earn a cash incentive of US $10 for each eligible participant they referred, for up to 5 participants, and US $50 in incentives.

Community partnerships were fostered by the TRUTH Study field team through outreach to LGBTQIA-specific organizations across the Los Angeles area. Specialty clinics in the Los Angeles area served as eligibility screening locations. Several high school and college Genders and Sexualities Alliances were identified, and they expressed interest in disseminating recruitment materials. Recruitment scripts were sent via email to college email listserves as well as community organizations. Although 79 participants were recruited using this community venue–based sampling, only 21 (27%) enrolled into the project. The TRUTH Study also ran advertisements via Craigslist to reach potential participants. Although previous outreach through sites that post sex work–related advertisements has been demonstrated to be successful, the passing of the Stop Enabling Sex Traffickers Act and the Fight Online Sex Trafficking Act and removal of these advertisements from Craigslist and other sites have significantly decreased the activity of these sites. Table 1 presents the recruitment data for each recruitment method.

Table 1. Enrollment by recruitment method.[a]

Recruitment method	Participants recruited (N=281), n (%)	Participants enrolled (N=participants recruited by this method), n (%)	Participants enrolled (N=108), n (%)
Physical venue	79 (28.1)	21 (26.6)	21 (19.4)
Social media	142 (50.5)	52 (36.6)	52 (48.1)
Other web-based methods	14 (5)	9 (64.3)	9 (8.3)
Direct referral	46 (16.4)	26 (56.5)	26 (24.1)

[a]Of the 281 potential participants screened for eligibility, 108 (38.4%) consented to participate in the project.

Tracking and Retention

Longitudinal research conducted with participants experiencing intersecting, stigmatized identities requires specific thoughtfulness and strategies. The TRUTH Study used techniques previously demonstrated to be effective in the HYM Cohort Study for participant tracking and retention [23]. This protocol had been adapted from one used in previous studies to address the complexities of retention with an evolving population in a major metropolitan area [30]. The study protocol included retention strategies such as incentivized monthly check-ins via the participant's preferred contact method (eg, SMS text message, telephone call, email, Snapchat, and Instagram); additional incentives for contact information updates if participants changed numbers, address, or social media handles; TRUTH Study in-person social events; and STI or HIV test result disclosure and connection to community resources when needed. Our tracking and retention protocol yielded a retention rate of 97.2% (105/108) across 3 waves of data collection.

Community-informed research was essential to building a project that facilitated a safe and inclusive environment for a population with various gender experiences. These steps were important for collecting sensitive information. This involved not only meeting with community members and forming working advisory boards but also hiring research teams with a variety of experiences and identities that represented the population under study. Representation within our field and research staff was necessary to demonstrate our commitment to well-informed practices and to allow our research participants to see themselves reflected within the project team.

A key component of the retention strategy for the TRUTH Study was to pair a field team member with each participant throughout their duration in the project. From the initial eligibility confirmation telephone call to consent visits, study visits, and STI and HIV testing, participants work with the same field team member. This allows the participant to build trust and rapport in the project and ensures that communication about the project is from a single, trusted source. Staff changes may occur; therefore, specific protocols were established to ease the transition. New staff members are introduced by the existing researcher either via the participant's preferred method of communication (SMS text message, email, etc) or, preferably, during an in-person visit. Consistently updated participant records with contact information, preferred pronouns, insurance status, and day-to-day information help to facilitate these changes as well as eliminate the need for participants to share this information repeatedly with different study staff members.

In addition, the protocol involves obtaining consent to gather multiple forms of contact information. Participants are asked to provide as much of their information as they feel comfortable sharing, including their mobile phone numbers, email addresses, and social media handles, as well as address information, relevant school or work information, and a trusted family or friend contact. Contact information often shifts; therefore, participants are incentivized US $10 to update their contact information with their interviewer, reaching out proactively in the event of a telephone number or address change.

Incentivized monthly check-ins with study staff are built into the study protocol to encourage retention in the study. Between each wave, participants can earn money each month for responding to a check-in inquiry from their assigned field team member. Monthly check-ins are an opportunity for field team members to verify that the contact information is still active and to ask whether participants need referrals to any resources. A rich database of LGBTQIA-specific resources has been created by the field team, and it is available to participants on our study website as well as in an easily distributed PDF file. Participants also use these check-ins as a time to share life updates ranging from difficulties to excitement, such as milestones related to their transition (hormone access or surgery), changes in their access to medical care (through insurance or housing status), or achievements (school graduations and new jobs). If a participant fails to contact their researcher for 2 consecutive check-ins, the provided tracking information and public records (eg, criminal justice records) are used to attempt to reconnect.

Working with multiply marginalized participants highlighted many unique challenges. Our participants needed to be figuratively *met where they were at*. This required the study team to be adaptive and responsive to participants' needs to reschedule after missing a study visit, extend hours to accommodate participant schedules, and allow for participants to show up late for visits or even walk in for an unscheduled visit. Part of linking 1 research staff member to a participant—for continuity and stability—involved the use of unique mobile phones and numbers for each study staff member. Bidirectional communication between staff members and participants allowed for telephone calls, SMS text messages, emails, and other social media messaging (eg, Snapchat, Facebook Messenger, and Instagram) in a more fluid fashion. As mentioned earlier, participants were incentivized to keep their contact information up to date with their assigned research staff member.

In addition, all staff members on the project were trained in gender affirmation and competency. All research assistants and coordinators were educated to not assume participants' pronouns or identities, research nurses conducting specimen testing were instructed on using chosen names that may differ from those in hospital records, and policies governing other hospital personnel who interacted with participants were updated to affirm transgender and nonbinary patients more accurately within their systems.

CAB and YCAB

CABs and YCABs play a critical role in supporting community-partnered and community-informed research. When working with research populations who have been historically denied agency in research narratives about themselves, it is essential to demonstrate accountability and to include community partners in meaningful ways.

Our CAB was formed by inviting members of the HYM Cohort Study CAB and members of service providers and organizations serving gender-diverse populations to an open house to introduce the study. After providing initial feedback, the members were invited back to future meetings to provide guidance and input

on the study. CAB members included service providers in the local community, policy makers who focus on transgender issues, STI and HIV test counselors, and medical leads from clinics specializing in transgender individual–related health care. The CAB met bimonthly leading up to the launch of the study and quarterly thereafter.

YCAB members were gender-expansive youth of color recruited from the original HYM Cohort Study as well as youth advocates recommended by existing participants. Study coordinators for the TRUTH Study worked with research assistants on the HYM Cohort Study to identify participants who identified as transgender or nonbinary and invited them to join the YCAB for the TRUTH Study. These YCAB members were also allowed to refer additional members to the YCAB from their social networks. The YCAB met monthly in preparation for the study launch and quarterly during data collection. Before the onset of the COVID-19 pandemic, meetings were held in person, where food as well as stipends worth US $50 were provided to attendees. Meetings moved to the web via videoconferencing software after pandemic lockdown restrictions began. Agendas for the 2 advisory boards often involved study updates, data sharing, data interpretation, and new measure creation. The advisory boards provided information about what data to collect and about the data needs of community organizations. The YCAB provided feedback on proposed new measures and piloted the measures before study launch. Members of the YCAB gave input on which questions could be eliminated to reduce the overall survey length and highlighted and provided suggestions on language that should be updated before being administered to participants.

Our CAB and YCAB were created to provide support and feedback for all components of the study, from eligibility criteria through participant recruitment, including the creation and interpretation of survey measures. It is because of the guidance of the YCAB and CAB that we expanded our eligibility for the project and were able to capture valuable information about TGMY of color, particularly nonbinary and transmasculine youth for whom there is little existing HIV-related research.

Measures

Overview

The TRUTH Study measures were adapted from the protocol previously used to conduct the HYM Cohort Study with YMSM of color in the Los Angeles area [23]. The HYM Cohort Study focused on young sexual minority men of color; therefore, measures had to be adapted to be relevant for a gender-diverse sample of multiple sexual identities. Our CAB and YCAB were instrumental in providing guidance on how to restate phrases in the original measures; for example, “attraction to men” in previous measures was changed to “LGBTQ identity.” In addition, meetings with the YCAB and CAB identified additional constructs relevant to gender-diverse youth that were not assessed in the HYM Cohort Study. For these constructs, additional measures were either adapted (if not written for gender-diverse populations), added (if already constructed for gender-diverse populations), or created by the study team in conjunction with the YCAB and CAB when no existing measures were found.

TRUTH Study participants completed 3 study visits, with consecutive visits spaced 6 months apart. Study visits consisted of self-report survey measures, urine collection for substance screening, biorepository specimen collection, and STI and HIV testing. Consistent with the HYM Cohort Study, survey measures were administered by research assistants, with the more sensitive topics being self-administered using a web-based survey (eg, STI and HIV testing results history, sexual behaviors, substance use, suicidality, and gender-based discrimination); the goal was to provide additional confidentiality and to encourage honesty in responses [31,32]. The interview and self-administered survey required approximately 90 minutes to complete. Participants received US $105 to compensate them for their time and effort completing all study procedures. A description of the study measures follows.

Demographic Characteristics

Survey measures to obtain demographic information were modeled from the HYM Cohort Study protocol. Information collected included age, language spoken inside and outside the home, race and ethnicity, religion, residential stability, educational history and current employment status, access to food and food security, incarceration, and foster care experience [23]. Updates to the methods used to obtain demographic data were influenced by our CAB and YCAB members to ensure care when gathering demographic data from participants with intersecting identities; for instance, TRUTH Study participants reported multiple gender identities, racial and ethnic group memberships, and sexual identities and orientations across all waves of data collection rather than being forced to choose only one identity facet.

Primary Outcome Measures

Alcohol, Tobacco, Marijuana, and Illicit Drug Use

Substance use within the TRUTH Study was measured using the same scales and assessments as the HYM Cohort Study protocol [23]. TRUTH Study participants completed self-administered scales to assess lifetime, past 6-month, and past 30-day substance use as well as biometric urine screening for substances at each study visit. These scales are from the Monitoring the Future and 2014 National Survey on Drug Use and Health studies and ask about use of alcohol, nicotine, marijuana, lysergic acid diethylamide, phencyclidine, mushrooms, cocaine, crack, methamphetamines, ecstasy, stimulants, heroin, fentanyl, poppers, and prescription drugs used without a physician’s order [33]. The scales address frequency of use as well as location, circumstances, and substance use associated with sexual behaviors. Additional questions were added to these scales pertaining to shared needle use regarding hormones and bodily injections, such as silicone.

The point-of-care biometric urinalysis test administered at survey visits used the Integrated E-Z Split Key Cup II-10 Panel (Alere Toxicology) that measures metabolites of amphetamines, methamphetamines, benzodiazepines, cocaine, ecstasy, phencyclidine, methadone, fentanyl, opiates, and marijuana. This test can detect marijuana use for up to 30 days and other drugs from 1 to 4 days after use [34,35]. Participants could opt

to receive a copy of their substance use results during their study visit.

Problem Alcohol and Marijuana Use

Alcohol and marijuana misuse was assessed using standardized measures, including the Alcohol Use Disorders Identification Test [36,37], which assesses frequency of participants' alcohol use, and items from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [38], and Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [39], which assess marijuana use and its associated life impacts.

Sexual Activity, Partners, and HIV Risk and Protective Behaviors

Survey measures looking at sexual activity, number and genders of sexual partners, and use of protective factors such as PrEP and condoms were adapted from the HYM Cohort Study protocol scales. The TRUTH Study team worked to generate affirming methods of measuring sexual activity for transgender and nonbinary participants because the HYM Cohort Study scales were adapted from the EXPLORE study specifically for YMSM [35,40]. As little is known about the sexual risk factors for nonbinary young people, care and consideration should be taken in adapting sexual activity scales for transgender and nonbinary populations so that adequate data are collected while respecting participants. On the basis of feedback from our CAB and YCAB members, options were added to increase participant comfort in answering sexual activity–related questions. Participants were prompted to enter the words they used to describe *penis* and *vagina*, and these words were populated into the survey module. This functioned to affirm participants' own language for their bodies and the bodies of their sexual partners, as well as to avoid distress related to dysphoria around gendered words for body parts. Additional types of partners and types of sexual interactions also needed to be added to the questionnaires. Participants preferred to be able to choose their partner's specific gender (such as *genderqueer* or *trans femme*) as opposed to choosing from *male, female, or intersex*. The specific questions used to assess sexual activity and partners are outlined in the HYM Cohort Study protocol [23].

HIV and PrEP knowledge was assessed in the self-administered STI and HIV testing section of the survey. HIV knowledge was assessed using a 2-part question from Hou et al [41] as well as a 15-point scale about status knowledge and treatment-based beliefs created by Kalichman et al [42]. PrEP knowledge and willingness were measured using a 10-item scale from Grov et al [43]. PrEP and HIV-related treatments were discussed with participants during the HIV testing process as per Los Angeles county HIV test counselor guidelines.

STI and HIV History and Test Results

Participants self-reported their lifetime and recent history of HIV and STI testing and HIV status. This section of the survey asked about testing behaviors, HIV and STI testing results, access to treatment, as well as any hesitance around HIV and STI testing. Condom use across partners as well as condom self-efficacy were also measured [44]. Participants were also asked whether they had exchanged sex for things such as money, hormones, transportation, or a place to stay ever in their lifetime and within the last 6 months.

Research staff members administered rapid HIV testing and a complete STI testing panel to participants at each study visit. HIV and STI testing protocols followed the methods used for the HYM Cohort Study [23], with the addition of optional site-specific vaginal swab specimen collection and gender-affirming testing administration instructions. HIV status was measured using a point-of-care whole blood finger-stick device. Participants self-collect vaginal or frontal, rectal, and pharyngeal specimens for *Neisseria gonorrheae* and *Chlamydia trachomatis* nucleic acid amplification. Syphilis testing was conducted using whole blood samples collected via venipuncture using rapid plasma regain and treponemal antibody testing. All research staff and nursing staff members associated with the project underwent an LGBTQIA health care training to be able to provide compassionate care.

Participants with positive test results were connected to members of the research staff certified in HIV and STI test counseling and then referred to an appropriate community clinical partner for treatment. Research staff members were available to participants via SMS text message, telephone, and email to assist with accessing care.

Measures of Overall Health, Health Care Access, and Mental Health

Overall health, well-being, and access to health care were measured using scales adapted from those used with the HYM Cohort Study [23]. Questions about insurance coverage, access to a primary health clinic, number of visits in the past 12 months, and reasons for health care visits were measured using items from the National Longitudinal Study of Adolescent to Adult Health and the National Survey of Children's Health [45]. Participants were asked about their perception of their own health, any chronic health conditions (including mental health diagnoses), and the level of impact these health conditions had on their everyday functional abilities. These scales were adapted to include questions about hesitance to seek care because of perceived gender-based discrimination, comfort discussing gender and sexual questions with a provider, disclosing one's gender to one's provider, and how often clinicians used correct pronouns. The importance of being seen in an LGBTQIA-specific clinic was also measured. Hormone and other bodily injection use (such as silicone) for gender presentation was assessed at each visit. This questionnaire asked about current hormone or injection use, frequency of use, source of hormones (prescription, a friend, or the internet), method of use, and method of administration (self-injection, nurse injection, etc). Access to mental health care providers to write letters for gender-affirming procedures such as hormones or surgery was assessed.

Possible Mediating and Moderating Constructs

Overview

Although we hoped to capture the mental well-being of the TRUTH Study cohort using clinical assessments, we also included measures that were hypothesized to be protective factors against negative mental health outcomes. The protective

factors included optimism, resilience, and mindfulness. Assessments of these factors were adapted from the HYM Cohort Study protocol with attention to possible life experiences specific to TGMY [23].

Mental Health, Emotion Regulation and Coping, Optimism, Resilience, and Mindfulness

Depression, anxiety, and somatization were measured using the 18-item Brief Symptom Inventory, which asks participants to rate, using a 5-point scale, how extensively a symptom or trait has bothered them in the last week [46]. Lifetime, past 6-month, and recent self-injury and suicidality were measured in a multistep, escalating scale (ie, questions about suicidal thought, ideation, and attempts were asked). Participants who responded yes to these questions were connected to transgender individual–specific mental health resources by their assigned research assistant.

Childhood Abuse and Trauma, Stressful Life Events, and IPV

Childhood abuse and trauma experiences were measured by the Bernstein Childhood Trauma Questionnaire [47]. IPV was measured using a 14-point scale adapted from Straus et al [48]. This scale measures both victimization and perpetration of IPV and specifically cites modern interactions that young people have, such as controlling social media or mobile phone use [49].

A 43-item stressful life events scale was adapted from the HYM Cohort Study [50] and updated to include items related to transgender individual–specific experiences. This scale asks participants whether they had experienced a stressful life event, and if yes, to rate the amount of stress that this event caused on a 10-point scale. Some of the adapted questions involved family arguments over gender, coming out to family members or friends, or losing a friend because of transitioning.

Social Support

Perception of general social support among family, friends, and a *special person* (such as partner or close friend) was measured using a 12-item scale [51]. Social support specifically relating to participants' transgender identity, such as support from family members, friends, and social belongingness within LGBTQIA communities, was measured through 4 questions adapted from Bockting et al [52].

Racism, Transphobia, and Discrimination

Perception of stigma against transgender and gender nonbinary people was measured using a 6-item scale asking participants to rank how they perceive other people's reactions to transgender people. This scale has been adapted for transgender and gender minority populations [53].

Participants complete a self-administered 54-item scale regarding the interactions they have had of lifetime and recent racism [54], transphobia, discrimination, and harassment [55]. During the second wave of data collection, we used a retrospective bullying questionnaire from Hamburger et al [56] to ask participants about their experiences across childhood, teenage years, and into young adulthood.

Positive Transgender Belongingness and Positive Transgender Identity

Positive sense of self and perceived belongingness within the transgender community were also assessed. Positive transgender identity was measured using a 24-item scale adapted from a scale previously used to measure positive LGBTQIA identity and community belongingness. Questions such as "I embrace my identity" and "I feel a connection to the community" were asked on a 5-point scale. The measure can be scaled to measure different factors associated with positive self-identity, such as authenticity, relationships, commitment to social justice, and self-acceptance and awareness [57].

Homegrown Scales

In collaboration with our YCAB and CAB members, we convened regular meetings to determine what research questions would be most beneficial and influential to the community. Feedback from our meetings led to the creation of several new scales. To capture the differing experiences of comfort being *out* to others about their gender identity, several questions were used to assess the age at which the participants first identified as transgender or felt that they had a gender identity that did not align with the sex assigned to them at birth, when they first told someone about their gender, and how often they share about their gender with others. Participants were asked about their pronouns and possible shifts in pronoun use; appropriate pronoun use by friends, family, coworkers, and community members; and how often they had been asked about their pronouns. They were also asked about experiences of gender affirmation and how they felt about achieving affirmation through clothing, social cues, medical procedures, and spirituality.

Qualitative Questions

Our YCAB encouraged us to use open-ended questions at the end of the second and third waves of data collection. Because of the unique experiences of TGMY of color and their intersectional experiences, the YCAB members believed that open-ended questions would allow for more expression and nuance from participants. In collaboration with the YCAB, the research team developed the following open-ended questions:

1. How has the TGMY community empowered you?
2. What makes you euphoric in your gender?

Biological Specimens and Biorepository

TRUTH Study participants consented to providing biological samples (10 mL ethylenediamine tetra-acetic acid anticoagulated whole blood sample and 1 rectal swab) for our biorepository during one of their study visits. Samples were stored in a freezer maintained at a temperature of –80 °F (–62 °C) for future use.

Results

The TRUTH Study cohort was recruited between May 25, 2018, and December 7, 2018. Three waves of data collection occurred between May 25, 2018, and April 9, 2020. Baseline data were presented at the Center for HIV Identification, Prevention, and Treatment Services annual conference in January 2020. Baseline and longitudinal data are being analyzed as of August 2022. In

July 2020, we received additional funding from the National Institutes of Health (5U01DA036926) to conduct additional waves of data collection across 5 more years with our existing cohort and to recruit 250 additional TGMY of color to participate. The study team leadership met in September 2022 to review the performance of the measures—especially those measures that were adapted or newly created—and to make recommendations for future measures to include in future waves. The team decided to retain new or adapted measures for at least one additional wave to assess performance over time.

Discussion

Overview

This paper describes the addition of a gender-diverse sample complementary to the sample in the HYM Cohort Study [23]. We discuss the process of forming 2 community boards to advise recruitment, enrollment, marketing materials, study measures, and study design. Further, we discuss our methods for adapting measures developed for sexual minority men and other populations to be sensitive to, and relevant for, TGMY of color. The longitudinal nature of the TRUTH Study allows us to augment questions at each wave to address historical and structural changes that may affect the lives of TGMY of color as well as gender-diverse youth of color; for example, multiple global pandemics and a shifting policy landscape.

Transgender and gender minority youth, particularly those of color, exist at the intersection of multiple complex identities and experiences. From public health reform and social justice advocacy to youth empowerment and positive self-identity, it is imperative to consider the strategies needed to address disparities in health care and other social determinants that place TGMY of color at risk for negative health outcomes. Research conducted with TGMY of color needs to acknowledge the historical hierarchical structures that exist to gatekeep individuals from appropriate care and empowerment and work to heal this through community-informed research practices created by, and for, transgender people.

Although our sample experiences a host of systemic barriers, through the guidance of our advisory boards and by engaging in appropriate gender affirmation trainings we were able to create a space that allowed for a retention rate of 97.2% (105/108) across the first 3 waves of data collection. Our advisory boards provided instrumental feedback on where to recruit participants, what data to collect, and how to assess constructs in the survey. Our approach of connecting participants to a single staff member for communication and study visits provided stability across the life of the study. Staff members were provided with mobile phones, which allowed them to have a single source by which participants could contact them to provide updates and stay connected between study visits. We believe that these strategies combined to help us achieve a high level of retention.

Inclusive and Nonjudgmental Measures

Researchers looking to engage participants with multiply marginalized identities should strive to ensure that their research procedures do not accidentally further victimize the participants. Making sure that the measures are inclusive and nonjudgmental can reduce stress during the survey process. Any person who may interact with participants during the study process (including those outside the study team) should be trained to understand how the language they use and the tasks they perform may affect participants. Only then can we begin to build trust between research and multiply marginalized communities.

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Data Availability

Data from this study are available upon email request to the senior author (MDK). To enhance participant confidentiality, any data users must go through a review process and sign a data use agreement with the institution responsible for data safety before receiving data from the Trans Youth of Color Study.

Conflicts of Interest

None declared.

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Abbreviations

CAB: community advisory board
HYM: Healthy Young Men's
IPV: intimate partner violence
LGBTQIA: lesbian, gay, bisexual, transgender, queer, intersex, and asexual
PrEP: pre-exposure prophylaxis
STI: sexually transmitted infection
TGMY: transgender minority youth
TRUTH: Trans Youth of Color
YCAB: youth community advisory board
YMSM: young men who have sex with men

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Protocol

The COVID-19 Schools Infection Survey in England: Protocol and Participation Profile for a Prospective Observational Cohort Study

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Abstract

Background: One of the most debated questions in the COVID-19 pandemic has been the role of schools in SARS-CoV-2 transmission. The COVID-19 Schools Infection Survey (SIS) aims to provide much-needed evidence addressing this issue.

Objective: We present the study protocol and participation profile for the SIS study, aimed at assessing the role of schools in SARS-CoV-2 infection and transmission within school settings, and investigating how transmission within and from schools could be mitigated through the implementation of school COVID-19 control measures.

Methods: SIS was a multisite, prospective, observational cohort study conducted in a stratified random sample of primary and secondary schools in selected local authorities in England. A total of 6 biobehavioral surveys were planned among participating students and staff during the 2020-2021 academic year, between November 2020 and July 2021. Key measurements were SARS-CoV-2 virus prevalence, assessed by nasal swab polymerase chain reaction; anti-SARS-CoV-2 (nucleocapsid protein) antibody prevalence and conversion, assessed in finger-prick blood for staff and oral fluid for students; student and staff school attendance rates; feasibility and acceptability of school-level implementation of SARS-CoV-2 control measures; and investigation

of selected school outbreaks. The study was approved by the United Kingdom Health Security Agency Research Support and Governance Office (NR0237) and London School of Hygiene & Tropical Medicine Ethics Review Committee (reference 22657).

Results: Data collection and laboratory analyses were completed by September 2021. A total of 22,585 individuals—1891 staff and 4654 students from 59 primary schools and 5852 staff and 10,188 students from 97 secondary schools—participated in at least one survey. Across all survey rounds, staff and student participation rates were 45.2% and 16.4%, respectively, in primary schools and 30% and 15.2%, respectively, in secondary schools. Although primary student participation increased over time, and secondary student participation remained reasonably consistent, staff participation declined across rounds, especially for secondary school staff (3165/7583, 41.7% in round 1 and 2290/10,374, 22.1% in round 6). Although staff participation overall was generally reflective of the eligible staff population, student participation was higher in schools with low absenteeism, a lower proportion of students eligible for free school meals, and from schools in the least deprived locations (in primary schools, 446/4654, 9.6% of participating students were from schools in the least deprived quintile compared with 1262/22,225, 5.7% of eligible students).

Conclusions: We outline the study design, methods, and participation, and reflect on the strengths of the SIS study as well as the practical challenges encountered and the strategies implemented to address these challenges. The SIS study, by measuring current and incident infection over time, alongside the implementation of control measures in schools across a range of settings in England, aims to inform national guidance and public health policy for educational settings.

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KEYWORDS

COVID-19; SARS-CoV-2; school-based; epidemiology; infection control

Introduction

Context and Rationale

The novel coronavirus *SARS-CoV-2* outbreak was declared a global pandemic by the World Health Organization on March 11, 2020 [1,2]. By this date, *lockdowns*, including school closures, had begun to be implemented worldwide [3]. Early evidence indicated that children aged <18 years were significantly less likely to develop severe disease or die than adults [4], but asymptomatic cases could also contribute to disease spread [5]. Evidence from previous influenza outbreaks had identified children as the main drivers of infection, with school closures having a positive impact on infection control in the community [6]. Early in the pandemic, however, the extent of asymptomatic infection and the role of children and school environments in the transmission and control of SARS-CoV-2 were unclear [3,7-9].

Evidence indicated that on March 11, 2020, a total of 29 countries had implemented national school closures, and by March 18, 2020, this had increased to 107 countries [10]. In England, schools were closed for in-person teaching from March 23, 2020, to all but children of key workers and vulnerable children [11]. However, school closures are linked to detrimental educational, social, mental health, and well-being impacts on children [12,13]. Negative economic and well-being effects are also seen in families, with inequity in such impacts seen across income backgrounds and ethnicity and in single-parent households [14,15]. Consequently, school closures have been considered a measure of last resort with the policy intent of limiting closures to a minimum. Therefore, there was an urgent need to understand transmission within schools and the potential risk of transmission to and from communities [16], as well as ways of minimizing these risks when schools were open [17-19].

Research and surveillance activities to assess SARS-CoV-2 transmission in communities, hospitals, and care homes in England were initiated during the lockdown in spring 2020 [20,21,22]. However, the investigation of SARS-CoV-2 transmission in schools in the United Kingdom was primarily limited to modeling studies conducted between March 2020 and June 2020 [23-25]. International outbreak investigations early in the pandemic suggested that although schools are a potential source of infection, for the most part, few infection clusters were linked to schools, attack rates were reported to be low, and there was evidence of reduced susceptibility to infection in younger children [26]. Some exceptions were noted; for example, school outbreak studies in France and Israel were considered linked to poor infection control practices [27-29].

As the first wave of the pandemic eased in England, schools began a phased reopening in June 2020, limited initially to academic years 1 (ages 5-6 years) and 6 (ages 10-11 years) in primary schools and years 10 (ages 14-15 years) and 12 (ages 16-17 years) in secondary schools. Government guidance was produced for schools on implementing social distancing and infection control measures, including limiting class sizes, grouping children in *bubbles* and limiting contact between bubbles; hand washing and hygiene; and requiring those with a positive SARS-CoV-2 test result, alongside their contacts, to remain at home. This partial reopening was successful in that there were very low rates of infection and outbreaks during the 6 weeks of partial reopening of schools [30,31]. From September 2020, all students were invited to return to full-time in-person teaching in England. In addition to concerns about the impact of increased transmission exposure on students, staff, and their families, there were additional challenges faced by staff in implementing, and both staff and students in following, school preventive measures [10,32].

Despite an increase in the number of studies investigating SARS-CoV-2 transmission and its impact on school-age children worldwide [33,34] and in England specifically [20,30,31,35], there remained a limited number of studies following large

cohorts of staff and students assessing both point prevalence and antibody conversion, school-level preventive measures, and changes in behaviors and perceptions during periods of high and low community infection rates. The Schools Infection Survey (SIS), a collaboration among the London School of Hygiene & Tropical Medicine, UK Health Security Agency (UKHSA), and Office for National Statistics (ONS), was therefore rapidly commissioned by the UK Department of Health and Social Care to provide critical data from the 2020-2021 academic year to fill this gap.

Aims and Objectives

The aim of the COVID-19 SIS was to assess the role of schools in SARS-CoV-2 infection and transmission within school settings and investigate how transmission within and from schools could be minimized by exploring the implementation and feasibility of school COVID-19 prevention and control measures. SIS specific objectives, within selected primary and secondary schools, were as follows:

1. Estimate SARS-CoV-2 antibody prevalence and incidence based on antibody conversion among students and staff, measured at termly intervals during the school year.
2. Measure the prevalence of current SARS-CoV-2 infection among students and staff, measured at half-termly intervals during the school year.
3. Monitor attendance rates and the proportion of and reasons for full or partial school closure.
4. Assess the feasibility; acceptability; and staff, student, and parent experience of school implementation of SARS-CoV-2 control measures and the factors affecting their implementation.
5. Conduct investigations of selected outbreaks in schools to determine the risk of transmission within and between classes and schools and among students, staff, and other household members.

In addition to the 5 primary objectives mentioned, we planned to investigate contact patterns and evaluate individual-, school-, and community-level risk factors.

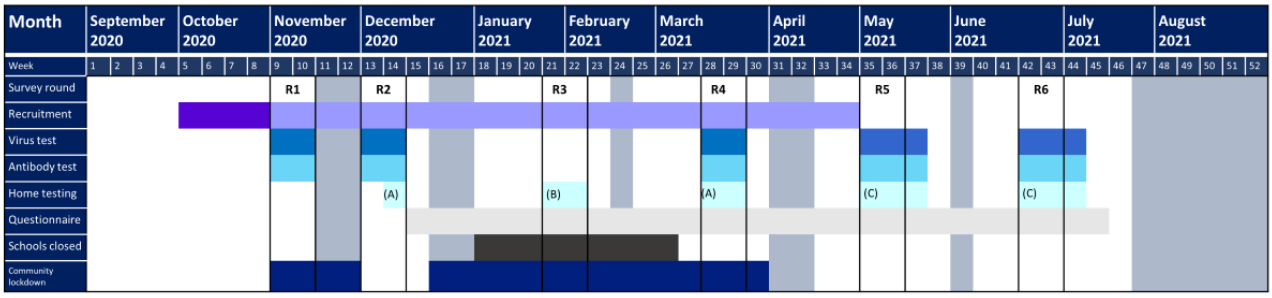
In this paper, we present the study design and protocol, recruitment, and participant profile across the 2020-2021 academic year and discuss SIS strengths, challenges, and adaptations during the study period—between November 2020 and July 2021.

Methods

Study Design

SIS is a cohort study in which biological samples for virus and antibody tests and questionnaire data were collected from staff and students at regular intervals throughout the school year (Figure 1), with antibody prevalence and conversion, as well as viral prevalence, at points in the academic year as key outcome measures. Electronic questionnaires were used to collect data on the risk factors for infection and additional indicators, such as prior positive tests for SARS-CoV-2. We also obtained school attendance records; conducted implementation research to assess the implementation of preventive measures within schools as well as perceptions of their feasibility, acceptability, and broader impact through surveys and semistructured interviews; and conducted detailed investigations in selected schools where there were suspected outbreaks.

Figure 1. The Schools Infection Survey study design and time line. Grey columns indicate school holiday periods. Dark purple indicates initial school and participant recruitment period and light purple indicates period of rolling recruitment for schools and participants. (A) indicates home-testing kits (antibody tests and viral swabs) for any participants who were not in school on the day of the school surveys, (B) indicates home-testing kits (antibody tests and viral swabs) for those who enrolled by January 28, 2021, and did not have an antibody result from either round 1 or 2 surveys. (C) indicates home-testing kits (antibody tests only) for any participants who were not in school on the day of the school surveys. R: round.



Study Setting and Population

SIS involved students and staff attending government primary and secondary schools in selected upper-tier local authorities (LAs) in England during the 2020-2021 academic year. The exclusion criteria for schools included special schools, student referral units and further education colleges (owing to the recognition that infection control issues and procedures were in many cases likely to differ in these settings), independent schools (for logistical reasons), and schools where other school-based COVID-19 studies were being conducted. Eligible participants included primary and secondary school students and staff for whom informed consent was provided. Year 11 students were excluded to minimize disruption of public examinations at the end of the academic year.

The design and implementation of the SIS study was informed by the prior COVID-19 Surveillance in School KIDs (sKIDs) study, which was initiated as schools partially reopened in June 2020 and involved weekly nasal swabbing and blood sampling among staff and students [30]. The sKIDs study also included an accompanying social science study of feasibility, challenges, and facilitators associated with the implementation of preventive measures at schools as well as the acceptability of biological

testing in schools [36]. Formative qualitative research in the form of interviews and focus group discussions undertaken in the sKIDs study, with head teachers, parents, and students, guided the development of many of the research questions in SIS.

Sampling

A multistage stratified sampling scheme was used. The first level of sampling was at the LA level. To study transmission, we aimed to oversample schools in parts of England where the risk of SARS-CoV-2 infection was higher at the beginning of the 2020-2021 school year. All 149 LAs in England were stratified according to the population rate of confirmed SARS-CoV-2 infection per 100,000 population from *pillar 2* testing—a centralized system of community-based swab testing—in the week, September 2, 2020, to September 8, 2020. Group 1 constituted the top 20% of LAs when ranked by transmission, and group 2 comprised LAs in the lower 80%. A total of 15 LAs were selected using simple random sampling, 10 from group 1 and 5 from group 2.

The sampling frame subsequently included all primary and secondary schools within the 15 selected LAs [37]. Sample allocation also prioritized secondary schools, as SARS-CoV-2 transmission appeared to be higher among older children [38]. Primary and secondary schools were sampled separately, with the aim of a sample ratio of 1:2 and approximately 70% (35 primary and 70 secondary) of schools from group 1 and 30% (15 primary and 30 secondary) from group 2. Because of the differing LA sizes and school numbers per LA, inverse probability weighting was used to distribute the sample more evenly across the LAs. For pragmatic reasons, the maximum number of academic trust–managed schools was capped at 4 per LA to allow efficient engagement.

In primary schools, where the average school population was 280 students, enrollment was offered to all staff and students. In secondary schools, which are larger, with an average school population of 990 students, for logistical reasons, we initially randomly selected 2 consecutive year groups (eg, years 7-8, 9-10, and 12-13; approximately 250 students) per school, in addition to offering enrollment to all staff [39].

Overall, 2 modifications were made to the sampling strategy following the commencement of SIS. First, in certain LAs where school enrollment in SIS was low after round 2, additional schools were sampled and invited to participate to increase the representativeness of all LAs sampled. Second, to increase student recruitment in secondary schools, schools were encouraged to open up enrollment to the remaining school years (except year 11) from January 2021.

Sample Size Considerations

The overall target sample size was principally influenced by pragmatic concerns, as it was constrained by antibody and virus testing capacity, with an estimated 40,000 tests deemed feasible for processing in laboratories per round. We assumed a response and follow-up rate of 60% among students and up to 90% among the staff. Schools were oversampled (approximately 250 schools) to compensate for school-level refusals and achieve participation of 150 schools.

We estimated cumulative incidence based on antibody conversion and its precision, assuming approximately 10% of students and staff would have a positive antibody test at enrollment, an average weekly incidence of 1 infection per 1000 individuals, with limited antibody reversion, and assuming a design effect of 2.3 for antibody testing to account for clustering because of sampling entire schools or school year groups. The design effect of 2.3 assumes an average prevalence of 10% antibody at enrollment and a between-school SD of 2.5% (ie, 95% of schools are between 5% and 15%), with 150 to 200 students enrolled per school. On the basis of the sample sizes, Table 1 presents the cumulative incidence of antibody conversion over different follow-up periods with statistical precision for each group at the 95% confidence level.

Table 1. Sample size required to detect certain antibody conversion rates with 95% CIs at different follow-up periods.

Individuals included and antibody conversion rate	4 weeks between follow-up	8 weeks between follow-up	12 weeks between follow-up
Secondary staff, approximate n=10,620			
Antibody conversion, % (95% CI)	0.4 (0.2-0.6)	0.8 (0.5-1.1)	1.2 (0.9-1.5)
Converting, n (95% CI)	42 (21-64)	85 (53-117)	127 (96-159)
Secondary students, approximate n=20,400			
Antibody conversion, % (95% CI)	0.4 (0.3-0.5)	0.8 (0.6-1.0)	1.2 (1.0-1.4)
Converting, n (95% CI)	82 (41-122)	163 (102-224)	245 (184-306)
Primary staff, approximate n=1440			
Antibody conversion, % (95% CI)	0.4 (0.0-0.9)	0.8 (0.1-1.5)	1.2 (0.3-2.1)
Converting, n (95% CI)	6 (3-9)	12 (7-16)	17 (13-22)
Primary students, approximate n=8460			
Antibody conversion, % (95% CI)	0.4 (0.2-0.6)	0.8 (0.5-1.1)	1.2 (0.8-1.6)
Converting, n (95% CI)	34 (17-51)	68 (42-93)	102 (76-127)

Engagement and Recruitment

Initial engagement and recruitment processes were carried out via email with the support of study engagement officers directly liaising with schools. We used a cascade approach: emailing a letter and information sheet to union officials, LA heads of education, directors of public health, and academic trust leaders. Head teachers at all 250 schools in the original sampling frame were contacted via email, with a letter detailing the study objectives and procedures. Head teachers were invited to enroll their school via a weblink and requested to email an invitation letter, information sheet, and registration link to all staff and parents or guardians in primary schools and all staff as well as parents from the 2 prespecified year groups in secondary schools. The schools were requested to email students aged ≥16 years (eg, in years 12 and 13). All eligible participants and parents or guardians were provided with instructions on completing a web-based informed consent form and enrollment questionnaire. Informed consent was obtained from staff, students aged ≥16 years, and parents or guardians of children aged 4 to 15 years via a secure web-based portal before enrollment. Verbal assent was obtained before biological sample collection at the school.

Because of the slow initial enrollment, several modifications were made to the engagement and recruitment strategies. First, a transition was made from a closed to an open cohort with rolling recruitment until round 5 in May 2021. Second, we developed a suite of paper-based communication materials to increase the accessibility of information, although enrollment was still digital via an email link, and several school-based internet-based forums were held to engage parents and students more directly. Finally, from 2021, participating schools were also provided with compensation (for staff time use to support the study and not linked to any recruitment target in the school or other contingency).

Time Line

School recruitment began on October 12, 2020, and all data collection and laboratory analyses were completed by September 2021. In total, 6 rounds of data collection were planned for the school year. The first round of surveys was conducted between November 3, 2020, and November 20, 2020, and the second round between November 30, 2020, and December 11, 2020, with the third, fourth, fifth, and sixth rounds planned for January 9, 2021, March 15, 2021, May 5, 2021, and June 14, 2021, respectively (Figure 1). Because of the second national lockdown and partial school closures starting on January 5, 2021, the time line and format of the round 3 surveys were altered, and a round of home testing for antibodies was implemented between January 29, 2021, and February 9, 2021.

Data Collection

Virus and Antibody Samples

Research teams visited schools on preagreed days with preprepared barcoded sample kits to collect virus and antibody samples from enrolled students and staff. Testing conducted in schools was not intended to replace routine national testing for those experiencing symptoms, and any staff or students experiencing symptoms were advised to visit routine services and were not expected to attend school on testing days. SARS-CoV-2 infection testing was conducted via nasal swabs for viral detection using reverse transcriptase–polymerase chain reaction (RT-PCR). For staff and secondary school participants, nasal swabs were self-administered and obtained from primary school children by nurses in the research teams. SARS-CoV-2 antibody testing for students was carried out on an oral fluid sample [40], in which children collected transudates from the gingival crevice using an Oracol foam swab (Malvern Medical Developments Ltd), thus limiting the contribution of salivary gland secretions. Oral fluid sampling was used for students as it is less invasive than blood sampling and is painless; therefore, it is more likely to encourage participation by students. SARS-CoV-2 antibody testing for staff was performed on a self-collected finger-prick capillary blood sample.

The home-based testing approach supplemented the in-school surveys from round 2 with virus and antibody tests sent to enrolled individuals unavailable at school on the survey day, who could be reached by telephone. Round 3 was implemented exclusively through home testing, during which any participant who had enrolled by the end of January 2021 but had not yet provided a sample for antibody testing (including participants in schools that had opted out of round 1 or round 2 testing) were contacted and sent a home-testing kit to obtain baseline measures for future antibody conversion estimates. From round 4 (March 2021) onward, home-test antibody kits were sent to individuals who were unavailable at school on the survey day.

Nasal swabs were sent to a national testing center for RT-PCR assay on an Applied Biosystems 7500 FAST system targeting a conserved region of the open reading frame (ORF1ab) gene, as well as the N and S genes of SARS-CoV-2 [30]. Oral fluid swabs were sent to UKHSA Colindale for detection of antibodies against the SARS-CoV-2 nucleoprotein using an in-house immunoglobulin G-capture–based enzyme immunoassay [40], and the staff capillary blood samples were tested with a validated commercial immunoassay for total antibodies against the SARS-CoV-2 nucleoprotein antigen (Roche cobas Elecsys Anti-SARS-CoV-2 assay; Roche Diagnostics). Positive RT-PCR test results were communicated to participants or parents via telephone within 48 hours of the laboratory results. The National Health Service Test and Trace was also informed of any positive results in line with current regulations, and participants were advised to self-isolate according to national guidelines. Negative viral RT-PCR test results were communicated via a secure participant web-based portal. Antibody results, whether positive or negative, were also communicated via a secure participant web-based portal.

Questionnaires

School-level information, including student and staff head counts, guidance received by the school on prevention, and implementation and feasibility of school infection prevention and control measures, was collected via headteacher questionnaires. Participants or their parents or guardians received a brief web-based questionnaire at enrollment, requesting information on demographic characteristics, postcode, household size, school year group for students, and role for staff. Following the collection of samples at each round,

participants were requested to complete additional web-based questionnaires, including questions on household composition, medical history including previous COVID-19 infection, recent symptoms, contacts within and outside of school, activities, travel, mental well-being, and COVID-19 vaccination sentiment and uptake. Further questions covered the adoption of and consistency with recommended prevention and control measures in schools. The questionnaires provided critical information for addressing all 5 study objectives and were completed through a secure participant web-based portal and were linked to samples through a unique identifier. Refer to Multimedia Appendix 1 for the questionnaires used during SIS. Staff and students aged ≥16 years completed the questionnaire themselves, and parents or guardians were requested to complete the questionnaire on behalf of, and in consultation with, their children, as appropriate. An extensive questionnaire was completed at the first visit, with subsequent updates of relevant information in each round of testing, using a shorter *follow-up* questionnaire.

Attendance Data

School-level absence data for participating schools were obtained from the Department for Education through the Educational Setting Status service for the 2020-2021 academic year to address study objective 3. These daily data are disaggregated by staff and students and include whether the school setting is open and the reason for closure if applicable, as well as daily student and staff absences in total and those related to COVID-19–related reasons (eg, suspected case, confirmed case, or potential contact with a case including self-isolation). In addition, questionnaires administered following the surveys contained questions on the number of days absent in the preceding 4 weeks, whether COVID-19–related, and if so, the COVID-19–related reason for absence.

Other Contextual and Linked Data Sources

In addition to the data collected by the study directly, contextual-level information available from other sources about participating LAs, schools, and participants was obtained, including open access school-level data such as location, school type, percentage of students eligible for free school meals (FSMs), performance, workforce, from the Department for Education [37,41] and postcode-level 2019 deprivation data from the Ministry of Housing, Communities & Local Government [42]. In addition, data on case rates from pillar 2 testing [43] and where possible, relevant estimates of community virus and antibody prevalence rates from the COVID-19 Infection Survey (CIS) were used for comparison [44]. At the school and individual levels, consent from participants was sought to link data obtained through this survey with other survey and administrative data held by the ONS, which included (1) test and trace regarding COVID-19 tests and results and (2) the National Immunization Management Service providing information on participants' COVID-19 vaccination status.

Qualitative Data

A nested longitudinal qualitative study was undertaken in a subsample of schools with key stakeholder groups (headteachers, teachers, parents or guardians, and students) to better understand the experience at schools during the pandemic; implementation, feasibility, and acceptability of school control measures; and impact of COVID-19 and mental well-being (study objective 4). Among schools indicating willingness to participate in the qualitative research, a minimum of 6 schools were purposively selected based on the following criteria: school type, local deprivation, and responses regarding the implementation of school measures in the head teacher questionnaire.

Semistructured interviews were conducted with head teachers, teachers, and parents or guardians at primary schools and with head teachers, teachers, parents or guardians, and students at secondary schools. Information about the study and consent forms were circulated to the participants in advance. All interviews were conducted via telephone and audio recorded with participant permission following the provision of informed consent. Repeat interviews were conducted with the same participants at another time point during the school year. A total of 74 interviews across 4 primary and 4 secondary schools were completed in rounds 1 and 2 of the nested qualitative study. In all, 43 interviews were conducted in round 1 between February 2021 and April 2021. In round 2, repeat interviews were conducted with 31 participants from round 1 between June 2021 and July 2021. The results of this nested qualitative study will be presented in future publications.

Outbreak Investigation

As part of its commitment to public health management of COVID-19 in institutional settings, UKHSA coordinated risk assessments and investigations in selected school *bubbles* with one or more positive cases, including wider testing among staff, students, and their households, as identified by the risk assessment. The outbreak investigation protocol, exploring study objective 5, used a home-testing approach based on SARS-CoV-2 RT-PCR testing results within SIS and early alerts of other SARS-CoV-2 infections notified by schools. Data from the SIS outbreak investigations have been combined with data from outbreak investigations conducted as part of the sKIDs study in primary schools and the sKIDs PLUS study in secondary schools [30,45].

Data Management and Analysis

Data Management

Data were collected via a secure web-based portal and linked by ONS. Participant ID and deidentified information were linked to the school by the school's unique reference number. The results of the nasal swabs and antibody tests were linked to participants' survey records using a barcoded ID. Deidentified data sets were made available to authorized investigators to be analyzed in the ONS Secure Research Service. The interview data were transcribed verbatim from audio recordings, with identifiers removed and enhanced with notes taken during the interview. Anonymized transcripts and notes are held on the London School of Hygiene & Tropical Medicine secure servers and managed and analyzed using MAXQDA (version 12; VERBI GmbH).

Results Reporting and Dissemination

Descriptive results were rapidly reported in publicly available bulletins published by ONS after each survey round to inform national policy discussions [46]. These include PCR-based viral test positivity and antibody test positivity, both of which are unadjusted for diagnostic test performance. The estimates were weighted to be representative of the relevant populations in the sampled LAs. The weighted test positivity for SARS-CoV-2 in each LA and time point was presented by the key population groups tested: primary school students and staff and secondary school students and staff.

A range of analyses addressing the study objectives will be presented in subsequent papers, including longitudinal analyses of antibody and infection prevalence, accounting for diagnostic test performance to address study objectives 1 and 2, and multilevel regression modeling to assess risk factors for infection and antibody prevalence and antibody conversion from negative to positive at the individual, school, and community levels. The correlation between school-level infection and COVID-19–related absence will be examined to address objective 3.

Objective 4, examining the implementation of preventive measures and staff well-being, will be addressed through quantitative analysis of the implementation of measures and associated challenges reported in the head teacher questionnaire and adherence to measures and teacher burnout reported in the staff questionnaire. Furthermore, qualitative analyses of the fidelity, feasibility, and acceptability of school implementation of COVID-19 control measures and their impact on well-being will use narrative data from interviews with head teachers, teachers, parents, and students. The general theory of implementation will be used as a theoretical framework to guide the design, analysis, and interpretation of findings [47]. Thematic analysis will be conducted to address the study objectives using a combination of both deductive and inductive coding approaches.

Objective 5, investigation of secondary attack rates and outbreaks, will be analyzed using mathematical modeling as well as through the analysis of school bubbles and their household contacts [45].

Current Analyses of Recruited Study Population

In this paper, we present a description of enrollment and the recruited population participating in SIS during the 2020-2021 academic year. School and individual participation are described in rounds 1 to 6. Enrolled schools are those, which submitted the school consent form and enrollment questionnaire before the first day of the survey round. The participating schools are schools visited by the survey team during that specific round. The eligible population in each round is estimated from the total staff census in participating primary and secondary schools, the total student census in participating primary schools, and all students in the 2 selected year groups in participating secondary schools. For schools that expanded enrollment to additional school years in January 2021, eligible students included all students (except year 11) during rounds 4 to 6. Enrolled individuals are defined as those who have submitted the consent form and enrollment questionnaire, and participating individuals are those who were present on the day the research team visited the school and had at least one sample taken.

Descriptive analyses of school-level characteristics of the sampled, eligible, and participating schools and participants were performed using unweighted frequencies and proportions for categorical variables. Individual-level sociodemographic characteristics are also described for those participating in any survey round. Data analyses were performed using Stata (version 16.0; StataCorp).

Ethics Approval

The study was approved by the UKHSA Research Support and Governance Office (NR0237) and London School of Hygiene & Tropical Medicine Ethics Review Committee (reference 22657). Electronic informed consent was obtained from staff, students aged ≥16 years, and parents or guardians of children aged 4 to 15 years via a secure web-based portal before enrollment. Verbal consent or assent was obtained before sample collection at the school. Informed consent was obtained before interviews. Telephone helplines and responses to frequently asked questions on a weblink were available. Schools, staff, and parents or guardians of participating students and the students themselves were free to withdraw consent at any time.

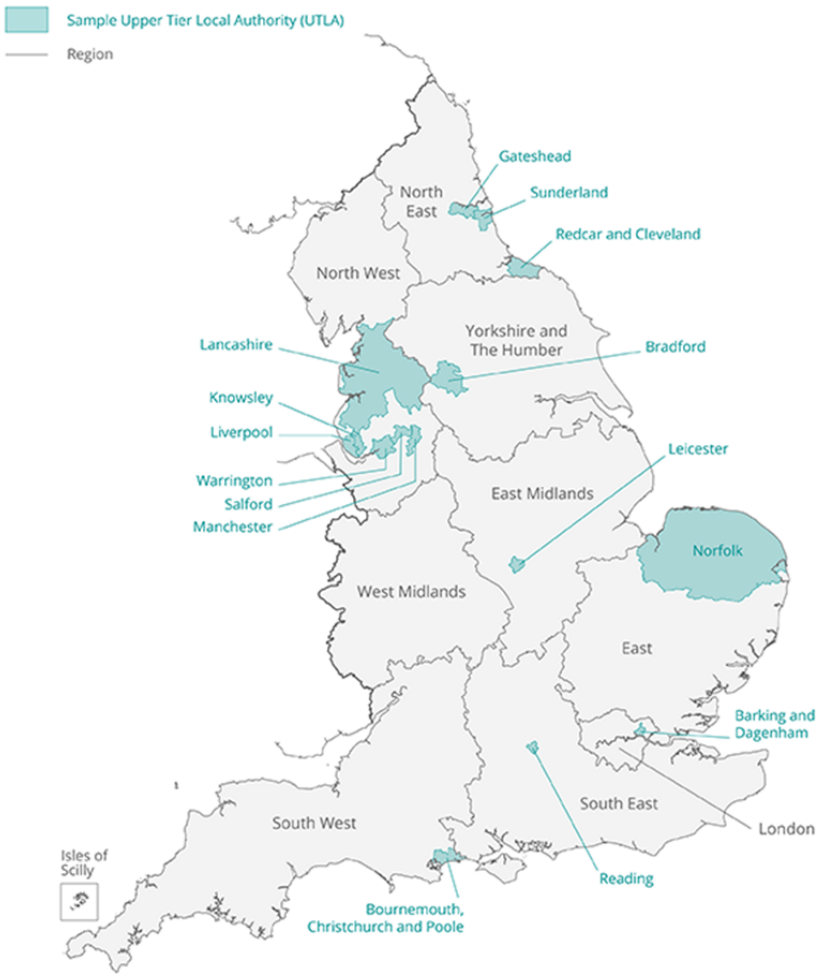
Results

Here, we provide a description of recruitment and participation by study round, as well as the characteristics of schools and individuals participating in the SIS study.

LA Selection

In total, 10 of the LAs classified as in the top 20% of transmission (based on pillar 2 data) and 5 of the LAs classified as in the lower 80% of transmission were randomly selected. The median LA-level case rate from pillar 2 testing, the week of September 2, 2020, to September 8, 2020, was 121.9 per 100,000 population for LAs classified as *high transmission* and 18.9 per 100,000 population for LAs classified as *low transmission*. These LA-level case rates provided a snapshot of regional transmission at the start of the school year, which subsequently changed substantially between September and December 2020, rendering this distinction irrelevant. The selected LAs are located in 8 of the 9 regions in England, with 6 LAs located in the northwest region, 3 LAs in the northeast region, and 1 LA in each of the other 6 regions (Figure 2).

Figure 2. Map of local authority areas participating in the Schools Infection Survey study. UTLA: Upper Tier Local Authority.



School Enrollment, Participation, and Characteristics

School enrollment began on October 12, 2020, with 51 primary and 74 secondary schools initially enrolled (Figures 3-6). The 2 all-through schools selected, opted to participate as both primary and secondary schools and so subsequently appeared in both samples. There were 3 LAs in which no primary schools had participated by the end of round 3 (Figures 7A and 7B). However, by the following school term (round 4), primary schools participated across all LAs, except for one (Figures 7A and 7B). Secondary schools from all 15 LAs were enrolled and participated in SIS from round 1 (Figures 7C and 7D).

Of the schools initially enrolled, following school withdrawals, schools opting out of testing rounds and enrolled schools with no registered individuals to participate in the survey rounds, 45 primary and 62 secondary schools participated in the round 1 survey, and 43 primary and 80 secondary schools participated in the round 2 survey (Figures 3-6). A total of 57 primary schools participated in rounds 4 to 6, and 91, 89, and 86 secondary schools participated in rounds 4, 5, and 6, respectively (Figures 3-6). There was a higher proportion of enrolled schools with either no participants enrolled in the survey or who opted out during rounds 1 and 2 in the autumn term than during rounds 4 to 6, especially for primary schools (Figures 3-6).

Figure 3. The Schools Infection Survey recruitment and participation profile for primary schools during rounds 1 to 3. Suppressed numbers are indicated by C Percentage of eligible refers to eligible participants within schools enrolled and participating in that round. LA: local authority.

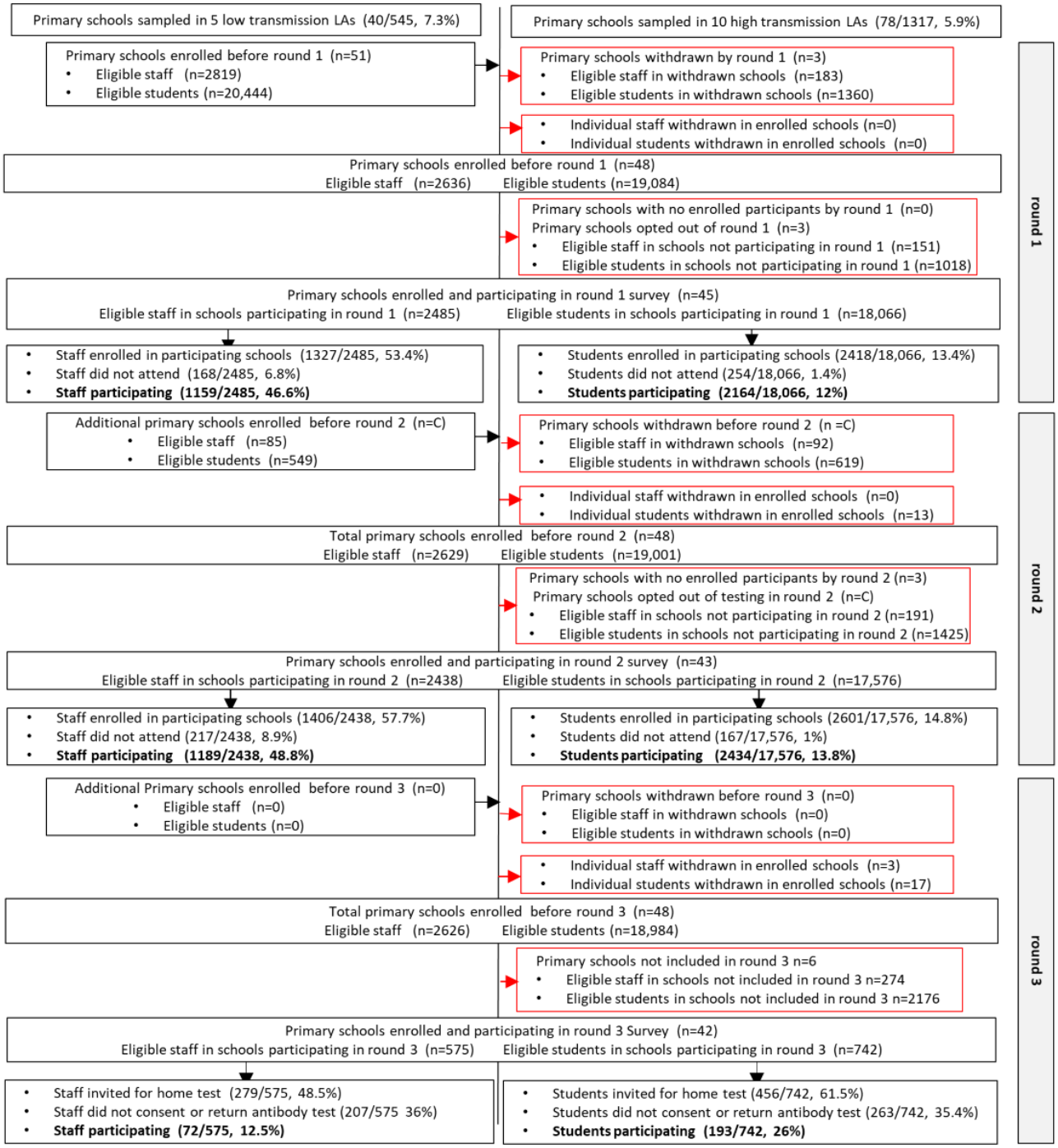


Figure 4. The Schools Infection Survey recruitment and participation profile for primary schools during rounds 4 to 6. Suppressed numbers are indicated by C Percentage of eligible refers to eligible participants within schools enrolled and participating in that round. LA: local authority.

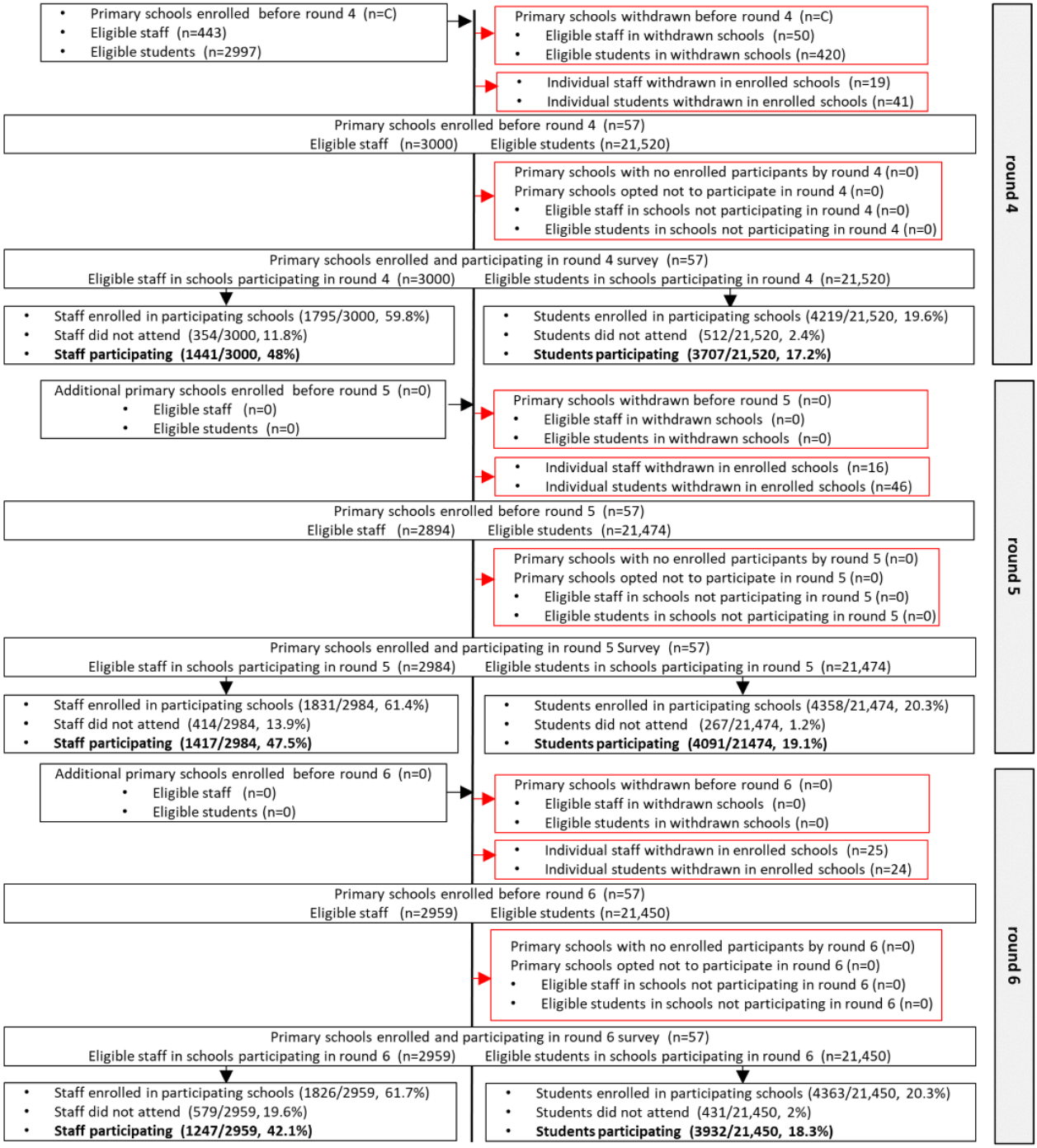


Figure 5. The Schools Infection Survey recruitment and participation profile for secondary schools during rounds 1 to 3. Suppressed numbers are indicated by C. Percentage of eligible refers to eligible participants within schools enrolled and participating in that round. In rounds 1 to 3, eligible secondary students refers to the 2 selected eligible classes. From January 2021, secondary schools were invited to open enrollment up to the whole school (excluding year 11), leading to an increase in eligible students in rounds 4 to 6. LA: local authority.

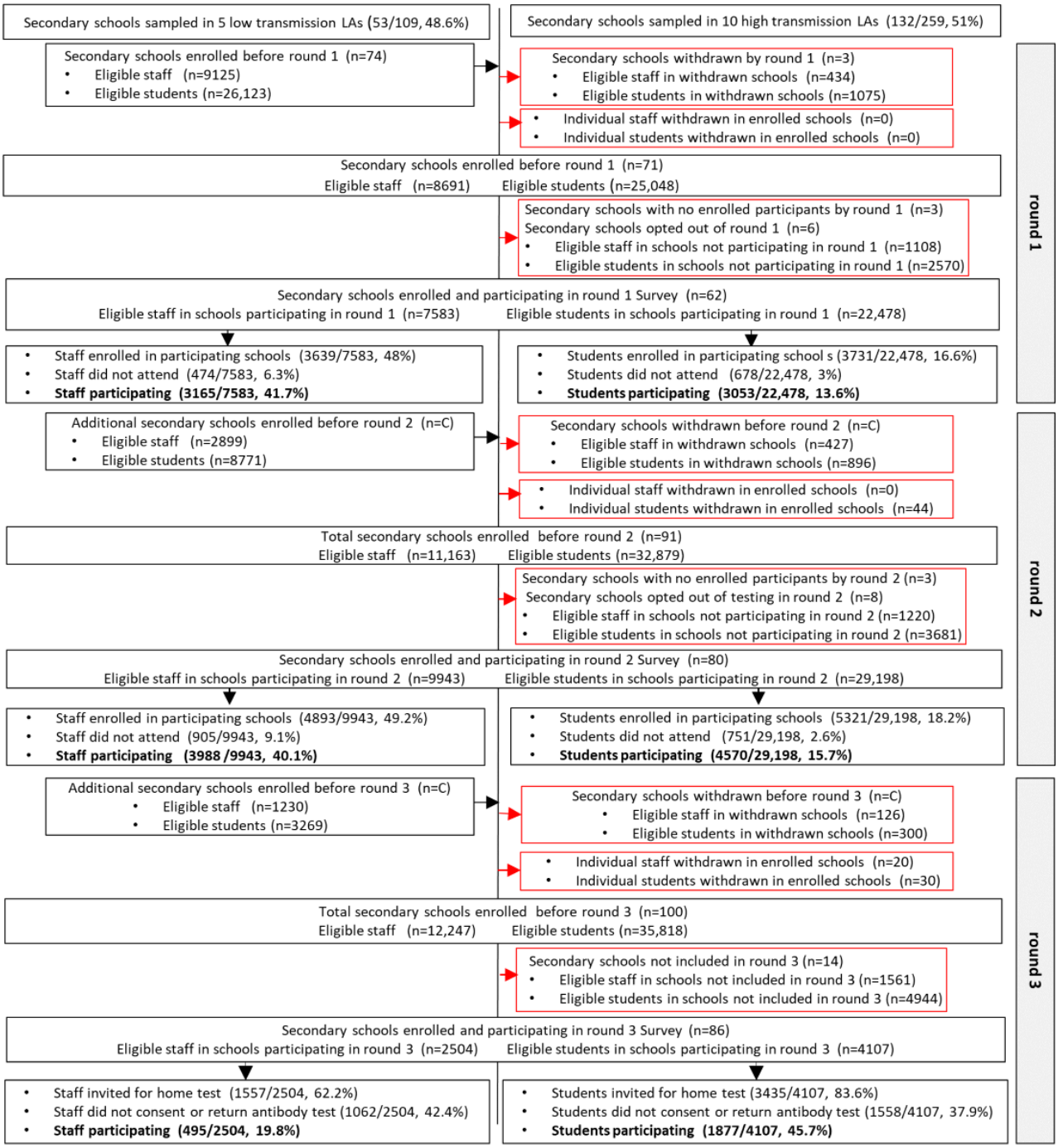


Figure 6. The Schools Infection Survey recruitment and participation profile for secondary schools during rounds 4 to 6. Suppressed numbers are indicated by C. Percentage of eligible refers to eligible participants within schools enrolled and participating in that round. In rounds 1 to 3, eligible secondary students refers to the 2 selected eligible classes. From January 2021, secondary schools were invited to open enrollment up to the whole school (excluding year 11), leading to an increase in eligible students in rounds 4 to 6. LA: local authority.

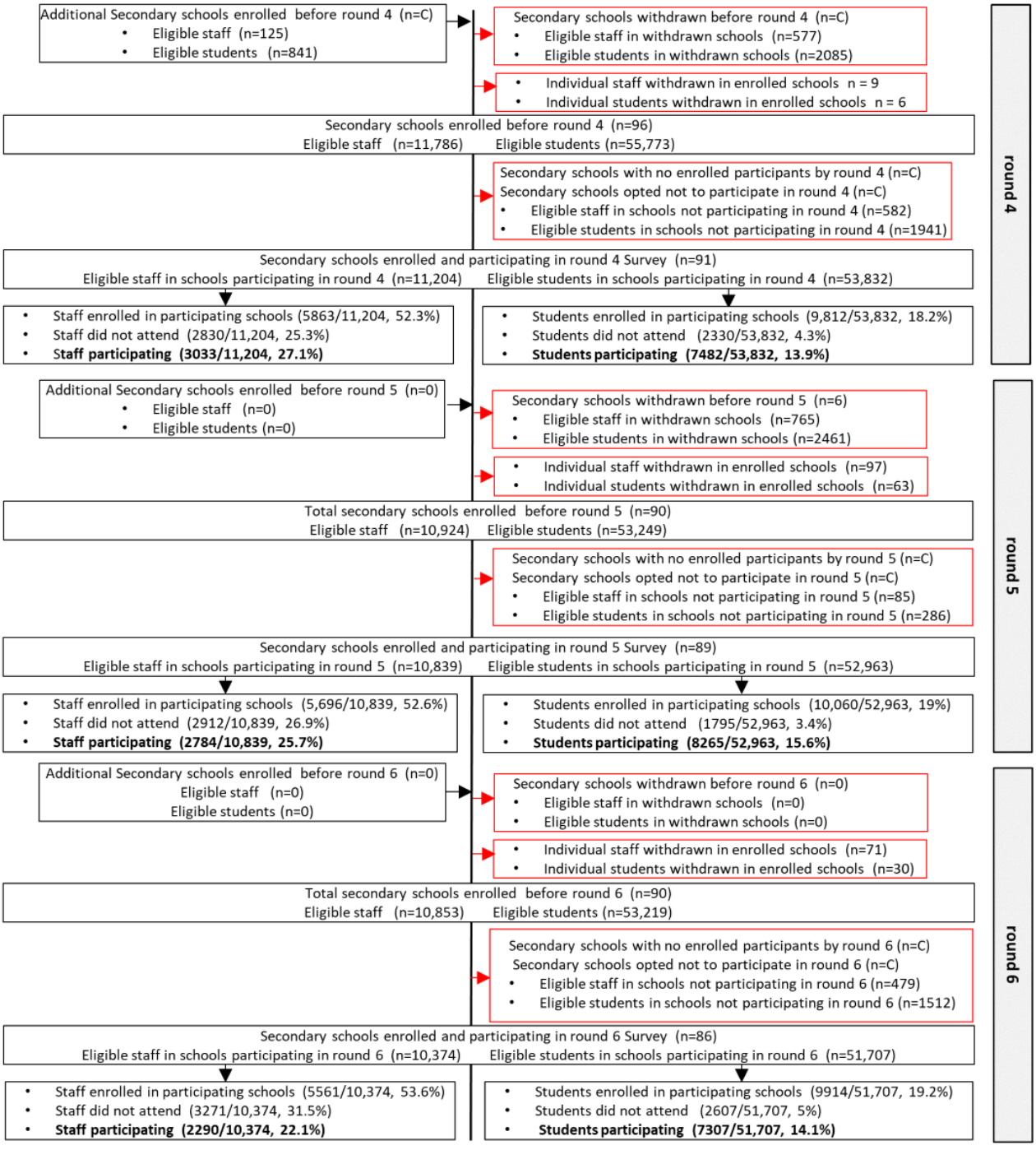
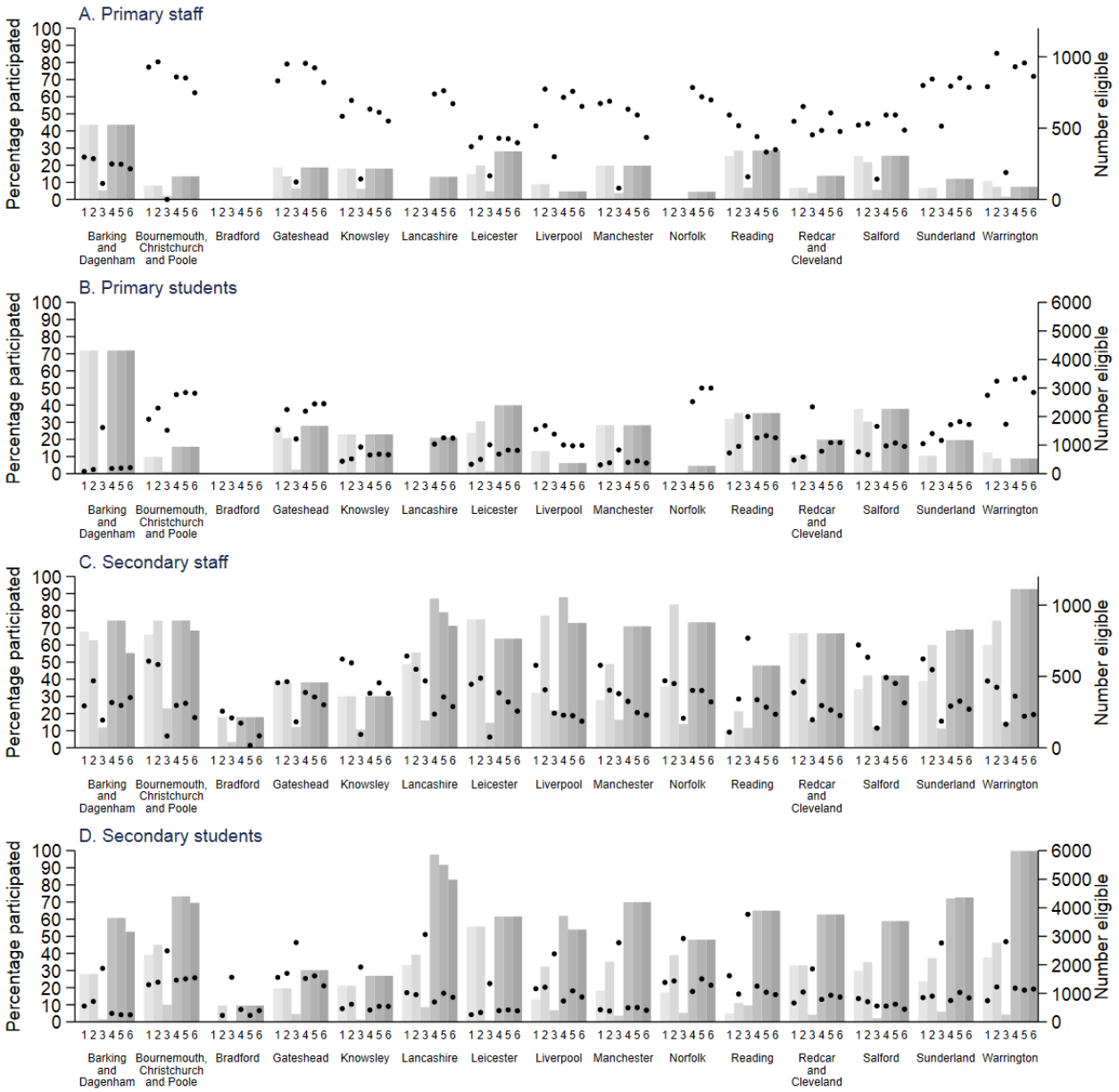


Figure 7. Local authority–level participation rate (percentage individuals participating of those eligible) during rounds 1 to 6 (black circles) for (A) primary school staff, (B) primary school students, (C) secondary school staff, and (D) secondary school students. Also shown are number of individuals eligible at rounds 1 to 6 (gray bars) and eligible individuals estimated from the total staff and student census in participating primary schools and the census of all staff and students in the 2 selected year groups (rounds 1 to 3) and expanded year groups (rounds 4 to 6) in participating secondary schools. Participating individuals are those who were present on the day the research team visited the school and who had at least one sample taken.



Primary schools participating in SIS were broadly representative of the sampled schools (Table 2). However, a higher proportion of sampled and participating schools appeared to be located in urban conurbations and were larger than schools across the sampled LAs. For instance, 49.2% (58/118) sampled and 50.8% (30/59) participating schools were in urban conurbations compared with 37.3% (694/1862) of schools in the sampled LAs. In addition, fewer sampled and participating schools were in the <10% students eligible for the FSMs band and the low absenteeism categories, relative to schools across sampled LAs. Again, secondary schools participating in SIS were broadly representative of the sampled schools (Table 3). Although sampled and participating schools appeared less likely to be in rural hamlets, villages, and towns than schools across sampled LAs, for other characteristics, secondary schools were more similar to those in sampled LAs.

Table 2. Characteristics of primary schools sampled and participating in the Schools Infection Survey (SIS) and the participants eligible and participating in SIS (any survey round).

	Schools in sampled LAs[a] (n=1862), n (%)	Sampled schools (n=118), n (%)	Participating schools (n=59), n (%)	Eligible staff in participating schools[b] (n=3112), n (%)	Participating staff (n=1891), n (%)	Eligible students in participating schools[b] (n=22,225), n (%)	Participating students (n=4654), n (%)
Location							
Transmission at time of sampling							
Low[c] (lower 80% LAs)	545 (29.3)	40 (33.9)	19 (32.2)	1250 (40.2)	647 (34.2)	8844 (39.8)	1523 (32.7)
High[d] (top 20% LAs)	1317 (70.7)	78 (66.1)	40 (67.8)	1862 (59.8)	1244 (65.8)	13,381 (60.2)	3131 (67.3)
Urban or rural							
Rural hamlet or village or town and fringe	436 (23.4)	15 (12.7)	9 (15.3)	260 (8.4)	177 (9.4)	1621 (7.3)	594 (12.8)
Urban city and town	732 (39.3)	45 (38.1)	20 (33.9)	1176 (37.8)	739 (39.1)	7830 (35.2)	2001 (43)
Urban conurbation	694 (37.3)	58 (49.2)	30 (50.8)	1676 (53.9)	975 (51.6)	12,774 (57.5)	2059 (44.2)
Sociodemographics							
School size (tertiles)							
Small: <202 students	547 (29.4)	17 (14.4)	10 (17)	230 (7.4)	179 (9.5)	1393 (6.3)	524 (11.3)
Medium: 202 to <338 students	668 (35.9)	43 (36.4)	22 (37.3)	848 (27.2)	630 (33.3)	5258 (23.7)	1320 (28.4)
Large: 338 to 1732 students	630 (33.8)	58 (49.2)	27 (45.8)	2034 (65.4)	1082 (57.2)	15,574 (70.1)	2810 (60.4)
Data not available	17 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Index of multiple deprivation of school postcode (2019)							
Most deprived	630 (33.8)	43 (36.4)	20 (33.9)	960 (30.8)	666 (35.2)	6685 (30.1)	1111 (23.9)
2	390 (21)	26 (22)	13 (22)	846 (27.2)	378 (20)	6384 (28.7)	927 (19.9)
3	330 (17.7)	19 (16.1)	8 (13.6)	437 (14)	282 (14.9)	3005 (13.5)	512 (11)
4	313 (16.8)	21 (17.8)	14 (23.7)	690 (22.2)	445 (23.5)	4889 (22)	1658 (35.6)
Least deprived	199 (10.7)	9 (7.6)	4 (6.8)	179 (5.8)	120 (6.3)	1262 (5.7)	446 (9.6)
Proportion of students eligible for free school meals band							
<10%	474 (25.5)	20 (17)	10 (17)	487 (15.6)	331 (17.5)	3467 (15.6)	1223 (26.3)
10% to <20%	521 (28)	38 (32.2)	22 (37.3)	1078 (34.6)	689 (36.4)	7566 (34)	1769 (38)
20% to <30%	368 (19.8)	28 (23.7)	11 (18.6)	868 (27.9)	391 (20.7)	6933 (31.2)	891 (19.1)
30% to <40%	267 (14.3)	20 (17)	11 (18.6)	446 (14.3)	309 (16.3)	2746 (12.4)	567 (12.2)
40% to 100%	214 (11.5)	12 (10.2)	5 (8.5)	233 (7.5)	171 (9)	1513 (6.8)	204 (4.4)
Data not available	18 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
School characteristics							
Previous year school absence data (% morning or afternoon absences across year)							
Low (1% to 3.7%)	697 (37.4)	31 (26.3)	16 (27.1)	779 (25)	556 (29.4)	5209 (23.4)	1959 (42.1)
Medium (3.8% to 4.6%)	641 (34.4)	44 (37.3)	22 (37.3)	1000 (32.1)	663 (35.1)	7172 (32.3)	1315 (28.3)
High (4.7% to 48.1%)	463 (24.9)	40 (33.9)	C (C)[e]	1155 (37.1)	581 (30.7)	8418 (37.9)	1172 (25.2)
Data not available	61 (3.3)	3 (2.5)	C (C)[e]	178 (5.7)	91 (4.8)	1426 (6.4)	208 (4.5)
Office for Standards in Education, Children's Services and Skills (OFSTED) rating							
Inadequate or requires improvement	150 (8.1)	13 (11)	4 (6.8)	273 (8.8)	140 (7.4)	1996 (9)	407 (8.7)
Good	1231 (66.1)	77 (65.3)	39 (66.1)	2095 (67.3)	1221 (64.6)	15,052 (67.7)	2809 (60.4)
Outstanding	242 (13)	18 (15.2)	10 (17)	366 (11.8)	316 (16.7)	2608 (11.7)	1064 (22.9)

	Schools in sampled LAs[a] (n=1862), n (%)	Sampled schools (n=118), n (%)	Participating schools (n=59), n (%)	Eligible staff in participating schools[b] (n=3112), n (%)	Participating staff (n=1891), n (%)	Eligible students in participating schools[b] (n=22,225), n (%)	Participating students (n=4654), n (%)
Data not available	239 (12.8)	10 (8.5)	6 (10.2)	378 (12.1)	214 (11.3)	2569 (11.6)	374 (8)
Student to teacher ratio							
<20	672 (36.1)	45 (38.1)	22 (37.3)	1182 (38)	627 (33.2)	8569 (38.6)	1442 (31)
20 to <51	1113 (59.8)	68 (57.6)	34 (57.6)	1681 (54)	1143 (60.4)	11,890 (53.5)	2964 (63.7)
Data not available	75 (4)	5 (4.2)	3 (5.1)	249 (8)	121 (6.4)	1766 (7.9)	248 (5.3)
School average progress scores in reading, writing, and mathematics[f]							
Low (−11.77 to −0.70)	497 (26.7)	26 (22)	12 (20.3)	481 (15.5)	318 (16.8)	3388 (15.2)	787 (16.9)
Medium (−0.67 to 0.93)	554 (29.8)	37 (31.4)	21 (35.6)	954 (30.7)	700 (37)	6659 (30)	2108 (45.3)
High (0.97 to 15.33)	572 (30.7)	40 (33.9)	18 (30.5)	941 (30.2)	590 (31.2)	6448 (29)	1157 (24.9)
Data not available	239 (12.8)	15 (12.7)	8 (13.6)	736 (23.7)	283 (15)	5730 (25.8)	602 (12.9)

[a]LA: local authority.

[b]Eligible: all staff and students in schools, which participated in any of the survey rounds 1, 2, 3, 4, 5, or 6.

[c]High transmission: top 20% LAs when ranked according to SARS-CoV-2 infection per 100,000 population from September 2, 2020, to September 8, 2020.

[d]Low transmission: lower 80% LAs when ranked according to SARS-CoV-2 infection per 100,000 population from September 2, 2020, to September 8, 2020.

[e]*C*: data suppressed (2 smallest categories suppressed).

[f]Average of the combined reading, writing, and mathematics scores.

Table 3. Characteristics of secondary schools sampled and participating in the Schools Infection Survey (SIS) and the participants eligible and participating in SIS (any survey round).

	Schools in sampled LAs[a] (n=368), n (%)	Sampled schools (n=185), n (%)	Participating schools (n=97), n (%)	Eligible staff in participating schools[b] (n=12,146), n (%)	Participating staff (n=5852), n (%)	Eligible students in participating schools[c] (n=56,519), n (%)	Participating students (n=10,188), n (%)
Location							
Transmission at time of sampling							
Low[d] (lower 80% LAs)	109 (29.6)	53 (28.6)	34 (35)	4536 (37.3)	2126 (36.3)	19,748 (34.9)	4114 (40.4)
High[e] (top 20% LAs)	259 (70.4)	132 (71.3)	63 (64.9)	7610 (62.7)	3726 (63.7)	36,771 (65.1)	6074 (59.6)
Urban or rural							
Rural hamlet or village or town and fringe	44 (12)	12 (6.5)	6 (6.2)	581 (4.8)	322 (5.5)	2516 (4.5)	545 (5.3)
Urban city and town	169 (45.9)	76 (41.1)	47 (48.5)	5869 (48.3)	2849 (48.7)	29,227 (51.7)	6056 (59.4)
Urban conurbation	155 (42.1)	97 (52.4)	44 (45.4)	5696 (46.9)	2681 (45.8)	24,776 (43.8)	3587 (35.2)
Sociodemographics							
School size (tertiles)							
Small: <202 students	147 (40)	65 (35.1)	35 (36.1)	3085 (25.4)	1535 (26.2)	16,280 (28.8)	2965 (29.1)
Medium: 202 to <338 students	128 (34.8)	66 (35.7)	37 (38.1)	4371 (36)	2279 (38.9)	22,334 (39.5)	3873 (38)
Large: 338 to 1732 students	90 (24.5)	C (C)[f]	25 (25.8)	4690 (38.6)	2038 (34.8)	17,905 (31.7)	3350 (32.9)
Data not available	3 (0.8)	C (C)[f]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Index of multiple deprivation of school postcode (2019)							
Most deprived	122 (33.2)	65 (35.1)	32 (33)	3539 (29.1)	1677 (28.7)	15,666 (27.7)	2156 (21.2)
2	92 (25)	53 (28.6)	28 (28.9)	3902 (32.1)	1850 (31.6)	16,612 (29.4)	2459 (24.1)
3	56 (15.2)	24 (13)	12 (12.4)	1487 (12.2)	652 (11.1)	6383 (11.3)	1412 (13.9)
4	58 (15.8)	26 (14.1)	14 (14.4)	1572 (12.9)	731 (12.5)	8805 (15.6)	1601 (15.7)
Least deprived	40 (10.9)	17 (9.2)	11 (11.3)	1646 (13.6)	942 (16.1)	9053 (16)	2560 (25.1)
Proportion of students eligible for free school meals band							
<10%	61 (16.6)	24 (13)	15 (15.5)	1914 (15.8)	883 (15.1)	11,675 (20.7)	3089 (30.3)
10% to <20%	133 (36.1)	65 (35.1)	40 (41.2)	5350 (44)	2596 (44.4)	23,006 (40.7)	4721 (46.3)
20% to <30%	79 (21.5)	42 (22.7)	19 (19.6)	2581 (21.2)	1206 (20.6)	11,392 (20.2)	1204 (11.8)
30% to <40%	60 (16.3)	36 (19.5)	14 (14.4)	1403 (11.6)	652 (11.1)	6303 (11.2)	809 (7.9)
40% to 100%	32 (8.7)	C (C)[f]	9 (9.3)	898 (7.4)	515 (8.8)	4143 (7.3)	365 (3.6)
Data not available	3 (0.8)	C (C)[f]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
School characteristics							
Previous year school absence data (% morning or afternoon absences across year)							
Low (1% to 3.7%)	27 (7.3)	15 (8.1)	9 (9.3)	1158 (9.5)	536 (9.2)	6344 (11.2)	1549 (15.2)
Medium (3.8% to 4.6%)	57 (15.5)	24 (13)	12 (12.4)	1358 (11.2)	607 (10.4)	7606 (13.5)	1304 (12.8)
High (4.7% to 48.1%)	267 (72.6)	139 (75.1)	72 (74.2)	9141 (75.3)	4510 (77.1)	40,115 (71)	7030 (69)
Data not available	17 (4.6)	7 (3.8)	4 (4.1)	489 (4)	199 (3.4)	2454 (4.3)	305 (3)
Office for Standards in Education, Children's Services and Skills (OFSTED) rating							
Inadequate or requires improvement	88 (23.9)	46 (24.9)	19 (19.6)	2136 (17.6)	1120 (19.1)	11,203 (19.8)	1588 (15.6)
Good	157 (42.7)	79 (42.7)	42 (43.3)	5716 (47.1)	2876 (49.1)	24,667 (43.6)	4726 (46.4)

	Schools in sampled LAs[a] (n=368), n (%)	Sampled schools (n=185), n (%)	Participating schools (n=97), n (%)	Eligible staff in participating schools[b] (n=12,146), n (%)	Participating staff (n=5852), n (%)	Eligible students in participating schools[c] (n=56,519), n (%)	Participating students (n=10,188), n (%)
Outstanding	45 (12.2)	25 (13.5)	16 (16.5)	1949 (16)	977 (16.7)	8949 (15.8)	2450 (24)
Data not available	78 (21.2)	35 (18.9)	20 (20.6)	2345 (19.3)	879 (15)	11,700 (20.7)	1424 (14)
Student to teacher ratio							
<20	329 (89.4)	164 (88.7)	83 (85.6)	10,625 (87.5)	5193 (88.7)	49,322 (87.3)	8884 (87.2)
20 to <51	13 (3.5)	6 (3.2)	5 (5.2)	586 (4.8)	338 (5.8)	2067 (3.7)	586 (5.8)
Data not available	26 (7.1)	15 (8.1)	9 (9.3)	935 (7.7)	321 (5.5)	5130 (9.1)	718 (7)
School average progress scores in reading, writing, mathematics[g]							
Low (−1.67 to −0.19)	132 (35.9)	68 (36.8)	35 (36.1)	3855 (31.7)	2052 (35.1)	17,111 (30.3)	2655 (26.1)
Medium (−0.18 to 0.19)	106 (28.8)	46 (24.9)	19 (19.6)	2723 (22.4)	1245 (21.3)	11,648 (20.6)	2707 (26.6)
High (0.20 to 2.16)	95 (25.8)	52 (28.1)	30 (30.9)	4213 (34.7)	2058 (35.2)	20,372 (36)	4134 (40.6)
Data not available	35 (9.5)	19 (10.3)	13 (13.4)	1355 (11.2)	497 (8.5)	7388 (13.1)	692 (6.8)

[a]LA: local authority.

[b]Eligible staff: all staff in participating schools at any of the survey rounds 1, 2, 3, 4, 5, or 6.

[c]Eligible students: students from the 2 consecutive years sampled in schools participating in rounds 1 to 3 and from all years (except year 11) in schools participating in rounds 4 to 6.

[d]High transmission: top 20% LAs when ranked according to SARS-CoV-2 infection per 100,000 population from September 2, 2020, to September 8, 2020.

[e]Low transmission: lower than 80% LAs when ranked according to SARS-CoV-2 infection per 100,000 population from September 2, 2020, to September 8, 2020.

[f]*C*: data suppressed (2 smallest categories suppressed).

[g]Average of the combined reading, writing, and mathematics scores.

Individual Participation and Characteristics

The participation rate (percentage individuals participating of those eligible) was 46.6% (1159/2485) and 41.7% (3165/7583) among primary and secondary school staff, respectively, during round 1 (Figures 3-6). By round 6, the staff participation rate had declined to 42.1% (1247/2959) and 22.1% (2290/10,374) in primary and secondary schools, respectively. The primary school student participation rate increased from 12% (2164/18,066) in round 1 to 18.3% (3932/21,450) in round 6, and for secondary school students, it remained consistent at 13.6% (3053/22,478) and 14.1% (7307/51,707) in rounds 1 and 6, respectively (Figures 3-6). Overall, the staff and student participation rates were 45.2% and 16.4% in primary schools and 30% and 15.2% in secondary schools, respectively. If round 3 was excluded, 53% of the staff enrolled and consented to participate in SIS and 34% participated on the day, and 18.3% of the students enrolled and consented and 15.2% participated in the study. During round 3, in which only individuals who had enrolled but had not provided an antibody test were eligible, 18.4% (567/3079) of the staff and 42.7% (2070/4849) of the students participated.

Figures 7A-7D illustrate the LA-level participation rate within the participating schools in each round. The LA-level primary student participation rate was the highest in Warrington (Figure 7B). The LA-level secondary student participation rates were all <40% if round 3 was excluded (Figure 7D). The primary staff participation rate was highest in Warrington, Gateshead, and Bournemouth, Christchurch and Poole (Figure 7A), and the secondary staff response rate was as high as 60% in Salford (Figure 7C).

Among the participating schools, school-level characteristics were consistent between eligible and participating staff (Tables 2 and 3). This pattern was observed in both the primary and secondary schools. However, the participation of primary students was nearly 2-fold greater in rural schools than in the eligible population, with 12.8% (594/4654) of participating students versus 7.3% (1621/22,225) of eligible students attending schools in rural locations (Table 2). The same trend was observed in small schools. Participation was observed to be higher in schools with low absenteeism in the previous year and in schools with a lower percentage eligible for FSM, with 26.3% (1223/4654) of participating students in schools in <10% eligible for the FSM band, versus 15.6% (3467/22,225) of eligible students in this band. Student participation was lower in schools located in the most deprived lower layer super output areas, based on school postcode, when compared with the eligible population, and almost 2-fold higher in the least deprived areas (446/4654, 9.6%) than may be expected based on the eligible population (1262/22,225, 5.7%; Table 2). Except for the rural school location and school size, these patterns appear similar for secondary school students' participation (Table 3).

Of those providing answers in the questionnaires, most staff who participated in SIS were female (1683/1866, 90.2% in primary and 4244/5776, 73.5% in secondary schools; Table 4). In primary schools, 56.4% (1054/1868) of staff members were aged between 35 and 54 years, whereas in secondary schools, 53.5% (3095/5785) of staff members were in this age band. In total 73.2% (5569/7605) were teaching staff, as opposed to pastoral care and administrative or maintenance staff. Just over half of the participating staff members (4026/7624, 52.8%) lived in multiple adult households with no children. A higher proportion of primary school teachers resided in the most deprived postcodes, 23% (425/1850), in contrast to secondary school teachers, 16.2% (924/5717).

Of those providing answers in the questionnaires, the gender distribution was equal across participating students, and 63.2% (9306/14,735) were in the 10- to 14-year age group. Of the primary and secondary students, 79% (3596/4553) and 86.3% (8698/10,077), respectively, were of White ethnic background (Table 4). There was a spread of participating students across school years, but <12% (1168/10,106) of secondary school students came from years 12 and 13 combined (ages 16-18 years). More than three-quarters of the participating primary school students lived in households with multiple children. A higher proportion of participating students at primary schools resided in more deprived locations, 27.5% (1257/4565) in the most deprived quintile compared with 16% (731/4565) in the least deprived quintile.

Table 4. Sociodemographic characteristics of individuals participating in the Schools Infection Survey (any survey round).

	Primary schools (n=59)		Secondary schools (n=97)	
	Participating primary staff[a] (n=1891), n (%)	Participating primary students[a] (n=4654), n (%)	Participating secondary staff[a] (n=5852), n (%)	Participating secondary students[a] (n=10,188), n (%)
Demographics				
Age group (years)				
<5	N/A[b]	346 (7.5)	N/A	N/A
5-9	N/A	3269 (71.1)	N/A	N/A
10-14	N/A	981 (21.3)	N/A	8325 (82.1)
≥15	N/A	N/A	N/A	1814 (17.9)
<35	502 (26.9)	N/A	1879 (32.5)	N/A
35-44	495 (26.5)	N/A	1712 (29.6)	N/A
45-54	559 (29.9)	N/A	1383 (23.9)	N/A
≥55	312 (16.7)	N/A	811 (14)	N/A
Age not available[c]	23	58	67	49
Gender[d]				
Male	183 (9.8)	2322 (50.6)	1532 (26.5)	5049 (49.9)
Female	1683 (90.2)	2270 (49.4)	4244 (73.5)	5076 (50.1)
Gender not available[c]	25	62	76	63
Ethnicity				
Asian or Asian British	96 (5.2)	528 (11.6)	222 (3.9)	617 (6.1)
Black African or Caribbean Black	12 (0.6)	114 (2.5)	56 (1)	222 (2.2)
Mixed or Multiple ethnic groups	20 (1.1)	264 (5.8)	118 (2.1)	446 (4.4)
Other ethnic group	6 (0.3)	51 (1.1)	30 (0.5)	94 (0.9)
White	1726 (92.8)	3596 (79)	5327 (92.6)	8698 (86.3)
Ethnicity not available[c]	31	101	99	111
Job group (staff)				
Senior leader	172 (9.3)	N/A	453 (7.9)	N/A
Middle leader	115 (6.2)	N/A	1180 (20.5)	N/A
Teacher	491 (26.6)	N/A	2032 (35.3)	N/A
Teaching assistant or special educator	598 (32.4)	N/A	528 (9.2)	N/A
Administration or pastoral	187 (10.1)	N/A	938 (16.3)	N/A
Cater or clean or maintenance	147 (8)	N/A	226 (3.9)	N/A
Other	133 (7.2)	N/A	405 (7)	N/A
Job group not available[c]	48	N/A	90	N/A
Year groups (students)				
Reception	N/A	543 (11.8)	N/A	N/A
Year 1	N/A	633 (13.8)	N/A	N/A
Year 2	N/A	672 (14.6)	N/A	N/A
Year 3	N/A	686 (14.9)	N/A	N/A
Year 4	N/A	680 (14.8)	N/A	N/A
Year 5	N/A	681 (14.8)	N/A	N/A

	Primary schools (n=59)		Secondary schools (n=97)	
	Participating primary staff[a] (n=1891), n (%)	Participating primary students[a] (n=4654), n (%)	Participating secondary staff[a] (n=5852), n (%)	Participating secondary students[a] (n=10,188), n (%)
Year 6	N/A	696 (15.2)	N/A	N/A
Year 7	N/A	N/A	N/A	2477 (24.5)
Year 8	N/A	N/A	N/A	2587 (25.6)
Year 9	N/A	N/A	N/A	2220 (22)
Year 10	N/A	N/A	N/A	1654 (16.4)
Year 12	N/A	N/A	N/A	657 (6.5)
Year 13	N/A	N/A	N/A	511 (5.1)
Year group not available[c]	N/A	63	N/A	82
Household characteristics				
Household size				
1-2	593 (32.2)	243 (5.3)	2313 (40.7)	740 (7.3)
3-5	1155 (62.6)	3749 (81.6)	3165 (55.6)	8224 (81.1)
≥6	96 (5.2)	605 (13.2)	211 (3.7)	1179 (11.6)
Household size not available[c]	47	57	163	45
Household composition				
Only adults	950 (50.9)	C (C)[e]	3076 (53.4)	922 (9.1)
One child	386 (20.7)	1005 (21.6)	1116 (19.4)	3377 (33.2)
Multiple children	532 (28.5)	3574 (76.9)	1564 (27.2)	5883 (57.8)
Household composition not available[c]	23	C (C)[e]	96	6
People per bedroom				
>2	112 (5.9)	571 (12.3)	308 (5.3)	750 (7.4)
>1 to 2	1128 (59.7)	3297 (70.8)	3342 (57.1)	6754 (66.3)
≤1	651 (34.4)	786 (16.9)	2202 (37.6)	2684 (26.3)
Information not available[c]	0	0	0	0
Index of multiple deprivation of household postcodes 2019				
Most deprived	425 (23)	1257 (27.5)	924 (16.2)	2248 (22.4)
2	369 (19.9)	985 (21.6)	1213 (21.2)	2081 (20.7)
3	315 (17)	715 (15.7)	1077 (18.8)	1653 (16.4)
4	383 (20.7)	877 (19.2)	1259 (22)	1924 (19.1)
Least deprived	358 (19.4)	731 (16)	1244 (21.8)	2148 (21.4)
Postcode not available[c]	41	89	135	134

[a]Data presented for all staff and students participating (providing samples for antibody or virus tests) in any of rounds 1, 2, 3, 4, and 5 or 6.

[b]N/A: not applicable.

[c]Data not available (ie, prefer not to answer or data unavailable), ≤3% for all characteristics. These are treated as missing data and therefore not included in the calculation of percentages

[d]Participants asked, *What is your gender?* (students) or *Which of the following describes how you think of yourself?* (staff), male or female or other or prefer not to say. Data are not available (ie, prefer not to answer or other or data unavailable).

[e]*C*: data suppressed (2 smallest categories suppressed).

Discussion

Principal Findings and Significance

The COVID-19 SIS was the largest cohort study to monitor the prevalence and transmission of SARS-CoV-2 in schools in England, a key setting and population group for the transmission of airborne infections, recruiting 22,585 participants from 59 primary and 97 secondary schools. Designed to meet an urgent policy requirement to inform pandemic response, the study aimed to characterize the extent of current and past SARS-CoV-2 infection in students and staff during the 2020-2021 academic year, including on school campuses, and investigate transmission from and to schools.

The 45.2% and 30% participation rates for staff in primary and secondary schools, respectively, are good relative to comparable studies [48] and in the context of the pandemic, although a higher uptake was predicted because of the willingness to participate in previous school-based studies [30]. The decline in staff participation across survey rounds in secondary schools (from 3165/7583, 41.7% to 2290/10,374, 22.1% between the first and last rounds) was not expected and could have been related to the increasing availability of staff vaccinations from early 2021 and a decreased perception of risk.

The overall participation rate of students was lower at an average of 15%, but this remained stable throughout the study period. This low rate could have been due to the requirement for parents to register their children via an email link, without being engaged with the process in the school. Staff participation appears resilient in terms of various school characteristics, such as whether the school is in a more deprived location, but student participation appears more sensitive to these factors. The sampling design did not seek to be representative of such factors, although it appears that a higher proportion of primary student participants resided in the most deprived postcodes at the individual level. Overall student participation was lower than might be expected in urban schools and schools in more deprived areas, which could in part indicate the digital divide and issues with sufficiently engaging parents as well as the differential ability to adhere to isolation measures if tested positive [49]. As the information, enrollment, consent, and questionnaire mechanisms were all sent via email, this could have biased enrollment toward families with greater access to electronic devices and a higher level of digital use and literacy [50]. All participating schools reported email as the primary route for communicating with parents, so it could be argued that this was unlikely to be the main factor leading to differential participation rates. However, parents affected by the digital divide would have lower access, and it was not possible for the study team to follow up with nonresponders via telephone to assist with any technological access issues.

Strengths and Limitations

SIS has several core strengths. These include the rapid and reactive nature of the study, with regular open access bulletins, enabling the results to feed directly into policy decisions and recommendations in real time. The longitudinal nature of the study facilitated the assessment of infection and antibody conversion over time and changes in behaviors and perceptions of the COVID-19 pandemic. In addition, consequences such as long-COVID, in children especially, will be explored [51]. Furthermore, SIS is adaptable to changing circumstances. New research aspects such as vaccine coverage in staff and perceptions of the feasibility and acceptability of new policy initiatives, such as mass testing in schools and vaccination, were subsequently incorporated via short pulse follow-up questionnaires as the policy environment evolved.

In addition to comparisons with pillar 2 testing, the linkage with the CIS provides opportunities for potential comparisons between the school-based population and the community population among parallel LAs and age groups, further contextualizing the findings [21,52]. For example, as the SIS study visits were conducted on school days, the findings are representative of students and staff in school, who would be expected not to have any symptoms. These results can then be compared with estimates of community prevalence in all school-age children as well as adults between the ages of 20 and 65 years regardless of school attendance or profession [21,52].

However, we also reflected on the practical challenges encountered in conducting research in schools during the pandemic. First, the initial school enrollment in SIS was slow, with schools in some LAs opting not to register for SIS. In addition, until December 31, 2020, the participation rate of individuals was lower than anticipated, particularly for students, potentially introducing nonresponse bias and limiting the representativeness of the findings. This low response rate is often inherent in surveys that require participants to respond to an email or letter in the first instance. In CIS, the equivalent community infection survey, the response rate (households registered) initially decreased from 51% when inviting 20,000 households who had previously taken part in ONS surveys to 14% when opened up via Address Base to a much larger sample of households that had not been engaged in ONS surveys [53]. The Real-time Assessment of Community Transmission Study documented response rates (tests returned of letters sent out) of 20.4% for PCR testing across 13 survey rounds and of 28.9% for antibody testing across 6 rounds [54].

As these challenges were encountered, a range of design modifications were made to the recruitment procedures, including sampling additional schools in certain LAs, transitioning from a closed to an open cohort, developing paper-based communication materials to increase the accessibility of information, and providing compensation at the school level. However, there remained no compensation at the participant level, as various other community and COVID-19 studies have implemented the use of vouchers [55], and this may have contributed to attrition in response to further questionnaires among participants. The expansion of secondary school eligibility beyond the 2 original year groups to other year groups in January 2021, with the aim of increasing student recruitment, was undertaken up by 52 secondary schools in total. Although it is recognized that this would likely not address nonresponse and representativeness, it would increase the precision of school-level estimates. The result was a consistent secondary school student participation rate of approximately

14% across rounds, as recruitment increased in rounds 4 to 6, along with the eligible population.

The second challenge, in rounds 1 and 2, especially during round 2 testing in December 2020, was that several schools opted not to participate in the survey and deferred testing until the start of the spring term in January 2021. Reasons for this included testing when schools were preparing for the end of term, concerns of school disruption at this busy time, and concerns about identifying asymptomatic positives, meaning bubbles and families would have to self-isolate, and families potentially losing income or not being able to gather over the Christmas period.

Third, during round 1, home testing was not available for enrolled individuals who were not at school on the day of the survey. However, the introduction of home testing for those absent on the day of the survey from round 2 and beyond enabled participants to be included in the antibody conversion analyses. This was especially important for round 3, which was affected by the school closures, as other school studies were [56] and was modified to an exclusive home-testing round, for those without baseline antibody results.

Finally, the study relied on parental responses to questionnaires in relation to children aged <16 years. Although they were asked to complete the questionnaire in consultation with their child (the participant), it would have been preferable to survey these students directly, either in person by the survey teams during sample collection or through web-based questionnaires conducted on school computers, in terms of both the response rates and usefulness of the data.

Conclusions

The SIS study aimed to enhance our understanding of the transmission of SARS-CoV-2 within schools by measuring past, current, and incident infection over time, the effect on outcomes such as school attendance and mental well-being, and the implementation and perceptions of control measures in schools. The findings of the ongoing analyses of these core study aims will be presented in subsequent publications with the aim of contributing substantially to the evidence base and informing future national policy.

Source, License, Copyrights, and Credits

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Data Availability

Deidentified study data are available for access by accredited researchers in the Office for National Statistics Secure Research Service for accredited research purposes under part 5, chapter 5 of the Digital Economy Act of 2017. For further information about accreditation visit the Secure Research Service website.

Disclaimer

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Authors' Contributions

JH, SML, SNL, CB, PM, NS, PND, ID, FD, and ER were responsible for conceptualization, study design, and methodology. JH, SNL, SML, ID, and ER obtained funding. JH, SML, SNL, JP, SI, JS, FD, and ER contributed to the project administration and provided technical or material support. PND, KEH, JS, NS, JP, GI, AJ, CB, PM, JH, SML, and SNL were involved in the data acquisition. WEO and KEH analyzed and interpreted the data with support from EA and JS. KEH, PND, WEO, SML, and JH drafted the manuscript. PM, NS, CB, AJ, JE, TGC, SNL, and GI critically revised the manuscript for intellectual content. All authors contributed to the review and editing of the manuscript. KEH, PND, and JH have the final responsibility to submit for publication. KEH and PND contributed equally to this paper. The COVID-19 Schools Infection Survey Study Group consists of investigators from London School of Hygiene & Tropical Medicine, UK Health Security Agency, and Office for National Statistics, who served as scientific advisers, critically reviewed the study proposal, and provided technical support and individuals from IQVIA, who managed the web-based portal and provided implementation support.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Schools Infection Survey Questionnaire Bank.
[PDF File (Adobe PDF File), 492 KB - resprot_v11i11e34075_app1.pdf]

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Abbreviations

CIS: COVID-19 Infection Survey
FSM: free school meal
LA: local authority
ONS: Office for National Statistics
RT-PCR: reverse transcriptase polymerase chain reaction
SIS: Schools Infection Survey
sKIDs: COVID-19 Surveillance in School KIDs
UKHSA: UK Health Security Agency

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Protocol

Efficacy and Safety of Direct Hemoperfusion Using Polymyxin B-Immobilized Polystyrene Column for Patients With COVID-19: Protocol for an Exploratory Study

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Abstract

Background: Polymyxin B-immobilized fiber column (PMX; Toraymyxin column) was approved for the relief of systemic inflammatory response syndrome caused by bacterial infection or endotoxemia. PMX reduces lung damage by removing leukocytes and cytokines in addition to endotoxin removal in the setting of idiopathic pulmonary fibrosis. Acute exacerbation of interstitial pneumonia pathologically presents with diffuse alveolar damage (DAD). PMX direct hemoperfusion (PMX-DHP) demonstrated efficacy, improving oxygenation. The SARS-CoV-2 virus causes COVID-19, which emerged in December 2019. The condition may become severe about 1 week after onset, and respiratory failure rapidly develops, requiring intensive care management. A characteristic of COVID-19–related severe pneumonia is ground-glass opacities rapidly progressing in both lungs, which subsequently turn into infiltrative shadows. This condition could be classified as DAD. As for the congealing fibrinogenolysis system, D-dimer, fibrin/fibrinogen degradation product quantity, and prolonged prothrombin time were significant factors in nonsurviving COVID-19 cases, associated with aggravated pneumonia. Clinical trials are being conducted, but except for remdesivir and dexamethasone, no treatments have yet been approved. COVID-19 aggravates with the deterioration of oxygen saturation, decrease in lymphocytes, and the occurrence of an abnormal congealing fibrinogenolysis system, leading to diffuse lung damage. Once the condition transitions from moderate to severe, it is necessary to prevent further exacerbation by providing treatment that will suppress the aforementioned symptoms as soon as possible.

Objective: This study aims to access treatment options to prevent the transition from acute exacerbation of interstitial pneumonia to DAD. The mechanism of action envisioned for PMX-DHP is to reduce congealing fibrinogenolysis system abnormalities and increase oxygenation by removing activated leukocytes and cytokines, which are risk factors for the aggravation of COVID-19–related pneumonia.

Methods: We will conduct a multicenter, prospective, intervention, single-group study to evaluate the efficacy and safety of direct hemoperfusion using PMX-DHP for patients with COVID-19. Efficacy will be evaluated by the primary end point, which is the rate of Ordinal Scale for Clinical Improvement after PMX-DHP of at least 1 point from a status of 4, 5, or 6 on day 15. The effect of PMX-DHP will be estimated by setting a control group with background factors from non–PMX-DHP patients enrolled in the COVID-19 registry. This study will be carried out as a single-group open-label study and will be compared with a historical control. The historical control will be selected from the COVID-19 registry according to age, gender, and severity of pneumonia.

Results: The study period is scheduled from September 28, 2020, through April 30, 2023. Patient enrollment was scheduled from the Japan Registry of Clinical Trials publication for March 31, 2022. Data fixation is scheduled for October 2022, with the publication of the results by March 2023.

Conclusions: From a clinical perspective, PMX-DHP is expected to become an adjunctive therapy to address unmet medical needs and prevent the exacerbation from moderate to severe acute respiratory distress syndrome in COVID-19 cases.

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KEYWORDS

polymyxin B-immobilized fiber column; PMX; diffuse alveolar damage; DAD; COVID-19; pneumonia; fibrinogenolysis; systemic inflammatory response syndrome; lung disease; lung damage; pulmonary; treatment; prospective intervention; health information; treatment information; therapy; COVID-19 therapy

Introduction

Regarding polymyxin B-immobilized column (PMX), Toraymyxin was approved in October 1993 for the relief of systemic inflammatory response syndrome caused by gram-negative bacterial infection or endotoxemia by "selectively adsorbing and removing endotoxin in the blood by whole blood hemoperfusion." It has been reported to be effective against acute lung injury/acute respiratory distress syndrome caused by sepsis, which is an indicator [1-4]. This is thought to be because PMX reduces lung damage by removing leukocytes and cytokines in addition to endotoxin removal. In terms of treatment results, idiopathic pulmonary fibrosis (IPF), which has been the subject of previous clinical studies, is the most common idiopathic interstitial pneumonia (accounts for about 50% of idiopathic interstitial pneumonia worldwide) and has a chronic and progressive course. Once advanced fibrosis progresses, irreversible honeycombing occurs, leading to an extremely poor prognosis [5,6]. The total number of Japanese patients with IPF is estimated to be at least around 10,000 [7]. Acute exacerbation of interstitial pneumonia pathologically presents with diffuse alveolar damage (DAD). In recent years, reports on PMX (Toraymyxin by Toray Industries Inc) direct hemoperfusion (PMX-DHP) for this acute exacerbation have mentioned its efficacy, which includes the improvement of oxygenation [8-15]. A study of 73 IPF cases with acute exacerbation has noted the improvement of oxygenation upon carrying out PMX-DHP [14]. Further, an exploratory study on the efficacy and safety of direct hemoperfusions using PMX-DHP for patients with IPF with acute exacerbation was conducted from 2014 to 2019 for the acute exacerbation of IPF. In this study, the survival rate of 20 enrolled cases 4 weeks after PMX-DHP was 65%, which far exceeded the 10% to 40% threshold survival rate in previous reports [15,16] and exceeded the expected upper limit of the survival rate of 60%. Moreover, the result was well above the expected lower limit of the 95% CI, which was 39%.

SARS-CoV-2 was identified as the causative virus of an unknown pneumonia (COVID-19) that emerged in Wuhan City, Hubei Province, China in December 2019. Depending on the case, the condition become severe about 1 week after onset, and respiratory failure rapidly develops, requiring intensive care management [17]. Patients may have markedly impaired oxygenation early in the course of the disease, which is said to be due to increased activity of the coagulation system; plasminogen activator inhibitor-1 expression is increased in older adults and in people with hypertension, obesity, and diabetes, which are risk factors for COVID-19; and in severe cases of COVID-19, STAT3 and plasminogen activator inhibitor-1 activation is escalated, leading to catastrophic consequences. A characteristic of COVID-19–related severe pneumonia cases is ground-glass opacities rapidly progressing in both lungs visible in chest computed tomography findings [18]. With subsequent progression toward severity, these opacities turn into infiltrative shadows [19]. This condition could be classified as DAD [20]. According to the analysis results of 191 COVID-19 cases in Wuhan, 100% of nonsurviving cases have sepsis while 93% have acute respiratory distress syndrome. The three most relevant risk factors in the early stage were age, Sequential Organ Failure Assessment score, and 1 μg/mL or higher D-dimer [21]. As for the congealing fibrinogenolysis system, according to a different report, D-dimer, fibrin and fibrinogen degradation product, and prolonged prothrombin time were significant factors in nonsurviving COVID-19 cases, suggesting that the effects of the congealing fibrinogenolysis system are associated with the aggravation of pneumonia [22]. As of February 2021, clinical trials and clinical studies are being conducted with several existing treatments, but except for remdesivir and dexamethasone, no drugs or treatments have yet been approved by the Japanese regulatory authorities.

As previously mentioned regarding the clinical significance of PMX-DHP, we believe that COVID-19 aggravates with the rapid deterioration of oxygen saturation, decrease in lymphocytes, and the occurrence of an abnormal congealing fibrinogenolysis system, leading to complex diffuse lung damage. Virus growth suppression caused by antiviral action can be expected if the initial growth rate is suppressed; however, once the condition transitions from moderate to severe, it is most necessary to address unmet medical needs to prevent further exacerbation by providing treatment that will suppress the aforementioned symptoms as soon as possible and prevent the transition to DAD. Simply put, we believe that, in addition to antiviral drugs, it is most necessary to acquire treatment options to prevent progression from rapidly worsening interstitial pneumonia to DAD. The complex mechanism of action envisioned for PMX-DHP is to reduce congealing fibrinogenolysis system abnormalities and increase oxygenation

by removing activated leukocytes and cytokines, which are risk factors for the aggravation of COVID-19–related pneumonia. Therefore, from a clinical perspective, PMX-DHP is expected to become an adjunctive therapy to address unmet medical needs and prevent the progression from moderate to severe condition. The scientific rationale of this study is to carry out PMX-DHP, in addition to regular medical care, for patients with COVID-19 and to aggregate and analyze the acquired information. This study will help determine PMX-DHP treatment options in the medical setting by quickly collecting and publishing information on patient background and on the efficacy and safety of treatment by PMX-DHP.

Methods

Study Design

We will conduct a multicenter, prospective, intervention, single-group study to evaluate the efficacy and safety of direct hemoperfusion using PMX-DHP for patients with COVID-19. Efficacy will be evaluated by the primary end point, which is the rate of Ordinal Scale for Clinical Improvement after PMX-DHP of at least 1 point from a status of 4, 5, or 6 on day 15, based on previous studies for COVID-19 treatment (Table 1) [23]. Further, safety will be confirmed by the incidence of serious adverse events and problems. The effect of PMX-DHP will be estimated by setting a control group with background factors from non–PMX-DHP patients enrolled in the COVID-19 registry at participating facilities. Since this study will carry out PMX-DHP, setting up a sham group is difficult in terms of ethics because the therapy is relatively invasive. As such, this study will be carried out as a single-group open-label study and will be compared with a historical control. The historical control will be selected from the COVID-19 registry according to age, gender, and severity of pneumonia.

Table 1. Purpose and end points.

Purpose	End points	Validity and reason for selection of end points
Primary		
To evaluate the efficacy of PMX-DHP[a]	• Improvement rate (decrease) of 1 point or more from status 4, 5, or 6 on day 15 based on the eight-category evaluation	Because it was the primary end point in previous studies for COVID-19 treatment
Secondary		
To evaluate the efficacy and safety of PMX-DHP	• Pathological improvement rate (status 1, 2, and 3 in the aforementioned eight categories) from the start of PMX[b]. • PaO2/FiO2 improvement on day 4 and day 8 • Changes in cytokines, coagulation markers, and urinary biomarkers • Occurrence of serious adverse events and problems • Invasive mechanical ventilation avoidance rate and duration of use • ECMO[c] avoidance rate and duration of use • Mortality rate	Evaluation of respiratory function, safety, and efficacy of PMX-DHP

[a]PMX-DHP: polymyxin B-immobilized fiber column direct hemoperfusion.

[b]PMX: polymyxin B-immobilized fiber column.

[c]ECMO: extracorporeal membrane oxygenation.

Eligibility Criteria and Recruitment

All of the following inclusion criteria must be met to participate in this study: dyspnea unexplainable by other diseases (heart failure, renal failure, etc), diagnosis with SARS-CoV-2 infection through polymerase chain reaction or loop-mediated isothermal amplification within 1 week, at least one lung opacity on imaging suggestive of consolidation, P/F ratio of 300 or below or an SpO2 of 93% or below (indoor air), being hospitalized, requiring supplemental oxygen, requiring nasal high-flow oxygen therapy or noninvasive mechanical ventilation or requiring invasive mechanical ventilation, 16 years or older at the time of consent, and written consent. Consent is obtained from patients with pneumonia who are hospitalized for COVID-19 and who may meet the eligibility criteria.

Consent is obtained in writing from the individual. Informed consent will be obtained from a representative of the patient if the patient is a minor or objectively judged to have insufficient understanding of the subject due to a serious illness. The representative will be selected from the patient's spouse, parents, siblings, children/grandchildren, grandparents, relatives living in the same household, or close relatives of the patient.

The following tests, observations, and evaluation will be performed as part of the screening test: vital information (date of birth, gender, height, weight, presence of oxygen therapy); clinical history (onset: date of onset, symptoms), treatment history (type, treatment period of therapeutic drugs/therapy), medical history, complications, allergies, date of admission, date of polymerase chain reaction positive result, concomitant drug confirmation (medication currently being taken by the patient shall be confirmed at the time of the screening), vital signs, blood test (hematological test, blood biochemical test), urinalysis, and imaging test (presence of pneumonia complications).

As a result of the screening, if the patient meets the enrollment criteria stated in the eligibility criteria, they will be enrolled to the study, and PMX-DHP will commence. Otherwise, the patient fails the screening and will no longer participate in the study.

The following exclusion criteria will be used: severe progression of multiple organ failure; P/F ratio of 100 or below; extracorporeal membrane oxygenation (ECMO); hospitalization for more than 15 days; platelet count of 20,000/μL or less; cytotoxic or biological treatments (anti-interleukin [IL]–1, anti-IL-6 [tocilizumab or sarilumab], T cell or B cell targeted treatment [rituximab, etc], tyrosine kinase inhibitor or interferon) within 4 weeks prior to consent; treatment with tumor necrosis factor inhibitor within 2 weeks prior to consent; treatment with convalescent plasma or intravenous immunoglobulin for COVID-19; and consideration by the principal investigator or subinvestigator to be unfit to participate in this study.

In case of nonparticipation in the study, administration of remdesivir, dexamethasone, and tocilizumab will be considered if indicated and not already administered. Furthermore, systemic management including oxygen therapy will be performed for deterioration of respiratory function.

A schematic illustration of the study design is presented in Figure S1 in Multimedia Appendix 1.

Sample Size Estimation

In this study, the efficacy of PMX-DHP will be evaluated by comparing the improvement rate (decrease) of 1 point or more from status 4, 5, or 6 on day 15 based on the eight-category evaluation with the COVID-19 registry. In a paper that reported on the compassionate use of remdisivir for COVID-19 cases [23], of 51 cases who were under invasive ventilation, noninvasive oxygen support, or low flow oxygen (corresponds to the status 4, 5, and 6 in this study), improvement by at least 1 stage was noted in 34 cases (approximately 57%; median follow-up period: 18 days). Further, in a randomized clinical trial investigating the effect of lopinavir-ritonivar on COVID-19 about 38% (75/199) of cases recovered (improved by 2 points or more on a 6-point scale) 14 days after randomization [24]. Based on the aforementioned, we assume that approximately 50% to 60% of non–PMX-DHP COVID-19 cases will improve by 1 point. On the other hand, although there is insufficient data on the expected effects of PMX-DHP, we can consider PMX-DHP effective if the improvement rate of cases in this study is 1.5 times that of the non–PMX-DHP cases.

We set a 2-sided type I error at 10%. When the improvement rate of non–PMX-DHP cases is approximately 55%; if there are 30 cases in this study; and the control group is set at 30, 60, and 90 cases, the detection power would be approximately 65%, 78%, and 83%, respectively. Similarly, if the improvement rate of non–PMX-DHP cases is approximately 50%, the detection power would be 54%, 67%, and 72%, respectively. If the improvement rate is approximately 60%, the detection power would be 78%, 90%, and 94%, respectively. However, when compared with control cases, the detection power fluctuates due to the adjustment in the confounding factor.

Intervention: Medical Device, Protocol, and Combination Therapy

The medical device used is an adsorptive blood-purifying device (product name Toraymyxin, model PHX-20R, approval 20500BZZ00926000). This blood-purifying device selectively adsorbs and removes blood endotoxin by whole blood hemoperfusion. This product is intended to improve the pathological condition by treating patients with severe pathological conditions associated with endotoxemia or thought to be due to gram-negative bacterial infections.

The appearance of this product is shown in Table 2 and Figure S2 in Multimedia Appendix 2.

Table 2. Structure.

	Toraymyxin (model PHX-20R)
Length (mm)	225
Maximum diameter (mm)	63
Body diameter (mm)	49
Blood volume (mL)	135 (±5)

This product is sealed one by one in a sterilized bag and packed in a box. Information about storage, delivery, disposal, potential serious side effects, and caution for concomitant treatment can be obtained at the manufacturer's website [25]. In general, an adverse event is an undesirable symptom, sign, disease, or abnormal laboratory test value that occurs in a patient regardless of their causal relationship with the study or the pharmaceuticals used in this study. An adverse event occurs after the start of treatment. An adverse event will be considered a serious adverse event if the principal investigator or subinvestigator rules that the following criteria have been met: death or risk of leading to death, events that require hospitalization at a medical institution for treatment or require the extension of hospitalization, impairment or risk of leading to impairment, or congenital diseases or abnormalities that could be inherited by later generations.

Dosage

While administering an anticoagulant drug (nafamostat mesilate: approximately 30-40 mg/hr or heparin approximately 40-60 U/kg one shot + approximately 40-60 U/kg/h), 1 Toraymyxin at a flow rate of 60-120 mL per minute should be administered for 3-6 hours (maximum of 24 hours), and at least 2 doses (maximum 3) should be used. The follow-up will be carried out up to 4 weeks after the end of PMX-DHP. PMX-DHP does not have to be conducted in consecutive days, but the interval between each session must be as short as possible.

The equipment operation for direct hemoperfusion will go as follows (Multimedia Appendix 3):

1. Prepare the extracorporeal circulation device (blood pump, anticoagulant infusion pump, monitoring of arterial and venous pressure of the inlet and outlet pressure of this product)
2. Precautions before use (inspection of exterior, confirmation of sterilization)
3. Cleaning and priming
4. Circulation:
    - Insert a double lumen catheter into the patient's femoral vein or internal jugular vein to serve as the site for blood access
    - Using a blood pump, perform whole blood hemoperfusion at a flow rate of 60-120 mL per minute, which will be determined according to the patient's condition
    - When using this product, anticoagulants (nafamostat mesylate, heparin) are administered by continuous infusion from the blood circuit on the blood removal side.
    - Duration of extracorporeal circulation is 3 to 24 hours per piece
    - The maximum working pressure of this product is 66 kPa (500 mHg). Note that the pressure difference between the inlet and outlet of this product may increase due to internal clogging caused by the formation of blood clots.

Heparin or nafamostat will be used in the anticoagulant therapy to be performed for direct hemoperfusion associated with PMX-DHP. Moreover, since the target patients of this treatment are within the scope of heparin and nafamostat, the anticoagulation treatment is not considered as the target treatment of this study.

There are no restrictions on the antiviral treatment for COVID-19; however, in principle, the antiviral treatment will not be changed during the study period.

Concomitant use with cytotoxic or biological treatments (anti-IL-1, anti-IL-6 [tocilizumab or sarilumab], T cell or B cell targeted treatment [rituximab, etc], tyrosine kinase inhibitor or interferon), tumor necrosis factor inhibitor, convalescent plasma, and intravenous immunoglobulin administration for COVID-19 are prohibited. Concomitant use of steroids, including dexamethasone and tocilizumab, is acceptable.

Statistical Analysis

The main purpose of this study is to verify the efficacy in PMX-DHP cases compared to the control in the COVID-19 registry for the primary end point. Particularly, the efficacy of PMX-DHP will be evaluated by comparing the improvement rate (decrease) of 1 point or more from status 4, 5, or 6 on day 15 based on the eight-category evaluation with the COVID-19 registry.

1. Not hospitalized with resumption of normal activities
2. Not hospitalized but unable to resume normal activities
3. Hospitalized not requiring supplemental oxygen
4. Hospitalized requiring supplemental oxygen
5. Hospitalized requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both
6. Requiring invasive mechanical ventilation
7. Requiring ECMO
8. Death

The status and the percentage of PMX-DHP cases at each evaluation time will be calculated, and the number and percentage of people whose day 15 status improved by 1 or more points from day 1 will be calculated. Furthermore, the following analysis will be planned for comparison with control cases.

Bias is included when comparing the rate of improvement of control cases for 15 days from the time of hospitalization against cases that underwent PMX-DHP several days after hospitalization. Therefore, the number of days from hospitalization to the date of PMX-DHP administration will be calculated for each case.

The effect of PMX-DHP will be estimated using the propensity score based on the data, which integrates this study and the registry. The propensity score will be created based on age, gender, body temperature, etc, and analysis methods such as matching will be used. A significance level on both sides of 5% will be used.

The following results will be calculated for cases enrolled in this study:

- Pathological improvement rate on day 15 (status 1, 2, and 3 in the eight categories) from the start of PMX. The number and percentage of people who reached status 1, 2, and 3 on day 15 at a 95% CI will be calculated. Furthermore, the same items will be calculated on day 29.
- P/F improvement on day 4 and 8. The descriptive statistics of P/F on day 1, day 4, and day 8 will be calculated and presented on a transition chart.
- Changes in cytokines, coagulation markers, and urinary biomarkers. The descriptive statistics of clinical laboratory test values that take continuous values will be calculated. For laboratory findings, which are classification variables, the number and proportions at each level will be calculated at each point in time.
- Invasive mechanical ventilation avoidance rate and duration of use. The number and proportion of people who underwent invasive mechanical ventilation between day 15 and 29 will be calculated.
- ECMO avoidance rate and duration of use. The number and proportion of people who underwent ECMO between day 15 and 29 will be calculated.

Similar to the primary end point, the efficacy of PMX will be evaluated for the aforementioned secondary end points using propensity scores based on data integrated with the enrolled cases in the registry.

The safety end point is the incidence and rate of adverse events. Multiplicity will not be adjusted in the analysis of safety end points. In the estimation of the ratio to the number of cases and presence or absence of occurrence, an exact 95% CI for the binomial distribution will be calculated for each group.

In addition to clinical laboratory items, continuous quantity data will be tabulated by group through descriptive statistics, while classification variables will be tabulated through the number of people or rate, among other appropriate methods.

Furthermore, PMX malfunctions will also be tabulated. Subgroup analysis will be performed by status and age at the time of enrollment.

Ethics Approval

This study will be reviewed by the Institutional Review Board for Clinical Research of National Center for Global Health and Medicine (certification CRB3200011).

Results

The study period is scheduled from September 28, 2020, the date of publication in the Japan Registry of Clinical Trials (jRCT), through April 30, 2023. Patient enrollment is scheduled from the jRCT publication to March 31, 2022. Data fixation is scheduled for October 2022, with publication of results by March 2023.

Discussion

We are conducting an interventional trial to evaluate the efficacy of PMX in moderately to severely ill patients with COVID-19 requiring oxygenation, believing that PMX may be useful in the treatment of COVID-19 by removing inflammatory cytokines and improving the coagulation system.

Anticipated Findings

Participation in this study may improve respiratory function and homeostasis of the congealing fibrinogenolysis system by receiving PMX-DHP. PMX-DHP can be performed in parallel with treatment using antiviral drugs, etc, that are expected to have a therapeutic effect on COVID-19, which may be beneficial to the patients. In addition to the direct benefits to the patients, if PMX-DHP is recognized as a standard treatment through this study, it may lead to the reduction of burden on patients with COVID-19 and reduction of medical expenses for society. Furthermore, patients may indirectly benefit once the research results concerning COVID-19 treatment help rehabilitate society. In this study, all eligible patients receive PMX-DHP but with the risk of pain, bleeding, and infection associated with catheter insertion.

Furthermore, the same dangers and discomfort similar to regular medical treatment may occur as a result of intravenous blood sampling and radiological imaging, for example, pain and discomfort associated with blood sampling and exposure to radiation imaging. The blood to be collected per sampling in this study will be 30 mL, which is medically acceptable, but since the frequency of blood collection is higher than in normal medical care, the burden on the patient may increase. Since blood will be collected for a total of 5 times, 150 mL of blood or more will be collected throughout the entire period of the study compared to regular medical care.

Limitations

The major limitations of this study are that it is an open-label trial, where the information is not withheld from trial participants (both the researchers and participants know that PMX therapy is being administered), and it is not a randomized parallel study, so the patients will be allocated to different groups in a nonrandom way. We plan to use the COVID-19 registry as a control group, but selection bias should be interpreted with caution [26]. Finally, the severity of COVID-19 depends on the mutant strain. Depending on the future epidemic, fewer cases may be severe, making it more difficult to incorporate.

Dissemination Plan

The results will be presented at national and international academic meetings, and submitted to peer-reviewed journals for publications.

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Conflicts of Interest

Based on the joint research agreement, the Toraymyxin column used in this study will be provided for free by the manufacturer and distributor Toray Industries, Inc. SI received a research grant from Toray Industries, Inc. AA has received research funding from Toray Industries, Inc. unrelated to this research.

Multimedia Appendix 1
Schematic overview of the study design. PMX-DHP: Polymyxin B-immobilized fiber column direct hemoperfusion.
[PNG File , 19 KB - resprot_v11i11e37426_app1.png]

Multimedia Appendix 2
External view of Toraymyxin.
[PNG File , 46 KB - resprot_v11i11e37426_app2.png]

Multimedia Appendix 3
Clinical example of Toraymyxin. PMX: polymyxin B-immobilized fiber column.
[PNG File , 20 KB - resprot_v11i11e37426_app3.png]

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Abbreviations

DAD: diffuse alveolar damage
ECMO: extracorporeal membrane oxygenation
IL: interleukin
IPF: idiopathic pulmonary fibrosis
jRCT: Japan Registry of Clinical Trials
PMX: polymyxin B-immobilized fiber column
PMX-DHP: polymyxin B-immobilized fiber column direct hemoperfusion

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Protocol

A Brief Educational Pre-exposure Prophylaxis Intervention in an Infectious Disease Clinic: Protocol for a Case Series Study

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Abstract

Background: Black men who have sex with men (BMSM) remain the highest group infected with HIV despite treatment with medications known as pre-exposure prophylaxis (PrEP). PrEP in combination with safer sex practices has shown efficacy in preventing HIV infection. Despite awareness campaigns, PrEP uptake remains low among BMSM. While brief educational interventions have value in fast-paced clinical settings with limited appointment times, a brief PrEP educational intervention has not been initiated with BMSM in a fast-paced outpatient infectious disease clinic in North Carolina.

Objective: The purpose of this study was to examine the effect of initiating a brief PrEP educational intervention to reduce HIV infection rates in BMSM in a fast-paced infectious disease clinic delivered by a doctoral-prepared nurse practitioner.

Methods: This case-series study uses a brief educational intervention to develop and pilot-test a brief PrEP educational uptake intervention with BMSM. The participants met with the nurse practitioner at 3 different time points: baseline, 4 weeks later (first visit), and at the 3-month follow-up (second visit). We used a pretest-posttest design to examine the primary outcomes of PrEP knowledge, medication adherence, and sexually transmitted infection outcomes.

Results: Due to the COVID-19 pandemic, the recruitment process was delayed. From November 1, 2019, to August 30, 2021, a total of 7 participants consented to participate in the study. Data analysis will be completed by the end of September 2022. We will submit a manuscript for publication consideration by December 2022.

Conclusions: Brief educational interventions delivered in a fast-paced infectious disease clinic have the potential to increase PrEP awareness and knowledge, medication adherence, and decreased rates of sexually transmitted diseases in BMSM. This protocol will contribute to the literature on the development of brief PrEP educational interventions and has the potential to be generalized to other populations (eg, women and adolescents).

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KEYWORDS

PrEP; men who have sex with men; protocol; case series design; HIV; pre-exposure prophylaxis; sexual health; HIV prevention; health education; educational intervention

Introduction

Background

Despite advances in HIV prevention care, Black men who have sex with men (BMSM) living in the southern region of the United States remain at a much higher risk of acquiring HIV when compared to other racial or ethnic groups [1,2]. BMSM living in this region of the country have been historically marginalized, have greater unmet social determinants of health needs, and have higher rates of HIV infection [3]. One of the southern states targeted for HIV prevention efforts is North

Carolina [1]. In 2019, North Carolina was the sixth-highest state for new HIV diagnoses, with higher rates among racial and ethnic groups [4].

Widespread lack of awareness and knowledge of pre-exposure prophylaxis (PrEP) among BMSM in the United States persists. Despite significant evidence of efficacy, there are barriers to PrEP awareness and uptake. First, there is a limited understanding of PrEP among health care professionals [5]. Few studies demonstrate that PrEP works as long as it is taken as prescribed, making adherence a challenge [6]. The successful implementation of PrEP is driven by four elements: (1) linkage of BMSM to PrEP providers, (2) access to PrEP medications, (3) adherence to the prescribed regimen, and (4) ongoing sexual risk reduction behaviors [7]. Another factor to consider with PrEP uptake is the history of medical mistrust in the African American community (eg, the Tuskegee experiment) [8]. One way to link BMSM to the PrEP care continuum is through the acceleration of new models of care with nurse practitioners (NPs).

Project Goal

The long-term goal of this study is to increase the rate of PrEP uptake in HIV-negative BMSM. The primary objective of this study was to develop a study protocol for a brief educational PrEP intervention delivered by a doctoral-prepared NP in a fast-paced infectious disease clinic. The success of PrEP uptake is dependent on behavioral variables such as knowledge of PrEP; willingness to take PrEP; and acceptability of, readiness for, and adherence to PrEP [7]. Understanding the demographic and behavioral predictors of intentions to use PrEP proved useful in identifying prospective participants for this study [7,8].

Methods

Design

For this pilot project, a case-series design was used to determine the impact of the integration of a PrEP protocol in HIV-negative BMSM. A case series is a group or series of case reports involving patients who are given similar treatment [9,10]. Case study data can include demographic information such as age, gender, ethnic origin, as well as information on diagnosis, treatment, response to treatment, and follow-up after treatment [9,10].

Sample

The target population was a convenience sample of HIV-negative BMSM who had engaged in anal sex without condoms or sex with men who have sex with men (MSM) diagnosed with a sexually transmitted infection (STI) in the past 6 months who received care from the infectious disease clinic. Inclusion criteria included the following: (1) participants had to be older than 18 years of age, (2) able to give consent, and (3) are not infected with hepatitis B or C. Exclusion criteria included being unable to provide consent, less than 18 years of age, HIV positive, and infected with hepatitis B or C. Due to the COVID-19 pandemic, the recruitment process was delayed. From November 2019 to August 2021, other health care professionals (nurses and pharmacists; n=4) informed prospective participants (HIV-negative MSM) about the study using the institutional review board (IRB)–approved recruitment flyer. Interested participants were referred to an infectious disease physician who screened for eligibility. Those eligible to participate in the study were scheduled and directed to the NP.

Setting

The protocol was delivered in an infectious disease clinic at a large medical center in southern United States. This clinic has a large clientele of BMSM. Approximately 20 BMSM are diagnosed with HIV each month, noting the urgent need for prevention efforts. The clinic's staff provides interprofessional services to more than 2000 patients seeking treatment for HIV prevention or treatment annually.

The Brief Educational PrEP Intervention Protocol

The evaluation of candidacy for HIV PrEP [11] was used to guide the design and development of the PrEP protocol. Additionally, guidelines from the Centers for Disease Control and Prevention, a review of the literature, and input from the clinical staff (infectious disease doctors, NPs, nurses, social workers, and patient navigators) were included [1-7,11]. On the first scheduled visit, the NP discussed the PrEP protocol and data collection procedures (eg, consent, laboratory results, and surveys). After completing the 24-item attitudes and behavior toward PrEP among high-risk HIV seronegative MSM survey [12] and the pretest 9-item PrEP knowledge survey [6], the participants received a brief face-to-face educational intervention accompanied by a PrEP 101 handout given at the end of the session (see Table 1 and Multimedia Appendix 1). The educational intervention provided information on PrEP indications, side effects, and how to take the medication. At this visit, the baseline specimens were also collected. PrEP laboratory tests included HIV antigen–antibody testing, a comprehensive metabolic panel, a hepatitis panel, as well as syphilis, and, if required, gonorrhea and chlamydia testing at anatomical sites of exposure. A medication pill log was provided to each patient to allow them to record when they had taken their PrEP medication. Condoms were available for distribution at each clinic visit. Two days later, a prescription was sent to the participant's pharmacy of choice after their laboratory results had been reviewed.

Before the follow-up sessions (4 weeks and 3 months from baseline), repeat laboratory results were ordered. At the follow-up session, the NP reviewed the laboratory results and the PrEP 101 handbook with each participant. Strategies to maintain PrEP adherence and identify the negative consequences of unprotected sexual encounters were emphasized, and condoms were distributed as needed. At the third visit, the 9-item PrEP knowledge survey was administered to assess PrEP knowledge retention (Table 1). The NP contacted the pharmacy to monitor prescription refills with each follow-up visit. The participants were given a US $25 gift card on the first visit and a US $25 gift card on the third visit. No monetary compensation was provided for the second visit (Table 1). Table 1 summarizes the measures used in this study.

Table 1. Description of protocol measures, expected outcomes, and assessment times.

Measure	Description	Outcome	Data collection
Evaluation of PrEP[a] criteria screening tool	• 25-item survey to evaluate eligibility for PrEP	Screening tool for eligibility	• Enrollment
Attitudes and behaviors toward PrEP among high-risk HIV-seronegative men who have sex with men	• 24 item: 5-point Likert scale, true or false, yes or no	Readiness to take PrEP	• Enrollment
Demographics	• 6 questions: age, gender, education, race or ethnicity, and exposures	Sample characteristics	• Baseline
Pre-/post-PrEP knowledge	• 9 questions: yes or no, true or false, select all what medications are used for PrEP, and what else should be used with PrEP to prevent HIV transmission	PrEP knowledge	• Baseline • Follow-up 1: 4 weeks • Follow-up 2: 3 months
Medication log and pharmacy outreach	• 7-day weekly log sheet of when medication is taken	Medication adherence	• Follow-up 1: 4 weeks • Follow-up two: 3 months
Blood work and swabs	• Rapid plasma reagin • Gonorrhea and chlamydia test at anatomical sites of exposure	Sexually transmitted infections	• Baseline • Follow-up 1: 4 weeks • Follow-up 2: 3 months
Blood work	• Complete metabolic panel, hepatitis panel • HIV antigen-antibody testing	Check kidney function, liver function, and HIV status	• Baseline • Follow-up 1:4 weeks • Follow-up 2: 3 months

[a]PrEP: pre-exposure prophylaxis.

Outcome Measures

We examined medication adherence, PrEP knowledge, and incidence of STIs that occurred while the participants were enrolled in the study. The number of participants on PrEP, those who stayed on PrEP, those who stopped taking PrEP, and those who tested positive for HIV while taking PrEP were examined. PrEP knowledge was measured with the 9-item PrEP knowledge survey (pretest and posttest), and medication adherence was measured by the number of participants who had their medications refilled and the number of dosages recorded taken on the medication log. STI data were obtained from the laboratory work (HIV testing and rapid plasma reagin blood specimen) and swabs (oral and rectal). Condom use was measured with the question: Over the past 3 months, did you use a condom with each sexual encounter? If they answered "no," then the next question was "Over the past 3 months, how many times did you use a condom while having sex?" We encouraged the participants to be open and honest with their responses (Table 1).

Data Collection, Management, and Analysis

All data were collected and managed using Excel (Microsoft Corporation) spreadsheets. The NP was the sole data collector for this study. As a result of the small sample size, all study outcomes were analyzed using descriptive statistics and inferential tests (*t* test, chi-square) to examine trends over time.

Confidentiality

Participants were informed that safeguards were in place to protect confidentiality and anonymity. All study-related information and spreadsheets were stored in a locked office and file cabinet at the study site. All participant information was coded by ID number to maintain confidentiality. We protected confidentiality by removing identifiers as soon as possible. Only members of the research team have access to the data, and only aggregate data will be presented for publication [13].

Ethics Approval

Approval from the Wake Forest University Institutional Review Board (IRB00052082) was required since the case study was categorized as a research study [9,10]. The study's protocol, surveys, and informed consent forms were reviewed to ensure respect, fairness, and safety in human subjects research [13]. The protocol was followed in accordance with the standards for human subjects research. The study participants were given the opportunity to opt out and were informed of their right to privacy. Each member of the research team completed the required training on proper methods of conducting research in compliance with federal and state requirements [13].

Harm

Because the participants were involved in a drug-related study, they were monitored for adverse effects. We defined an adverse event as an event that occurred during the study that resulted in physical, psychological, or social harm to the participant [13]. Upon giving consent, if a participant experienced an adverse event but did not start to receive PrEP, the event would be reported as not related to PrEP. If PrEP was discontinued as a result of an adverse event, the research team would record the event and data, leading to the discontinuation of the medication,

which would be reported to the IRB. Adverse events that are life-threatening or extreme or require hospitalization will be reported to the IRB within 1 week of the event [13]. If a serious adverse event occurred after the study was discontinued, it will not be reported as an adverse effect unless the research team recognized that the event may have been caused by PrEP or the study protocol.

Results

A total of 7 African American men consented to participate in the pilot study. Data analysis is to be completed by late September 2022. We will submit a manuscript for publication consideration by December 2022.

Discussion

Anticipated Findings

We hypothesize that the brief educational intervention will show an increase in medication adherence and PrEP knowledge and a decrease in the rates of STIs. The educational protocol for this study implored a multimodal approach. The combination of intervention approaches (1-on-1 education, handouts, etc) with a clinical outcome (HIV-negative status with PrEP uptake) has been shown to have the highest improvement in medication adherence [14].

Interventions with brief follow-up periods have been effective for long-term chronic medication adherence [12,15]. Similar to Centers for Disease Control and Prevention guidelines, the follow-up periods were 4 weeks and 3 months [12]. For a PrEP program to be effective, it must be accessible to those who would benefit the most from it [16]. In this study, the NP called the pharmacy to verify medication refills. An alternative to the calls to the pharmacy could be a web-based management system, which is effective for optimizing PrEP uptake with automatic refill SMS text messaging [17].

Strengths and Limitations

One strength of this project is the setting. Currently, the state of North Carolina ranks in the top 10 states with high rates of STIs [4]. STIs have been known to be precursors to HIV infections. Consistent with the literature, another strength was the use of an infectious disease clinic with educated health care professionals to increase PrEP accessibility to those at high risk of HIV [12]. This setting offered treatment not only for HIV prevention but for STI treatment. Lastly, NPs are readily available to be included in new models of the PrEP care continuum [18].

There were 4 limitations to this study. The first limitation was the use of a convenience sample of HIV-negative men from 1 infectious disease clinic in a single geographic location; therefore, the findings cannot be generalized to other groups of HIV-negative men. The second limitation was the use of medication logs. The self-reporting of PrEP uptake does not ensure medication adherence [14]. While the NP confirmed that the medications were being refilled and picked up at the pharmacy, daily doses could be missed. The third limitation was that some patients may no longer see the need to take a daily dose of PrEP and could benefit from PrEP on demand if they were no longer in a committed relationship, which was not explored in this study. The fourth limitation was that the case study design is time-consuming and the findings cannot be generalized to a wider population. However, this design allows for greater depth in the data that other designs do not allow [19]. Nevertheless, this study provides insights into the use of a brief educational PrEP intervention in a fast-paced clinic.

Future Directions

We developed a strategic dissemination plan in partnership with other infectious disease clinics in the health care setting. The research process and our findings will be shared with clinical staff, in a peer-reviewed journal, and at a research conference.

Conclusions

This study will close the gap in identifying opportunities to deliver current HIV prevention education to minority MSM in a fast-paced clinical setting. The study's findings will add to the current literature on the effect of a brief PrEP educational intervention on increasing PrEP knowledge, improving medication adherence, and reducing HIV seroconversion among BMSM. This study aligns with the End the Epidemic Plan for America to reduce the rates of HIV infections by 90% by the year 2030.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Pre-exposure Prophylaxis (PrEP) protocol handout.
[DOCX File , 22 KB - resprot_v11i11e33093_app1.docx]

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Abbreviations

BMSM: Black men who have sex with men
IRB: institutional review board
MSM: men who have sex with men
NP: nurse practitioner
PrEP: pre-exposure prophylaxis
STI: sexually transmitted infection

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Protocol

Investigating the Effects of Hyperbaric Oxygen Treatment in Necrotizing Soft Tissue Infection With Transcriptomics and Machine Learning (the HBOmic Study): Protocol for a Prospective Cohort Study With Data Validation

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Abstract

Background: Necrotizing soft tissue infections (NSTIs) are complex multifactorial diseases characterized by rapid bacterial proliferation and progressive tissue death. Treatment is multidisciplinary, including surgery, broad-spectrum antibiotics, and intensive care; adjunctive treatment with hyperbaric oxygen (HBO_2) may also be applied. Recent advances in molecular technology and biological computation have given rise to new approaches to infectious diseases based on identifying target groups defined by activated pathophysiological mechanisms.

Objective: We aim to capture NSTI disease signatures and mechanisms and responses to treatment in patients that receive the highest standard of care; therefore, we set out to investigate genome-wide transcriptional responses to HBO_2 treatment during NSTI in the host and bacteria.

Methods: The Effects of Hyperbaric Oxygen Treatment Studied with Omics (HBOmic) study is a prospective cohort study including 95 patients admitted for NSTI at the intensive care unit of Copenhagen University Hospital (Rigshospitalet), Denmark, between January 2013 and June 2017. All participants were treated according to a local protocol for management of NSTI, and biological samples were obtained and stored according to a standard operational procedure. In the proposed study, we will generate genome-wide expression profiles of whole-blood samples and samples of infected tissue taken before and after HBO_2 treatment administered during the initial acute phase of infection, and we will analyze the profiles with unsupervised hierarchical clustering and machine learning. Differential gene expression will be compared in samples taken before and after HBO_2 treatment (N=85), and integration of profiles from blood and tissue samples will be performed. Furthermore, findings will be compared to NSTI patients who did not receive HBO_2 treatment (N=10). Transcriptomic data will be integrated with clinical data to investigate associations and predictors.

Results: The first participant was enrolled on July 27, 2021, and data analysis is expected to begin during autumn 2022, with publication of results immediately thereafter.

Conclusions: The HBOmic study will provide new insights into personalized patient management in NSTIs.

Trial Registration: ClinicalTrials.gov NCT01790698; https://clinicaltrials.gov/ct2/show/NCT01790698

International Registered Report Identifier (IRRID): DERR1-10.2196/39252

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KEYWORDS

necrotizing soft tissue infection; hyperbaric oxygen treatment; host-pathogen interaction; transcriptomic; sepsis; machine learning; infection; soft tissue infection; study protocol; NSTI; treatment; oxygen; tissue; data; validation; immunology; immune system; mechanism; response; genome; longitudinal; biomarker; signaling

Introduction

Necrotizing soft tissue infections (NSTIs) are severe infections of the soft tissue surrounding the bones that are frequently accompanied by septic shock and multiorgan failure. Advanced supportive care in the intensive care unit is frequently required [1]. The reported mortality rate of NSTIs varies among studies and countries, with an overall mortality of 24% and average 30-day mortality rates of 20% to 40% [2-5]. In our cohort, we found a 30-day mortality rate of 14%, and amputation was performed in up to 13% of cases [6]. The infections are characterized by rapid bacterial proliferation and progressive tissue destruction of the fascia and deep skin layers. This process is triggered by white blood cell infiltration causing thrombosis of the veins and arteries perforating the fascia. Accompanied by further microorganism proliferation and biofilm formation, this progresses to the occlusion of nutrient vessels with subsequent ischemia and tissue death and potentially reduced antibiotic effects [7-9].

The contemporary treatment strategy is a combination of empirical broad-spectrum antimicrobial therapy, aggressive surgical debridement, and cardiovascular support. Hyperbaric oxygen (HBO_2) treatment is used worldwide as an adjunctive treatment in NSTI as a means of reducing tissue loss and death [10-13]. Treatment with HBO_2 leads to hyperoxia. Besides improving oxygen supply to hypoxic and ischemic tissues, it has been suggested that HBO_2 treatment promotes beneficial immunomodulatory activities and antibacterial actions [14-17], resulting in improved survival [18-20]. The immunomodulatory effects of HBO_2 treatment for infectious diseases include coagulopathy, endothelial activation, and altered cellular metabolism; these effects have been revealed using the traditional approach of biomarker discovery [21-25]. However, the mechanisms of action of HBO_2 treatment for NSTI on a molecular gene-expression level and the genetic associations with clinical and demographic variables have not yet been investigated, and a coherent understanding of the pathophysiological effects of HBO_2 in NSTIs is needed [10].

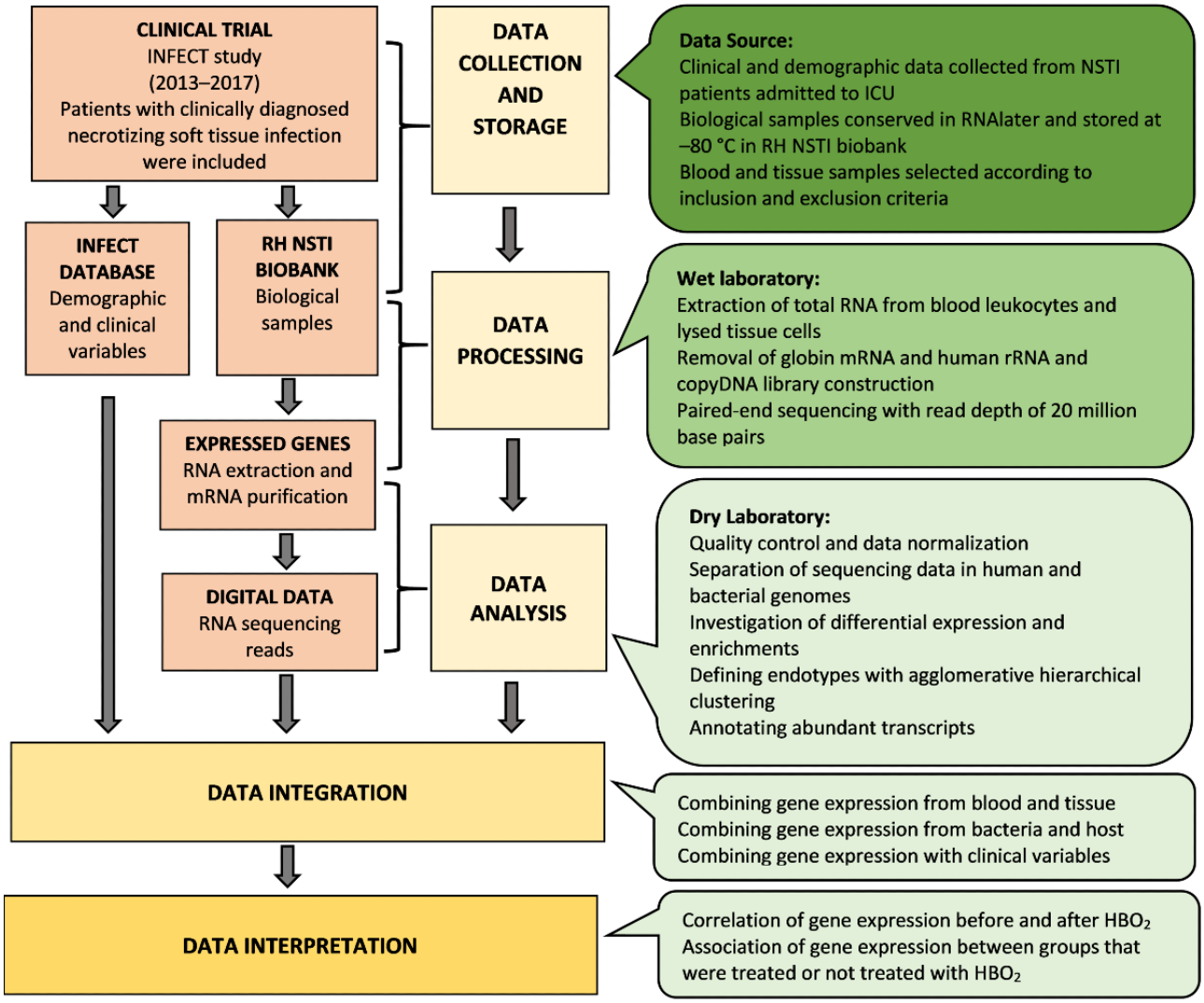
NSTIs are caused by a variety of microbes, and affected patients are highly heterogeneous, including both young immunocompetent individuals and individuals with severe comorbidities [5]. The disease complex may be driven as much by the biology of the host response as by the type of microbe invading the host. This view is supported by earlier studies that show that NSTI patients infected with group A *Streptococcus* were more likely to develop septic shock [6]. It is not surprising that the human genome holds variants related to infection, given that infectious diseases have been the largest cause of death during our evolution [26]. The multifaceted, heterogeneous nature of disease may explain the lack of success with identification of biomarkers. Bacterial toxin–mediated inflammation is associated with altered expression of more than 3700 human genes, making gene-expression analysis a potentially useful tool for discovery-oriented studies of the pathogenesis of sepsis and severe infections [27]. Traditional analysis of exposure and outcome does not fully utilize the power of combined gene expression data [28]. This paper presents a transcriptomic study protocol for examining host and pathogen interactions using a data-driven approach with unsupervised analysis. Our hypotheses are that genetic diversity accounts for the variation in outcomes that follow interactions between humans and the potentially life-threatening pathogens in NSTIs and that these interactions are modulated by HBO_2 treatment.

Methods

Study Design and Setting

This is a prospective observational study. All participants were enrolled in the Systems Medicine to Study Necrotizing Soft Tissue Infections (INFECT) study, a clinical study that systematically collected blood and tissue samples with the purpose of including these samples in a biobank for bioinformatics studies of large biochemical groups. For the Effects of Hyperbaric Oxygen Treatment Studied with Omics (HBOmic) study, we will screen this biobank (the Rigshospitalet NSTI biobank) for patients that meet our eligibility criteria, starting with the 2017 data and working backward until we meet our desired sample size. The HBOmic study will analyze gene expression in samples of peripheral blood leukocytes and samples from infected tissue sites. The transcriptome will be compared in patients before and after they undergo HBO_2 treatment and in patients who were and were not treated with HBO_2. The workflow of the study is illustrated in Figure 1.

Figure 1. Workflow of the HBOmic study. HBO_2: hyperbaric oxygen treatment; ICU: intensive care unit; INFECT: Systems Medicine to Study Necrotizing Soft Tissue Infections; mRNA: messenger RNA; NSTI: necrotizing soft tissue infection; RH: Rigshospitalet.



Eligibility Criteria

Participants are included in the HBO_2 treatment group if they had been clinically diagnosed with NSTI according to previously defined criteria [6], had been treated with HBO_2 during the initial acute phase of the infection, had blood samples withdrawn before and after HBO_2 treatment, and had been subjected to surgical debridement with sampling of infected tissue before and after HBO_2 treatment. Participants are included in the non–HBO_2 treatment group if they had been clinically diagnosed with NSTI according to previously defined criteria [6], had 2 blood samples withdrawn at different time points during the initial acute phase of the infection, had been subjected to surgical debridement twice with sampling of infected tissue at 2 different time points during the initial acute phase of the infection, and had not been treated with HBO_2 between sample collection. Participants were excluded from the study if they were alive and unwilling or unable to give informed consent.

HBO_2 Intervention

The HBO_2 treatment was performed in a hyperbaric multichamber (Drass Galeazzi SpA, Type HPO4000, HPE50.2.A) that had been modified to deliver intensive care treatment during pressurization, including mechanical ventilation (Servo-I-30 HBO Editor, Maquet), cardiovascular monitoring (Intellivue, Phillips, MP30), and multiple intravascular infusions (Perfusor Space, Braun). All participants who underwent HBO_2 treatment were treated according a standardized treatment protocol, which aimed at a minimum of 3 HBO_2 treatments, with the first treatment administered as soon as possible after hospital admission. The treatment duration of each session was 90 minutes at a pressure of 284 kPa without air breaks and a compression and decompression rate of 15 minutes.

Concomitant care was also protocolized and aimed at 3 surgical revisions during the first 24 hours after diagnosis, with repeated revisions thereafter as necessary. Antibiotic treatment with meropenem, ciprofloxacin, and clindamycin and intensive care treatment were adapted to individual needs [6].

Studies and Outcomes

Study 1 aims to obtain transcriptome profiles of peripheral whole blood before and after HBO_2 treatment to reveal treatment-dependent gene regulation of the septic response to infection. The primary outcome will be the change in gene expression in whole-blood samples before and after HBO_2 treatment. In study 2, we will perform simultaneous transcriptional profiling of infected human tissue and bacterial gene expression before and after HBO_2 treatment to reveal treatment-dependent alterations in microbial virulence mechanisms and interactions with the host immune system. The primary outcome will be the change in gene expression in samples of infected tissue before and after HBO_2 treatment. Study 3 aims to integrate the molecular response to sepsis with the immune response that unfolds in the tissues that are the source of the NSTI, including changes in the response to treatment with HBO_2 treatment. The primary outcome will be the correlation of the transcriptional profile of the whole blood and infected human tissue in patients with NSTI, before and after HBO_2 treatment.

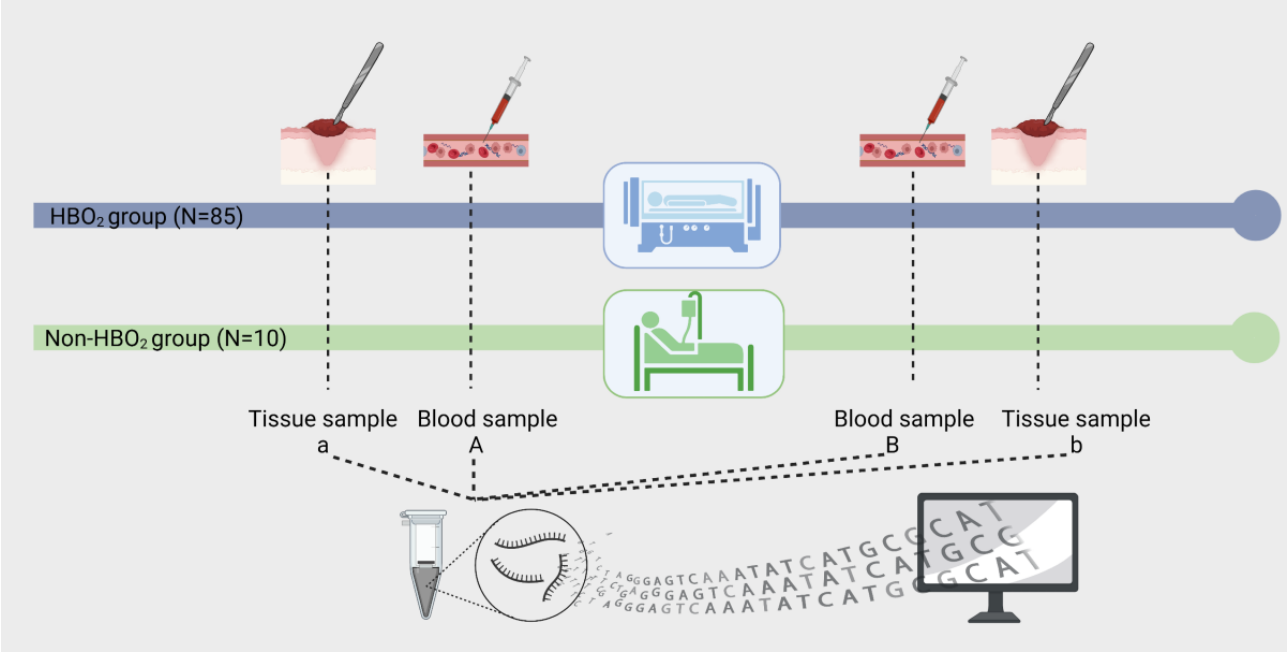
Study Population

All participants were diagnosed with NSTI by the surgeon at the primary operation. The diagnosis was based on the presence of necrotic or deliquescent soft tissue with widespread undermining of the surrounding tissue, as determined by the surgeon. The diagnosis was systematically cross-checked by study investigators, and patients were excluded from the study if necrotic or deliquescent tissue was not described in the patient records. Detailed characteristics of the participant population have been published elsewhere [6].

Participant Timeline

Participants included in the study followed the participant timeline illustrated in Figure 2.

Figure 2. Participant Timeline. Whole-blood samples and tissue biopsies taken during surgical debridement were stored in RNAlater. All samples were immediately frozen and stored at –80 °C until processing. Hyperbaric oxygen treatment was administered at 284 kPa for a minimum of 90 minutes. Patients had received 0 (ie, the non–hyperbaric oxygen group), 1, or 2 hyperbaric oxygen sessions when the follow-up samples "B" and "b" were taken.



Data Collection and Storage

Clinical Variables

All clinical variables for the included participants are available through the INFECT project's INFECT database, which contains more than 2000 variables, including baseline variables, time variables related to hospital admission, variables monitored at the intensive care unit and during surgical procedures, tissue sampling and microbiological findings, and variables related to long-term outcomes and quality of life measures. A full list of variables is available in the appendix to a previous publication [29].

Biological Samples

Each tissue biopsy was collected during surgical debriding. Sample volumes ranged from 0.5 to 0.75 cm^2. Immediately after collection, the tissue was placed in a 1-ml sterile natural tube (Cryo.s) and covered and stabilized in 0.5 ml RNAlater (Thermo Fisher Scientific). A tissue specimen of the same size was also placed in a 1-ml sterile natural tube (Cryo.s) without RNAlater. Then, the tubes were placed directly in a thermal container on dry ice and transported to a freezer in the same building, where they were frozen at –80 °C for storage. All tissue samples were previously categorized by type of tissue (muscle, fascia, or soft tissue), the degree to which the tissue was affected by infection (normal, infected without necrosis, or necrotic) and whether it was collected from the margin or the center of the infection. This categorization of the tissue samples was a subjective clinical categorization performed by the surgeon in the acute setting based on the look and texture of the biopsied area, not a pathological, microscopically verified classification. We selected samples in accord with a predefined strategy; the categorization of each sample was noted.

Whole blood was collected with an arterial catheter using a 10-ml lithium heparin tube; 2.5 ml of the blood was transferred to a sterile natural tube (Cellstar) with a sterile 10-ml syringe and mixed with 5 ml of RNAlater. The content was mixed by turning the tubes upside down a few times before they were transported on dry ice to a freezer in the same building, where they were stored at –80 °C. All samples were handled with sterile procedures. Blood was collected with the vacuum technique, and a discard tube was used prior to blood collection.

The blood and tissue samples included in this study were stabilized with RNAlater (Thermo Fisher Scientific). The data and time of sampling were noted, along with any deviations from standard operational procedures.

Ethics Approval

The study presented in this protocol abides by the principles outlined in the Declaration of Helsinki. The INFECT study is registered at ClinicalTrials.gov (NCT01790698). During the INFECT study, informed consent for collection and storage of the biological material for future research was given. We will follow the genomics guidelines of the Danish National Committee on Health Research Ethics, including the special requirements for research projects involving extensive mapping. Also following the Danish National Committee on Health Research Ethics (journal number 2010299, locally in journal number 1151739), renewed informed consent for this study was obtained from living participants. This study was approved by Capital Region at Knowledge Center for Data Reviews (P-2020-1186).

Data Processing

RNA Purification, Library Preparation, and Sequencing

A volume of 300 to 500 µL of anticoagulated whole blood will be used to extract total RNA from leukocytes using the RiboPure RNA Purification Kit (Thermo Fisher Scientific). Infected tissue biopsies (10-30 mg) will be disrupted and homogenized with TissueLyser (Qiagen), and total RNA of both human and bacterial origin will be isolated using the RNeasy Plus Mini Kit (Qiagen). We will use the NEBNext Globin & rRNA Depletion Kit (New England Biolabs Inc) for strand-specific messenger RNA (mRNA) purification using probes that are selective for globin mRNA, cytoplasmic ribosomal RNA (rRNA), and mitochondrial rRNA with human, mouse, and rat samples. In all biological samples, first- and second-strand copyDNA (cDNA) will be synthesized based on ligation adaptor techniques (NEBNext Globin & rRNA Depletion Kit [human, mouse, and rat]). Each step will be performed according to the manufacturer's instructions and an internal standard operational procedure. The obtained cDNA library will then be sequenced with dual RNA sequencing with paired-end sequencing of 150 nucleotide fragments on the Illumina Novaseq6000 platform with a targeted sequencing read depth of 20 million reads.

Data Validation and Quality Check

We have performed a validation test of the data processing method using 8 tissue samples and 8 whole blood samples to estimate the quantity and integrity of the extracted RNA, the quality of the cDNA libraries, and the sequencing output.

Quality Check Methods

All data processing was performed as described in this protocol. The quality check of the extracted RNA and the prepared libraries was performed on a Fragment Analyzer with the included ProSize software (version 3.0; Agilent Technologies, Inc). Quantity was measured with Qubit fluorometric quantification. Quality checks of the RNA sequence data were performed in MultiQC (version 1.7; Seqera Labs). We performed computational calculation of the transcript integrity number (TIN) as a measure of the RNA degradation level across all the transcripts that were annotated in the computational databases [30].

Quality Check Results

The results of the pilot quality check are summarized in Table 1.

Table 1. Results of the quality check.

Measurements	Whole blood samples	Infected tissue samples
RNA quantity (ng), median (IQR)	6560 (2540)	830 (2471)
RNA quality number, mean (SD)	9.6 (0.37)	2.9 (1.55)
Illumina sequencing Q30 quality score[a], median (IQR)	93.55 (0.4425)	93.49 (0.245)
Obtained reads per sample (n), median (IQR)	29,178,943 (8,718,838)	31,009,818 (5,969,336)
Transcript integrity number, mean (SD)	57.7 (1.92)	55.0 (5.83)
Coefficient of variation, mean (SD)	0.34 (0.346)	0.82 (0.73)

[a]Indicates the probability of 1 in 1000 incorrect base calls.

In 1 tissue sample, we were not able to extract any RNA; this sample was thus excluded from further analysis. In the remaining 15 samples, we obtained sufficient RNA in both the whole-blood and tissue samples. The RNA in the whole-blood samples was of high quality (the RNA quality number [RQN] ranged from 8.8 to 10.0), but the RQN in the tissue samples was low. Transcript quality control and a preliminary bioinformatics analysis showed acceptable values, with average TINs of 58 (SD 1.92) and 55 (SD 5.83) for the whole-blood and tissue samples, respectively, along with a good quality of reads and a high number of unique reads.

Using the number of reads per gene, the weighted trimmed mean of the M (log ratio) values, and the TIN, we defined a linear model to calculate coefficients of variation of 0.34 (SD 0.346) and 0.82 (SD 0.73) for the whole-blood and infected tissue

samples, respectively, with the estimateDisp method in the Bioconductor package edgeR. Descriptive statistics were calculated in R (version 4.1.2).

Evaluation of Quality Check

The infected tissue samples were collected from soft tissue with varying degrees of necrosis, and therefore varying degrees of degradation were already expected in vivo. Necrosis is premature cell death, and although it is believed that necrosis causes RNA degradation in its later stages, the order of progress of RNA decay is unknown [31]. Based on a visual inspection of electropherograms, the RNA in some of the tissue samples appeared more degraded than the whole-blood samples, as also reflected in the lower RQN. However, tissue samples are also generally expected to have higher prokaryotic RNA content than blood samples; therefore, the calculated RQN in these infected tissue samples might have been falsely low. The ProSize software can only be programmed to analyze either eukaryotic or prokaryotic rRNA. When calculating the RQN, ProSize considers the entire electropherogram, including the small and large ribosomal peaks, the baseline resolution between them, and the degradation in front of the small ribosomal peak. As the prokaryotic ribosomal RNA complexes are smaller than the eukaryotic ribosomal complexes, they will appear in front of the eukaryotic complexes, resulting in a falsely low RQN value. Moreover, the tissue samples used in this study are degraded in vivo and high levels of degradation are known to affect the reliability of the RQN [32].

Based on the findings in the quality check, we decided to adhere to the strategy for data processing presented in the protocol. We will not dismiss samples due to a low RQN calculation alone. Biological samples with ≥100 ng of RNA may proceed to library preparation irrespective of the calculated RQN value, depending on a visual inspection of the electropherogram. The TIN will be computed after mapping the sequenced reads onto the human genome to obtain an estimate of human RNA degradation on the transcript level. Libraries with sufficient RNA and an inset fragment size of >300 base pairs will continue to next-generation sequencing.

Data Analysis

Quality Assessment of the Sequencing Data

Quality control of sequence reads will be done using the tools FastQC (version 0.11.2), RSeQC (version 2.6.4) [33], and fastq_screen (version 0.11.4). The proportion of human rRNA reads will be checked with the split_bam.py tool in RSeQC. Quality control will be performed separately for reads of human and bacterial origin. The cutoff for the percentage of duplicate reads and the number of unique reads will be defined post hoc to minimize the number of excluded samples while considering the risk of introducing biases to the analysis. The median TIN will be calculated for all samples to evaluate RNA degradation on the transcript level. The influence of RNA degradation on the results will be evaluated by performing a sensitivity analysis.

Alignment of Reads to the Genomes of Interest

Sequencing reads will be aligned onto the human and bacterial genomes. Adaptors, low-quality bases, the first 12 bases, and reads shorter than 25 nucleotides will be removed with Trimmomatic [34].

Reads will be mapped using STAR software (version 2.7.3a) separately against the human and bacterial genomes [35]. Up to 2 mismatches will be allowed during mapping, and the minimum number of overlap bases to trigger mate merging and realignment will be set to 5. Otherwise, default settings will be used. Duplicate reads will be removed using the MarkDuplicates function of Picard software.

The featureCounts function of the Rsubread R package will be used to quantify reads in exons. Bacterial typing will be performed by assigning species- and genus-level annotations to a phylotype of previously described isolates using relevant databases to identify microbiomes [36].

Clustering Analyses

Interindividual heterogeneity will be investigated using unsupervised hierarchical clustering for the most variable probes. Endotypes will be defined by agglomerative hierarchical clustering from samples taken before HBO_2 therapy according to the microbial community composition, the microbial expressed virulence mechanisms, and the host immune response. Clusters will be tested for quality and stability by multiple iterations, and group membership will be consolidated using *k* means to ensure that membership is due to true cluster structure rather than stochastic picks.

Differential Expression Assessment

Differential gene expression analysis will be performed using edgeR or similar software by comparing individual patients and patients stratified to each of the endotypes and by comparing each endotype to the other endotypes [37]. The data will be fit to a gene-wise generalized linear model that will include relevant covariates, such as the degradation level of the samples (ie, the TIN). Differential gene usage will be assessed by quasi-likelihood tests and adjusted for multiple comparisons with the false discovery rate. Gene coexpression networks will be determined to obtain insight into the biological function of the included genes.

Functional Enrichment of Gene Sets

Genes showing treatment-dependent differential regulation will be explored, as will genes involved in gene networks and signaling pathways related to, for example, host immunity, inflammation, and redox homeostasis. Gene set enrichment analyses will be performed with ranked log fold changes using state-of-the-art enrichment tools, such as the gseGO function in the clusterProfiler R package [38]. Related functions will be used to visualize the results together with state-of-the-art enrichment tools, such as the DOSE R package functions [39].

Data Integration and Interpretation

Differential gene expression data discovered before and after treatment with HBO_2 will be compared with gene expression profiles from blood and tissue samples taken at similar time points from NSTI patients that were not treated with HBO_2. Participants from the HBO_2 group will be matched with

participants from the non-HBO_2 group on key variables in the downstream gene expression analyses.

Furthermore, starting from the endotypes identified before HBO_2 treatment, we will annotate endotypes and monitor immunomodulatory effects of HBO_2 treatment as dynamic changes in the endotypes.

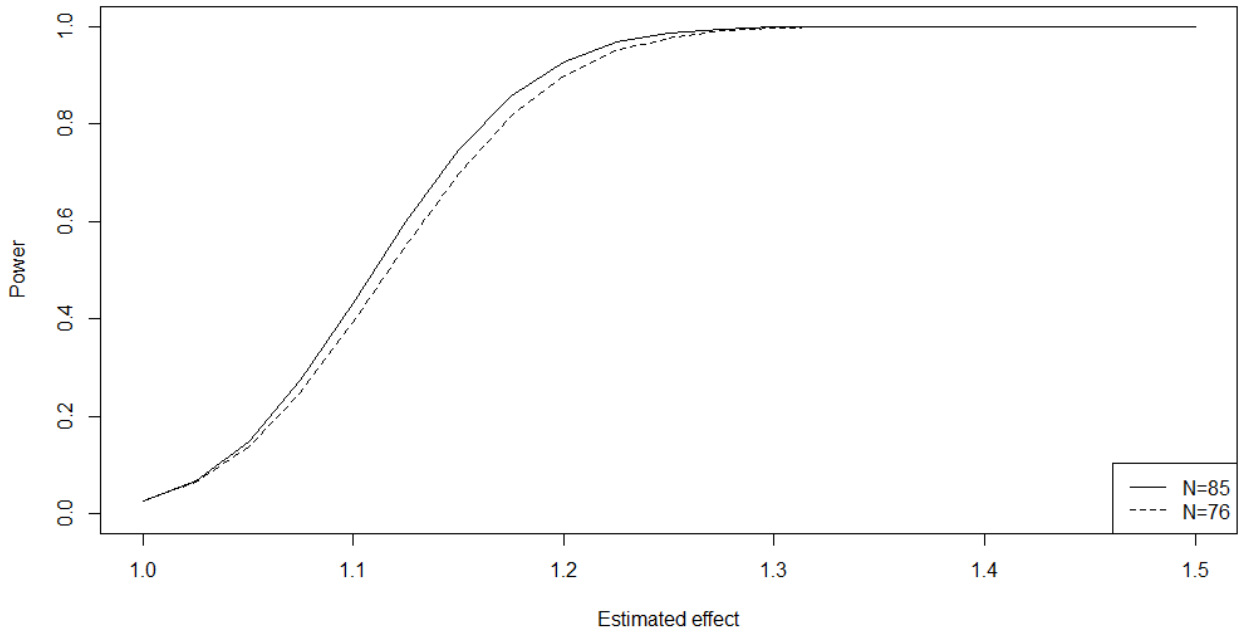
Highly abundant microbial genera expressed in the initial clusters will be compared to relevant virulence factor databases before and after HBO_2 treatment. The microbial diversity associated with NSTIs and how their pathological mechanisms may be altered in response to HBO_2 treatment will be integrated with the host immune response.

A comparison between whole blood and infected tissue will be performed with a quantitative and qualitative comparison of the clusters obtained from the 2 tissue types before and after HBO_2 treatment. Endotypes or subgroups will be associated with demographic and clinical variables in the INFECT database. Linear models will be applied to fit group membership with gene expression and clinical variables and identify predictors.

Sample Size

The genome-wide transcriptional response to HBO_2 has not previously been addressed in any type of tissue or disease. Hence, the number of biological replicates necessary to observe a significant difference in gene expression before and after HBO_2 treatment is unknown. Based on the depth of gene coverage for all expressed genes and the overall coefficient of variation for the blood samples found in the pilot study, we estimated the sample size for the 2 conditions according to published methods for the primary outcome of this paper's "study 1" [40]. Assuming a coefficient of variation of 0.34 for the whole-blood samples, a depth of coverage of human reads of 218, a risk of type I error of 5%, and a risk of type II error of 20% (with a power of 80%), the number of participants per group required to detect a 25% difference between conditions is 38, giving a total sample size of 76 participants. However, the differential expression analysis will focus on the majority of genes that are better behaved, and we therefore expect a stronger power [40]. On the other hand, we also expect that approximately 10% of samples will fail quality control. Therefore, we decided to include 85 participants in the study. Figure 3 depicts the power for estimated effect sizes. Regardless of the estimated effect sizes, all biological and clinically relevant findings will be reported in the exploratory analysis.

Figure 3. Power for estimated effect sizes for analyses of whole blood samples including either 85 or 76 participants.



Results

Patient recruitment in the clinical setting was completed in 2017. Screening of the resulting biobank for eligible participants for the HBOmic study according to the inclusion and exclusion criteria has been completed. Informed consent for participation in the HBOmic study has been obtained from all eligible study participants, and the first participant was enrolled on July 27, 2021. Data analysis is expected to begin during autumn 2022, with publication of results immediately thereafter.

Discussion

In the HBOmic study, we anticipate being able to identify NSTI endotypes with differential responses to HBO_2 treatment based on transcriptional responses. We will analyze longitudinal genome-wide transcriptional data in systematically collected daily blood and infected-tissue samples from patients with NSTI, which will allow us to capture immunomodulatory changes associated with critical events following HBO_2 treatment in this rare disease complex. NSTI is a heterogeneous and dynamic disease, and the biological variability of the specimens under

study is expected to be high. To account for this, we have included a relatively large cohort of septic patients with NSTI. The study is highly feasible, because we have already performed the described data validation, including testing the quality of the samples and the resulting sequencing data. In the pilot study, 1 sample failed quality control and was dismissed from further analysis. We have therefore estimated that 10% of samples may fail quality control, which we have accounted for in the sample size estimation. We will identify molecular differences with a broad-spectrum analysis of transcriptomic data with a systems approach, in which specific parameters have not been chosen as they will be by default everything or anything. In that sense, this data-driven research will deliver unbiased and unprecedented information about immunomodulatory changeability during disease progression and treatment. On the other hand, this approach has inherent limitations and biases, including gene panel selection bias and sequencing bias in library construction and amplification bias. To minimize technical biases during the processing of this high number of samples, we will carefully design our batches with bridging and perform sensitivity analyses in response to degradation markers. A systems approach to this heterogeneous disease complex implies the investigation of many markers, which might make it challenging to identify the most relevant biomarkers and increases the risk of nonreproducible results. Future approaches could include identifying genes predictive of group membership in our cohort, and then, in a validation cohort, assigning group membership to individuals based on their expression of the predictive gene set and evaluating the robustness of the prediction. Another future approach could be to perform multiomic analyses. Combining transcriptomics with genomics could shed light on the link between genotype and any phenotypes identified in the clustering analysis. For this, mapping to expression quantitative trait loci would allow us to focus on genes that are expressed differently in blood and infected tissue. This would allow distinguishing responders and nonresponders on the genetic level. On the other end of the omics sequence, proteomics would give insight into protein modifications, and in combination with our differential expression analysis proteomics would give a more precise view of the differential protein abundance and thereby strengthen the identification of candidate biomarkers for clinical trials. However, transcriptomics is the first step in which environmental effects can impact the translation from DNA to cellular function, and it thereby constitutes an appropriate initial application.

The availability of transcriptomic data from pathogens and hosts from 2 different tissues (ie, whole blood and soft tissue) at separate time points with an intermediate intervention is unique and will provide real-time snapshots of cellular and extracellular signaling pathways that are up- and downregulated in different clinical subgroups. The HBOmic study will provide new insights into personalized patient management in NSTIs and selection for future clinical trials.

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Data Availability

The human sequencing data underlying the results of this study will not be openly available due to their sensitive nature. The Danish National Committee on Health Ethics has rejected making the human genetic data generated in this study publicly available in any form. Bacterial sequence data that support the findings of the studies described in this protocol will be deposited in a public repository (such as ArrayExpress or GEOCIBEX).

Authors' Contributions

JV, LR, AB, MH, and OH contributed to the study concept and design. JV and MH contributed to obtaining renewed informed consent from the participants, the collection of samples, and record keeping. JV, LR, AB, and OH contributed to data processing and preliminary analysis. JV, LR, and OH drafted the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

cDNA: copy DNA
HBO_2: hyperbaric oxygen
HBOmic: Effects of Hyperbaric Oxygen Treatment Studied With Omics
INFECT: Systems Medicine to Study Necrotizing Soft Tissue Infections
mRNA: messenger RNA
NSTI: necrotizing soft tissue infection
RQN: RNA quality number
rRNA: ribosomal RNA

TIN: transcript integrity number

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Protocol

Prevalence of Antibiotic-Resistant Bacteria and Antibiotic-Resistant Genes and the Quantification of Antibiotics in Drinking Water Treatment Plants of Malaysia: Protocol for a Cross-sectional Study

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Abstract

Background: Antimicrobial resistance is a known global public health threat. In addition, it brings serious economic consequences to agriculture. Antibiotic resistance in humans, animals, and environment is interconnected, as proposed in the tricycle surveillance by the World Health Organization. In Malaysia, research and surveillance of antimicrobial resistance are mainly performed in clinical samples, agricultural settings, and surface waters, but no surveillance of the drinking water systems has been performed yet. Hence, this policy-driven study is a combined effort of microbiologists and engineers to provide baseline data on the magnitude of antimicrobial resistance in the drinking water systems of Malaysia.

Objective: The aim of this study was to study the baseline level of antibiotic-resistant bacteria in the drinking water distribution systems of Malaysia by collecting samples from the pretreatment and posttreatment outlets of water treatment plants in a selected state of Malaysia. We aimed to determine the prevalence of antibiotic-resistant bacteria, the occurrence of antibiotic-resistant genes, and the level of antibiotics present in the drinking water systems.

Methods: This is a laboratory-based, cross-sectional study in a selected state of Malaysia. Water samples from 6 drinking water treatment plants were collected. Samples were collected at 3 sampling points, that is, the intake sampling station, service reservoir outlet station, and the distribution system sampling station. These were tested against 7 types of antibiotics in triplicates. Samples were screened for antibiotic-resistant bacteria and antibiotic-resistant genes and quantified for the level of antibiotics present in the drinking water treatment plants.

Results: We will show the descriptive statistics of the number of bacterial colonies harvested from water samples grown on Reasoner's 2A agar with or without antibiotics, the occurrence of antibiotic-resistant genes, and the level of antibiotics detected in the water samples. The sampling frame was scheduled to start from November 2021 and continue until December 2022. Data analysis is expected to be completed by early 2023, and the results are expected to be published in mid-2023.

Conclusions: This study provides baseline information on the status of the antimicrobial-resistant bacteria, the presence of resistance genes as contaminants, and the level of antibiotics present in the drinking water systems of Malaysia, with the aim of demonstrating to policymakers the need to consider antimicrobial resistance as a parameter in drinking water surveillance.

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KEYWORDS

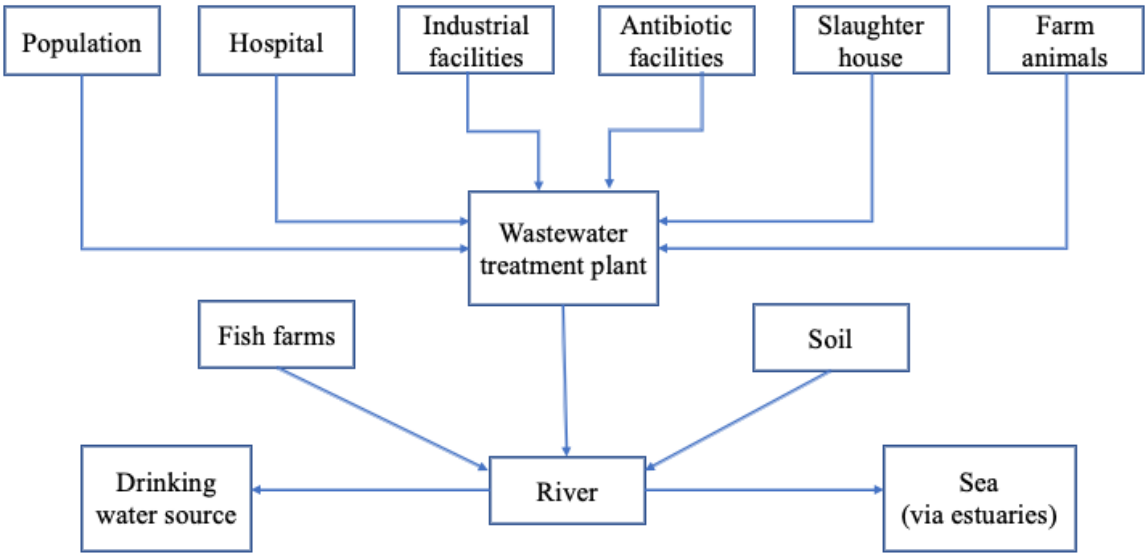
drinking water; river; safe; antibiotic; resistant; antimicrobial; sanitation; Malaysia; Asia; bacteria

Introduction

Background

Access to clean and safe water is of the utmost importance worldwide. For general well-being, human beings use water for daily consumption and hygiene purposes. Water also serves as an important factor for maintaining a sustainable environment and plays an important role in climate change issues. Unfortunately, environmental water also plays a prominent role in the spread of antibiotic-resistant genes (ARGs) and antibiotic-resistant bacteria (ARB). Over 80% of all wastewater in low-income countries is estimated to be discharged untreated directly into rivers, lakes, or the oceans [1]. High-risk areas such as waste discharges of pharmaceutical production facilities, hospitals, and other health care facilities have been identified as specific hotspots for ARGs and ARB. Antibiotics released into the environment may also promote the selection of ARB and ARGs, which find their way into the soil and natural water bodies [2] (Figure 1).

Figure 1. Route of antibiotic-resistant bacteria and antibiotic-resistant genes from various anthropogenic sources to a drinking water source. Adapted from Stalder et al [2].



Antimicrobial resistance (AMR) occurs when microorganisms develop the ability to resist antimicrobial treatment designed to inhibit their growth and kill them. Bacteria, as the most extensively studied for AMR in both clinical and environmental settings, can exchange resistance genes between species in a microbial population [3]. Infected humans and animals can act as reservoirs and spread these resistant bacteria into the environment through various routes. Furthermore, misuse of antimicrobial agents can accelerate the process of AMR.

Tracking of the spread of antibiotic-resistant microorganisms provides insights into the transmission of antibiotic-resistant strains and resistance genes from humans or animals to the environmental reservoir and back to human use and consumption [4,5]. Studies have suggested that aquatic systems such as drinking water sources [6], wastewater effluents [7], and wastewater discharge from hospitals act as reservoirs for antibiotic-resistant microorganisms [8]. Metagenomics (the study of genetic material from environmental samples) analysis has revealed that wastewater treatment plants are a hotspot for ARGs and their mobile genetic elements [9,10]. The nutrient-rich wastewater brings together microbes from the environment, humans, and animals originating from domestic, industrial, agricultural, and medical activities, and allows the spread of ARGs between microbial species [11]. Although wastewater treatment plants can reduce the concentrations of pathogens, ARB and their ARGs have been detected in effluents and biosolids [12] and effluent-receiving rivers [7]. The effluent-receiving river, which eventually is used as a drinking water source, can also contain resistant bacteria from fish farms and soil.

The World Health Organization calls for coordinated actions to minimize the emergence and spread of AMR by providing technical assistance to countries to develop national health action plans and urging more research and development on AMR. As

of October 2021, 148 countries have finalized their National Action Plan, which aligns with the objectives of the Global Action Plan on Antimicrobial Resistance [13]. In Malaysia, the collaborative effort between the Ministry of Health and the Ministry of Agriculture and Agro-based Industry has resulted in a Malaysian Action Plan on Antimicrobial Resistance (MyAP-AMR) 2017-2021 [14]. The MyAP-AMR details out plans to minimize AMR in both health care practices and agricultural sectors; their aims among others are to increase the awareness of antimicrobials, promote appropriate usage of antibiotics in clinical settings, and decrease pollution influenced by the direct use of antibiotics in poultry farms [14]. Furthermore, contamination of drinking water sources, including water pollutants such as antimicrobials/antiseptics, is ranked third in the list of "Top 10 Environmental Health Issues in Malaysia" released by the National Environmental Health Action Plan, Malaysia [15]. The United Nations 2030 Agenda for Sustainable Development has listed "Goal 6: Clean water and sanitation" as one of its 17 sustainable development goals to stimulate actions between 2016 and 2030 in areas of critical importance [1].

A few published studies in Malaysia have reported the presence of pharmaceutical residues from surface water in Malaysia. The presence of human pharmaceutical products, which include antidiabetic agents, antihypertensive agents, hypolipidemic agents, β-2 adrenergic receptor agonists, antihistamines, analgesics, and sex hormones, in river water and sewage effluent were reported, but no antibiotics were detected [16]. Al-Qaim et al [17] reported the presence of caffeine, prazosin, enalapril, carbamazepine, simvastatin, hydrochlorothiazide, diclofenac sodium, and mefenamic acid in surface waters. Praveena et al [18] reported the presence of pharmaceutical residues, including antibiotics, in 3 rivers in Selangor, Malaysia. These researchers found that ciprofloxacin was detected in all the samples, with the highest concentration in the rivers [18]. In another study, Lee et al [19] evidenced carbapenem-resistant *Vibrio parahaemolyticus* isolated from marine and freshwater fish samples in Selangor, which suggested the spread of AMR into the food chain [19]. Presumptive *Escherichia coli* isolates that showed resistance to chloramphenicol, penicillin, tetracycline. and kanamycin were detected from soil at recreational parks in villages in Sabah, Malaysia [20]. Antibiotic-resistant *E. coli* and genes (*tet* and *sul*) were also detected in wastewater effluents and the river waters of Larut River, Perak, which were associated with anthropogenic activities [21]. Ho et al [22] reported that 86% of *Enterococcus faecalis* from River Melayu in Johor State, Malaysia, was multidrug-resistant and associated with a local sewage treatment plant and other anthropogenic activities [22].

Monitoring of AMR in the Drinking Water System

Drinking water treatments have previously been shown to act as a source of antibiotic resistance, and water distribution systems could serve as an important reservoir for microbial resistance [23]. Although ARB have been discovered in tap water around the world, little is known about their specific patterns of resistance [24]. Chen et al [6] reported the distribution of *E. coli* from 2 drinking water sources in Hangzhou city, China, which were resistant to tetracycline, ampicillin, piperacillin, trimethoprim, sulfamethoxazole, and chloramphenicol. [6]. Gu et al [25] reported 317 ARG subtypes in drinking water treatment plant (DWTP) bulk water and sand biofilm with widespread detection of genes encoding bacitracin, multiple drugs, and sulfonamide in Guangzhou, China. In Germany, enterobacterial *ampC* resistance genes were detected from wastewater, surface water, and drinking water biofilms [26]. In another study by Xi et al [27], ARGs (*cat*, *cmr*, bla_{TEM}, *blaSHV*, *suII*, *suIII*) and heterotrophic ARB (total heterotrophic ARB) were detected in all finished water and tap water samples from several cities in Michigan and Ohio, United States. The levels of bacteria in the source water were higher than those in tap water; however, the levels of ARB in tap water were higher than those in finished water, demonstrating that there was regrowth of bacteria in the drinking water distribution systems. Furthermore, ARGs were found at higher concentrations in tap water than in finished water and source water [27]. ARG *int1*, conferring resistance to ampicillin, was detected in coliform isolates from restaurants in Bangladesh [28], and *blaNDM-1* was isolated from drinking tap water in Karachi, Pakistan [29]. In South Africa, the total count of coliforms in random household tap water was reported to be higher than that in raw water intake during winter and summer [30].

The presence of biofilm-producing bacteria such as *Pseudomonas* spp has been associated with microbial resistance in the drinking water system. Bacterial biofilm is formed by a consortium of bacteria and acts as a mechanism for better survival to make its producers more resistant to antibiotics and disinfectant chemicals compared to planktonic cells [31]. Biofilm detachment upon treatment with a disinfectant in drinking water distribution systems leads to an increasing amount of ARB in tap water [32]. A study in Bulgaria found significant differences in the ARB population in biofilms from 4 DWTPs [33]. In the United Kingdom, significant correlations were reported between surviving bacteria from chlorinated drinking systems and resistance (measured by the minimum inhibitory concentrations) against tetracycline, sulfamethoxazole, and amoxicillin [34].

Outbreaks in hospitals caused by multidrug-resistant *Pseudomonas aeruginosa* have been linked to the formation of biofilms in wastewater systems [35] and tap water [36] contaminations as well as in domestic drinking water plumbing systems [37]. In South China, Su et al [38] reported the presence of bacteria and *tet* genes (tetracycline resistance) in tap water after treatment although it was much lower than that in source water and suggested that *Pseudomonas* spp played a role in the proliferation and dissemination of ARGs [38]. In France, multiresistant *Pseudomonas* spp (but not *E. coli*) was detected in treated (treatment: flocculation, deposition, and sand filtration, and chlorination reservoir) drinking water from both spring water and the tap system [39]. Bergeron et al [40] reported the presence of ARGs, *tetA* and *sul1*, and ARB, including *E. coli*, *Enterobacter cloacae*, *P. aeruginosa*, and *Klebsiella pneumoniae*, in the raw intake water in Louisiana, United States. No ARGs or ARB were found in the treated and distributed water, although bacterial DNA in the form of 16s rRNA was consistently found [40].

Although there is no conclusive evidence on the "safe limit" of ARB or ARGs in drinking water worldwide, several studies have been conducted in other countries, including China, which have indicated the presence of antibiotic residues, ARB, and ARGs in their water systems. These data have been used to warrant further research and put up new efforts to improve their DWTP systems (eg, to improve the filtration system). For example, Liu et al [41] reported that hybrid carbon membranes of thick graphene oxide and activated carbon effectively remove tetracycline from water by 98.9% [41]. Su et al [38] reported that ARGs still existed in tap water after treatment and the use of granular activated carbon filtration in the DWTPs in China increased ARG abundance [38].

Several hospital-acquired outbreaks caused by gram-negative bacteria such as *Acinetobacter baumannii* and *P. aeruginosa* have been associated with contaminated water distribution systems [35,42,43]. The presence of *E. coli* has been used as an indicator of fecal contamination in drinking water. Multidrug-resistant *E. coli* has been isolated from food sources [44], urinary isolates [45], as well as hospital and municipal effluents [46]. However, it is more interesting to elucidate whether there is a relationship between environmental-driven resistance and clinically acquired resistance in bacteria or whether the resistance is strictly either environmental or clinical.

AMR is an important global issue that needs to be addressed holistically so as to prevent people from dying owing to ineffective antibiotic treatment and to avoid antibiotic resistance eventually, leading us to the postantibiotic era [47]. In Malaysia, research and surveillance of AMR are mainly performed on clinical samples, agricultural settings, and surface water (rivers) but none on the drinking water system. Hence, this may increase the risk of exposure to ARB and ARGs, which are not being monitored at present.

The aim of this study is to address the abovementioned gaps by determining the prevalence of ARB and the occurrence of resistant genes (ARGs) in a natural water source, drinking water treatment system, and water distribution outlets in Malaysia. We will do this by investigating the most common microbial species and their phylogenetic relationships before the water treatment and after the water treatment and in different DWTPs by determining the occurrence of ARB and ARGs and by quantifying the level of antibiotics.

Methods

Study Design

This is a cross-sectional study using laboratory-based methodologies (Figure 2). The DWTPs in the Malaysian state of Selangor will be chosen because of several factors such as the availability of published evidence of AMR in surface water and freshwater fish, large population, presence of both industrial and agricultural settings, and logistic factors from the sampling location to the laboratories.

We will use simple random sampling to choose a sample. We will randomly generate a number for each DWTP by using Excel and identify the sample. We assume that all the DWTPs are homogenous (Figure 3). The sample size will be chosen based on the manageable samples for processing. Samples will be collected at 3 sampling points, that is, intake sampling station, service reservoir outlet station, and distribution system sampling station for 7 antibiotics (amoxicillin, chloramphenicol, ciprofloxacin, gentamicin, tetracycline, sulfamethoxazole, and vancomycin), and the analysis will be performed in triplicates. In this preliminary stage, antibiotics are selected based on the most commonly prescribed antibiotics in Malaysia [48] and surveillance data from the Antibiotic Resistance Surveillance Reference Laboratory, Institute for Medical Research, Malaysia [49]. Therefore, the number of samples to be collected from each DWTP was calculated as follows: 3 sampling points × 7 antibiotics × 3 replicates = 63 samples. Sampling will be performed at 3 points as follows: point 1, intake sampling point (river source, immediately before going into DWTPs); point 2, service reservoir outlet sampling station (posttreatment DWTP); and point 3, distribution system sampling station/main tap (immediately before distribution to households).

Figure 2. Flow of the experimental work. AMR: antimicrobial resistance; ARB: antibiotic-resistant bacteria; ARG: antibiotic-resistant gene; BLAST: Basic Local Alignment Search Tool; HPC: heterotrophic plate count; NCBI: National Center for Biotechnology Information; PCR: polymerase chain reaction; R2A: Reasoner's 2 agar.

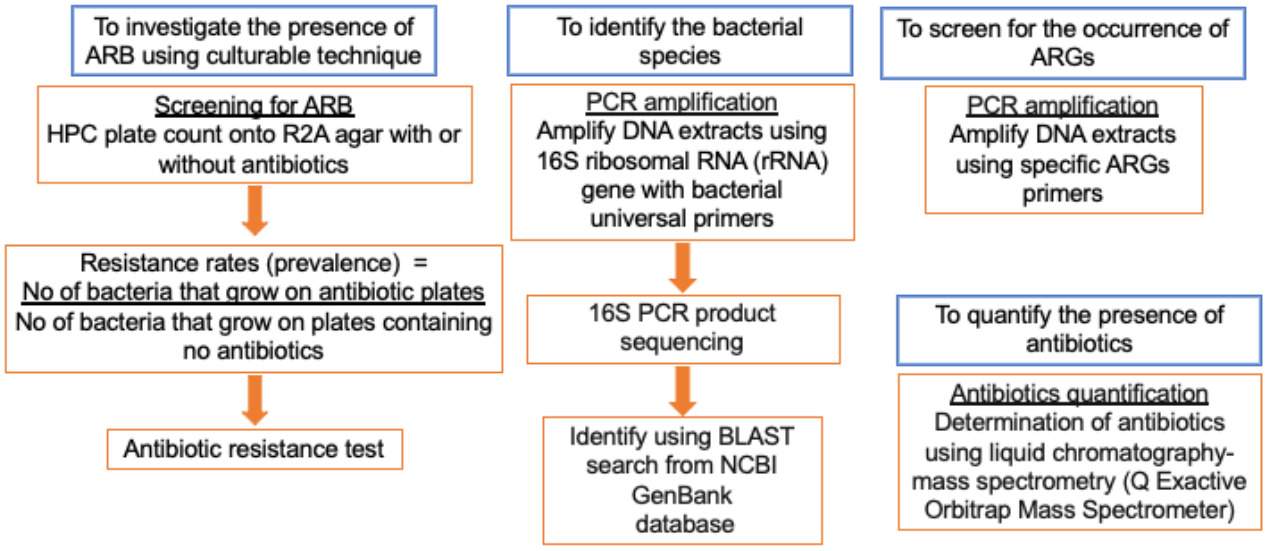
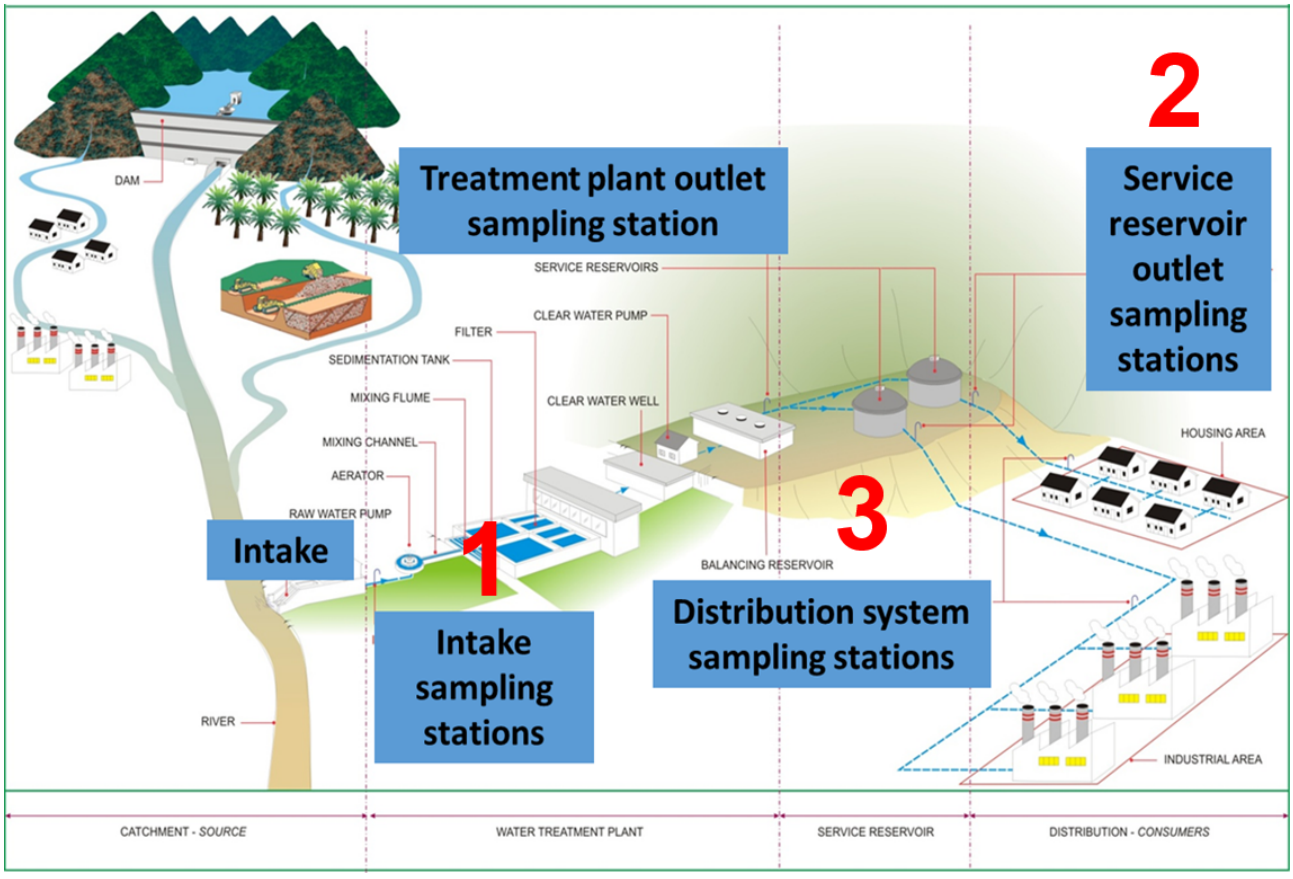


Figure 3. Schematic diagram of a drinking water treatment plant in Malaysia (Source: Engineering Services Division, Ministry of Health, Malaysia).



Sample Size and Power Calculation

Sampling size was calculated using prevalence [50], as follows:

Number of DWTPs in Selangor = 34

Prevalence range of heterotrophic ARB in a drinking water plant [27]: 1.17%-39.55%

$$n = z^2P\ (1\text{-}p)/d^2$$

Assuming the prevalence (p) would be 40%, p=0.40; *d*=0.05

$$= 1.96^2\ (0.3955)\ (0.6045)/0.05^2$$
$$= 3.8416\ (0.239)/0.0025$$
$$= 0.9181/0.0025$$
$$= 367.24$$

Where n=sample size, z=1.96 for a confidence level (α) of 95%, p=assumed prevalence, and d=precision (corresponding to effect size).

Inclusion and Exclusion Criteria

All DWTPs are monitored under the National Drinking Water Quality Program, Selangor State Health Department, Ministry of Health of Malaysia. There are no exclusion criteria.

Microbiological Analysis

Water Sampling

Samples will be handled properly by trained laboratory personnel to ensure aseptic techniques, and other procedures will be performed according to the quality management system for microbiological analysis. Water sampling will be performed following the Standard Methods for the Examination of Water and Wastewater [51]. Briefly, samples for microbiological analysis will be collected in 1-L sterile wide-mouth screw-capped bottles. To maintain the sample's integrity, a proper sample collection technique will be applied to ensure that water samples will be representative of the water being tested. Sampling at raw water intake locations will not be performed if there is rain or any unusual reported cases of contamination at the DWTPs. Samples will be collected from 3 points, namely, raw water intake sampling point, posttreatment outlet tap at the DWTP, and distribution tap at the residential area. Grab sampling will be performed with no manipulation of volume, such as pouring or adding to the sample to avoid contamination. To avoid exterior contamination at the posttreatment and main tap, the tap will be sterilized thoroughly using a flame torch. Sampling points at the distribution system will be chosen to demonstrate water quality throughout the network and to ensure that no localized contamination occurs. Water will be allowed to run through the tap for up to 5 minutes prior to sample collection to clear the piping line, which may harbor bacteria that do not reflect the actual water quality. Samples will be kept in an ice-packed cooler maintained at 4 °C and transported back to the laboratories for immediate processing within 48 hours.

Screening for Antibiotic-Resistant Heterotrophic Bacteria

We will be using culture-dependent methods and molecular techniques to determine the prevalence of ARB, identify them, and investigate the occurrence of ARGs present in DWTPs to answer each specific objective. A heterotrophic plate count on Reasoner's 2A agar (Oxoid) will be used to determine the ARB in the collected water samples. Bacteria in river water (sources) are expected to be present at much higher concentrations at approximately 350 colony-forming units (CFUs)/100 mL [52]. Samples from river water sources that have high concentrations of bacteria will be serially diluted to obtain single bacterial colonies for further analysis. The membrane filtration method will be used for testing lower bacterial concentrations from posttreatment and main tap samples. A previous study estimated that the number of bacteria that can be harvested from chlorinated drinking water is approximately up to 200 CFUs/100 mL [34]. Negative control plates and an aseptic technique will be applied to ensure that there is no contamination occurring during laboratory processing. Plates will be incubated at 37 °C for 2 days followed by 27 °C for another 5 days according to Gao et al [53] with some modifications. For river water samples, plates will be incubated at 37 °C for 24 hours where optimum bacterial colony size is achieved. The experiment will be performed in triplicates, instead of duplicate plates for each sample. The Kirby-Bauer test for antibiotic susceptibility (also called the disc diffusion test) will be used to determine the susceptibility of bacterial isolates to various antibiotics, namely, amoxicillin, ciprofloxacin, vancomycin, gentamycin, chloramphenicol, sulfamethoxazole, and tetracycline (Oxoid).

Screening for ARGs

The polymerase chain reaction method will be used for the rapid and accurate identification of bacteria by using universal primers targeting the 16S rRNA gene [54]. The 16S rRNA gene sequencing is a highly useful tool for identifying bacteria at the genus/species level and in differentiating between closely related bacteria species [55]. The DNA sequences obtained will be subjected to phylogenetic analysis. Phylogenetic network analysis is used to elucidate any occurrences of horizontal gene transfer of 16S rRNA in bacteria [56]. The development of phylogenetic trees is an important step for determining the diversity of resistant bacteria in the environment and for characterizing emerging pathogens (if there are any) to provide information to the relevant stakeholders. Cell-associated ARGs in the drinking water system (from isolated resistant bacteria) and cell-free ARGs from water samples (which may add potential risk) in DWTPs will be investigated. Eleven specific primers specific to genes of interest will be used to amplify the genes and to screen for the presence of each ARG in each water sample (Table 1). Genomic DNA will be extracted using a commercial DNA isolation kit according to the manufacturer's instructions. The DNA extracts will be kept at –20 °C until further analysis.

Table 1. List of the published primers representing the occurrence of bacterial DNA and antibiotic-resistant genes [40,57,58].

Gene name	Resistance mechanism
16S rRNA gene	N/A[a]
ermB	Ribosomal protection
Sul1	Enzymatic modification
tetA	Efflux
tetW	Ribosomal protection
tetX	Enzymatic modification
mecA	β-lactam binding protein
BlaNDM-1	Hydrolysis
BlaOXA-23	Enzymatic degradation
BlaOXA-51	Efflux
BlaTEM	Hydrolysis
VanA	Amino acid cleavage

[a]N/A: not applicable.

Chemical Analysis

Samples for antibiotic quantification (Figure 3) will be collected in 1-L high-density polyethylene sample bottles. High-performance liquid chromatography will be used to quantify the level of the 7 selected antibiotics. A high-performance liquid chromatography system (Textbox 1 and Table 2) will be used to quantify the level of antibiotics from all samples following the method by Kim et al [59].

Before quantification, samples will be preconcentrated and eluted to achieve satisfactory accuracies and sensitivities [59]. The procedure/steps will be carried out as follows:

1. Sample collection and treatment
2. Sample preconcentration using a nitrogen evaporator
3. Sample clean-up by automated solid-phase extraction
4. Analysis using liquid chromatography–mass spectrometry (Q Exactive Orbitrap Mass Spectrometer, Thermo Fisher Scientific)

Textbox 1. The high-performance liquid chromatography system used in this study.

Internal standard

1. Amoxicillin-d4 (Toronto Research Chemicals)

External standard

1. Amoxicillin trihydrate (Dr Ehrenstorfer GmbH)
2. Ciprofloxacin hydrochloride (Dr Ehrenstorfer GmbH)
3. Vancomycin hydrochloride (Dr Ehrenstorfer GmbH)
4. Gentamycin sulfate (Dr Ehrenstorfer GmbH)
5. (+/-) chloramphenicol (Cambridge Isotope Labs Inc)
6. Sulfamethoxazole (Dr Ehrenstorfer GmbH)
7. Tetracycline hydrochloride (Dr Ehrenstorfer GmbH)

Analytical column

Waters Xbridge C18 Column 50 mm×2.1 mm id, 2.5 µm at 35 °C

Solvent gradient

A: Water liquid chromatography-mass spectrometry grade (Merck)

B: Acetonitrile with 0.1% (v/v) formic acid (Sigma-Aldrich)

Flow: 0.8 mL/min

Table 2. Solvent gradient for the determination of antibiotics by high-performance liquid chromatography.

Retention time (min)	Flow rate (mL/min)	Mobile phase A (water liquid chromatography-mass spectrometry grade) (%)	Mobile phase B (acetonitrile with 0.1% (v/v) formic acid) (%)
0	0.80	95	5
1	0.80	95	5
12	0.80	70	30
13	0.80	0	100
17	0.80	0	100
17.1	0.80	95	5
23	0.80	95	5

Ethical Considerations

No clinical samples will be collected. This study has been exempted from ethics approval by the Medical Research and Ethics Committee, Malaysia. Data will be disseminated to the Drinking Water Quality Surveillance Program (DWQSP), Engineering Services Division, Ministry of Health, as our main stakeholders and collaborator, and through a peer-reviewed publication or presentation following approval from the Ministry of Health, Malaysia.

Statistical Analysis

A paired 2-sided *t* test will be used to compare the prevalence of heterotrophic ARB in source water and tap water. Data in replicates for the quantification of antibiotics (in parts per trillion) will be recorded in Excel. All DNA sequences obtained will be analyzed using the Chromas program (Informer Technologies Inc) for any missing nucleotides or errors. The Basic Local Alignment Search Tool will be used to determine the species identities of the sequences and to find the pattern of occurrence between sampling points and between DWTPs. The sequences will be aligned, and then a phylogenetic relationship will be constructed using the Lasergene software (DNASTAR).

Data Management

Data will be recorded in Microsoft Excel. DNA sequences will be kept in FASTA files. All positive ARB samples will be recorded for resistance profiles and will be kept as environmentally derived ARB culture collections for future studies.

Results

Outcomes

This project was funded in June 2020. The sampling frame was scheduled to start from November 2021 and continue until December 2022. To date (July 2022), we have sampled 4 DWTPs at 3 points, that is, the river (source), posttreatment outlet (DWTP), and the main distribution tap. Results will be reported as the prevalence of ARB in the drinking water system and the level of antibiotics present in the drinking water system a**s** the primary outcome. As the secondary outcome, bacteria isolated from the primary outcome will be tested to investigate whether they are carrying ARGs in the drinking water system. Descriptive statistics will be performed on the number of bacterial colonies harvested from water samples grown on Reasoner's 2A agar with or without antibiotics, the level of antibiotics detected in the water samples, and the occurrence of ARGs. Data analyses are ongoing and expected to be published in 2023.

Microbiological Analyses

The prevalence of heterotrophic ARB in source water will be compared with that in other sampling points. Only strains that are able to grow on Reasoner's 2A agar containing antibiotics will be subjected to analysis for antibiotic susceptibility and ARGs. Each antibiotic-resistant strain will be inoculated on Muller-Hinton media (Oxoid) for testing. Results from the antibiotic susceptibility test (Kirby-Bauer disk assay) will be compared to Clinical and Laboratory Standards Institute disk measurement standards for specific bacteria and antibiotics. However, for isolates that are not included in the Clinical and Laboratory Standards Institute list, results will be interpreted by adopting the European Committee on Antimicrobial Susceptibility Testing database or by considering inhibition diameters ≥10 mm as susceptible [60]. The zone of inhibition will be measured to determine the susceptibility or resistance of the organism to each drug and will be reported accordingly as susceptible, intermediate, and resistant. The presence of the 16S rRNA amplicon indicates bacterial DNA, and specific gene amplicons indicate the presence of ARGs. Data will be recorded as follows: the total heterotrophic plate count in the water samples will be reported as CFUs/100 mL. The resistance rate (prevalence) and multiresistant index will be reported in percentages. The percentage of resistance rate (prevalence) and multiresistance index will be calculated as follows:

Resistance rates (prevalence%) = Number of bacteria that grow on antibiotic plates/number of bacteria that grow on plates containing no antibiotics

Multiresistance index = Number of antibiotics to which isolate is resistant/number of antimicrobials to be tested

The presence of ARGs will be marked by determining the amplification by the specific primers of each gene of interest. DNA will be visualized using 2% agarose gel. Positive bands of sample DNA using 16S rRNA primer sets indicate the presence of bacterial DNA, while positive bands in samples using specific ARG primer sets show the presence of ARGs at the particular sampling points.

Chemical Analyses

The preconcentration technique will be used for each antibiotic to achieve parts per trillion detection. The concentrations of the antibiotics will be quantified and determined whether the levels correspond with the ARB at each site.

Discussion

Principal Findings

From our preliminary analysis in 3 DWTPs, we found multidrug-resistant *Enterobacteriaceae* as well as heterotrophic ARB in river water sources. The spread of ARB has been associated with wastewater discharge [61] and other anthropogenic activities [21]. Of the 56 isolates of *E. coli* and *Salmonella* spp tested, 24 (40%) were multidrug-resistant isolates, 14 (58%) were resistant to at least 3 antibiotics, 4 (17%) were resistant to 4 antibiotics, 5 (21%) were resistant to 5 antibiotics, and 1 (4%) was resistant to 6 antibiotics. Similarly, the presence of multidrug-resistant *E. coli* in rivers [62,63] and drinking water sources has been reported in other countries such as China [6], United States [27], and Iran [64], thereby highlighting the importance of efficient effluent treatments from AMR hotspots before being discharged into the rivers [7].

The outcomes of this study would provide a basis for holistic research in AMR by determining the extent of AMR present in Malaysia and the likely paths of transmission from the environment to the public. The prevalence data on antibiotic resistance generated from this study will also help the relevant stakeholders in Malaysia to steer evidence-based policies to control and prevent the possible transmission of ARB in drinking water systems to humans [65] and to complement with other current AMR research and monitoring in Malaysia.

The DWTP in Malaysia consists of a river catchment as the water source, water treatment plant, service reservoir, and finally, the distribution outlet from where it goes to every house (Figure 3). The monitoring of the drinking water system in Malaysia currently falls under the DWQSP, the Ministry of Health. To date, Malaysia is still lacking in the research and monitoring of antimicrobials (ARB and ARGs) in drinking water systems (source water, DWTP, and tap water). The current microbiological parameters being monitored are fecal coliforms and *E. coli*. In the future, to have this parameter stated in the National Water Quality Standard would help to indicate whether the water is safe enough for daily consumption. Furthermore, we would be able to inform other ministries to be aware of the proper disposal of leftover antibiotics, which can end up in wastewater or rivers, and inform them about the importance of efficient drinking water treatment for human consumption.

We have identified several strengths in this study; first, this study provides baseline data on ARB in the drinking water system of Malaysia. Second, this study will illustrate the burden of ARGs in the drinking water treatment systems in urban areas. Third, these results will be used to provide evidence and increase the precision of the quantitative estimates of exposure related to ARGs in drinking water and finally provide baseline data for AMR in national safe drinking water. We anticipate limitations such as the recovery of bacteria from low nutrient media when cultivated in enriched media, which will require optimization of the incubation period and temperature, and a lack of reference data on minimum inhibitory concentrations to interpret all types of bacteria, especially the less commonly known bacteria present in a water system.

There are several impacts anticipated from this study. First, we may elucidate the magnitude of the problem by providing baseline information on the level of ARB and ARGs present in our drinking water system in Selangor, Malaysia. Second, we may improve the water treatment system to be more sustainable, safe, and clean, particularly for long-term daily water consumption [66]. Countries like China have incorporated intervention studies by testing various filtration systems to continuously improve their water treatment system. Finally, this study may improve the public health system and environmental health.

Findings from this study will be used to determine whether AMR is a problem in our drinking water by providing information on the status of ARB and the presence of ARGs in drinking water systems. Depending on the magnitude of AMR in the drinking water system, further actions/key measures can be taken (future research or by providing evidence to the stakeholders) to reduce or eliminate the contaminants from entering our drinking water system. This study would help to draw a holistic picture of the occurrence of antibiotic resistance in the environment, apart from other anthropogenic sources such as human effluents that may contribute to antibiotic resistance, by considering water as a potential reservoir for humans to be exposed to antibiotic resistance. This study will provide information on the status of ARB and the presence of resistance genes as contaminants in drinking water systems, which are not being monitored in the National Drinking Water Quality program by the Ministry of Health at present. Further actions and key measures can be taken for future research or expert advice to reduce or eliminate contaminants from entering our drinking water system. This study will broaden a research niche in AMR concerning the environment and human health risks in Malaysia.

Conclusion

AMR is a public health challenge that requires the concerted efforts of multiple agencies. AMR management in clinical and agricultural settings is more established compared to that in DWTPs in Malaysia. The output from this study will provide evidence and key measures to benefit and assist the current DWQSP to reduce the risk of antibiotic resistance transmission to the public. Rationally, if the resistance is decreased at the local level, it can help prevent the global antibiotic resistance crisis from growing even bigger.

Recommendation

Data from this study will be used to embark on future research based on the tricycle (human, food and environment) approach by incorporating the possible sources of pollutants. This will enable us to determine the prevalence of AMR within the same localities and thus enable researchers to elucidate the possible route of transmission of AMR in a defined setting, especially into the rivers as drinking water sources.

Acknowledgments

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Data Availability

Data will be kept in the Ministry of Health and will be disseminated following approval from the Director-General of Health, Malaysia.

Authors' Contributions

ZAM initiated the study, applied for funding, and is the principal investigator. SKB and MAJJ were involved in the development of laboratory techniques. LC was involved in giving expert advice on antimicrobial resistance and molecular techniques. NA gave expert advice on antimicrobial resistance in Malaysia. NAM provided important statistical contributions. All authors contributed to the content of this study.

Conflicts of Interest

None declared.

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Abbreviations

AMR: antimicrobial resistance
ARB: antibiotic-resistant bacteria
ARG: antibiotic-resistant gene
CFU: colony-forming unit
DWTP: drinking water treatment plant
DWQSP: drinking water quality surveillance program
MyAP-AMR: Malaysian Action Plan on Antimicrobial Resistance

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Corrigenda and Addenda

Correction: A Rehabilitation Program for Individuals With Chronic Low Back Pain: Protocol for a Randomized Clinical Trial

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In "A Rehabilitation Program for Individuals With Chronic Low Back Pain: Protocol for a Randomized Clinical Trial" (JMIR Res Protoc 2022;11(10):e31345) the authors noted 3 errors.

1. In the originally published article, the Methods section of the Abstract appeared as follows:

> *The trial was approved by the Human Research Ethics Committee in September 2018.*

This has been corrected to:

> *The trial was approved by the ethics committee for research involving human beings of the Federal University of Pelotas (reference number: 5.717.390) in September 2022, and it will be conducted until August 2023.*

2. In the originally published article, the Results section of the Abstract appeared as follows:

> *The trial was funded in 2018. Patient recruitment will begin at the end of 2021, as it involves patients who are on the waiting list of a public service and requires the health manager's permission to start the data collection, considering the current health scenario. Results are expected to be achieved by August 2022.*

This has been corrected to:

> *The researchers are being trained to apply the questionnaires and carry out the interventions. Patient recruitment will begin at the end of 2022 and results are expected to be achieved by August 2023.*

3. In the originally published article, the Results section appeared as follows:

> *The trial was funded in 2018 and presented to the municipal authorities. Its practical applications were discussed in August 2022, and the data collection process was structured to include the updating of patient contacts. Patient recruitment will begin at the end of 2022, as it involves patients who are on the waiting list of a public service and requires the health manager's permission to start the data collection, considering the current health scenario. Results are expected to be achieved by August 2023.*

This has been corrected to:

> *The trial was presented to the municipal authorities and its practical applications were discussed in August 2022. The researchers are being trained to apply the questionnaires and carry out the interventions. Patient recruitment will begin at the end of 2022 and results are expected to be achieved by August 2023.*

The correction will appear in the online version of the paper on the JMIR Publications website on November 17, 2022, together with the publication of this correction notice. Because this was made after submission to full-text repositories, the corrected article has also been resubmitted to those repositories.

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Protocol

Reorganizing Pharmaceutical Care in Family Medicine Groups for Older Adults With or at Risk of Major Neurocognitive Disorders: Protocol for a Mixed Methods Study

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Abstract

Background: The latest global figures show that 55 million persons lived with major neurocognitive disorders (MNCDs) worldwide in 2021. In Quebec, Canada, most of these older adults are cared for by family physicians in interdisciplinary primary care clinics such as family medicine groups (FMG). When a person has a MNCD, taking potentially inappropriate medications or polypharmacy (5 different medications or more) increases their vulnerability to serious adverse events. With the recent arrival of pharmacists working in FMGs and their expanded scope of practice and autonomy, new possibilities for optimizing older adults' pharmacotherapy are opening.

Objective: This project aims to evaluate the impact of involving these pharmacists in the care trajectory of older adults living with MNCD, in an interdisciplinary collaboration with the FMG team, as well as home care nurses and physicians. Pharmacists will provide medication reviews, interventions, and recommendations to improve the pharmacotherapy and support offered to these patients and their caregivers.

Methods: This 2-step mixed methods study will include a quasi-experimental controlled trial (step 1) and semistructured interviews (step 2). Older adults undergoing cognitive assessment, recently diagnosed with MNCD, or receiving care for this at home will be identified and recruited in FMGs in 2 Quebec regions. FMGs implementing the intervention will involve pharmacists

in these patients' care trajectory. Training and regular mentoring will be offered to these FMGs, especially to pharmacists. In control FMGs, no FMG pharmacist will be involved with these patients, and usual care will be provided.

Results: Medication use (including appropriateness) and burden, satisfaction of care received, and quality of life will be assessed at study beginning and after 6 months of follow-up and compared between groups. At the end of the intervention study, we will conduct semistructured interviews with FMG care team members (pharmacists, nurses, and physicians) who have experienced the intervention. We will ask about the feasibility of integrating the intervention into practice and their satisfaction with and their perception of the intervention's impacts for older adults and their families. We will assess the effect of improved pharmaceutical care for older adults with or at risk of MNCDs through the involvement of FMG pharmacists and a reorganization of pharmaceutical care.

Conclusions: The inclusion of pharmacists in interdisciplinary care teams is recent and rising, strengthened by more substantial pharmacist practice roles. Results will inform the processes required to successfully involve pharmacists and implement developed tools and procedures transposable to other care settings to improve patient care.

Trial Registration: ClinicalTrials.gov NCT04889794; https://clinicaltrials.gov/ct2/show/NCT04889794

International Registered Report Identifier (IRRID): DERR1-10.2196/42577

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KEYWORDS

primary care; older adults; neurocognitive disorders; pharmaceutical care; mixed method study

Introduction

The latest global figures show that 55 million persons lived with major neurocognitive disorders (MNCDs) in 2021, and this number is expected to rise to 78 million in 2030 and 139 million in 2050 [1]. Older adults with MNCDs are more likely to be exposed to polypharmacy or potentially inappropriate medications than those without this condition [2]. Polypharmacy, the simultaneous use of 5 or more different medications, increases older adults' vulnerability to falls, emergency department visits, hospitalizations [3], and loss of autonomy [4]. For example, adverse effects of medications can be a precipitating factor in delirium [5]. In turn, delirium increases the risk of prolonged hospitalization and functional decline and doubles the mortality rate [6]. Better pharmacotherapy management for vulnerable older adults may prevent this iatrogenic chain leading to autonomy loss. According to several recent studies and literature reviews, interdisciplinary interventions that include pharmaceutical care and knowledge exchange sessions with health care teams can reduce inappropriate medication [7,8] or prevent the onset of delirium for at-risk individuals [9].

Since October 2015, the Quebec Ministry of Health and Social Services has provided resources to integrate pharmacists into interdisciplinary family medicine group (FMG) teams to improve medication use [10]. These pharmacists are working in the clinic, together with other health care professionals, in the provision of direct patient care. As of April 2021, 328 (88.6%) of the 370 FMGs had an agreement in place with 1 or more pharmacists, according to the Ministry. The pharmacist presence in the FMG was a mean of 16.3 and 19.1 hours per week in 2018 and 2020, respectively [11,12]. In January 2021, their role was further expanded by increased practice rights [13]. Notably, pharmacists can now initiate or modify a pharmacotherapy independently under certain conditions and, even more liberally, within a collaborative practice agreement with physicians [13].

Pharmacists are the health care professionals best trained to identify inappropriate medications [14], thus improving prescribing, reducing evitable health care utilization and medication costs, and contributing to the clinical improvement of many health conditions [14-16] and patients' experience [17], specifically when part of the health care teams. Additionally, FMG pharmacists are particularly well positioned to review and optimize medications for patients undergoing cognitive assessment who frequently have inappropriate medication therapy [18]. A prior study examined this new model of functioning for pharmaceutical care in FMG among persons with complex care needs [19]. According to this study, the mean number of medications prescribed per person was 14.2, and FMG pharmacists identified an average of 7.2 problems related to pharmacotherapy during their evaluation and follow-up of 4 to 6 months [19]. A prior study in Quebec long-term care facilities on the increased role of pharmacists practicing in these settings demonstrated that it was possible to reorganize care, based on expanded pharmacists' and nurses' scope of practice, to reduce polypharmacy and inappropriate medications in older adults in long-term care [20]. Collaboration and work satisfaction among health care providers also improved [21,22].

Presently, not all FMGs have a pharmacist in their team, and when present, the FMG pharmacist is not always involved in the care trajectory of older adults with MNCDs. This study, therefore, aims to involve FMG pharmacists systematically in the care of these patients, a role which has been encouraged by the Quebec Alzheimer Plan [23,24]. This study will assess whether pharmacists' systematic involvement in these patients' care, together with their increased practice roles, can reduce treatment burden, polypharmacy, or potentially inappropriate medications and improve patients' care, their satisfaction with care, and quality of life. We developed the intervention, called GPS (Évaluation de l'impact de la réorganisation du travail en GMF sur la pharmacothérapie et le soutien à l'autonomie des personnes âgées ayant un trouble neuro-cognitif majeur) together with the stakeholders of the Quebec Alzheimer Plan. Patient partners have also been involved in the study from its beginning

and helped develop all recruitment and interviewing material. The intervention's goal is to reduce the number of adverse effects due to inappropriate pharmacotherapy and its consequences on functional decline and loss of autonomy in older adults with MNCDs. We hypothesize that the intervention will decrease (1) the number of prescribed medications, (2) the proportion of patients with potentially inappropriate medication, and (3) patients' perceived treatment burden and increase (4) patients' satisfaction with care and (5) their quality of life.

Methods

Study Design

We based our methodology on the Medical Research Council's conceptual model on how to evaluate complex interventions [25]. We will use mixed methods, including a quasi-experimental controlled trial (step 1) and semistructured interviews (step 2). For step 1, information on health conditions and medication utilization at study entry and follow-up (ie, after 6 months) will be collected for all included participants. Participating patients will also complete 3 validated questionnaires in either French or English to assess their perceived treatment burden, quality of life, and satisfaction with care. The Multimorbidity Treatment Burden Questionnaire, (MTBQ) [26,27], the EQ-5D-5L [28], and the self-administered Physician Enabling Skill Questionnaire (PESQ) [29] will be used. Pharmacists will also report their interventions and suggestions during the 6-month follow-up. In step 2, we will invite all health professionals who implemented the intervention (ie, pharmacists, nurses, and physicians) to participate in a semistructured interview where they will be asked about the ease to integrate the intervention into their practice, their satisfaction with it, and their perception of its impacts for older adults and their families.

The GPS intervention

First, nurses and physicians in intervention FMGs (exposed) will be asked to refer all older adults undergoing cognitive evaluation OR referred to a memory clinic OR recently diagnosed (<12 months) with a MNCD to the FMG pharmacist. Moreover, home care teams will be asked to refer older adults receiving home care for MNCDs to the FMG pharmacist. FMG pharmacists will perform a medication review. A medication review is a structured and comprehensive evaluation of a patient's pharmacotherapy with the aim of identifying and resolving problems and improving health outcomes [30]. This medication review involves an interview with each referred older adult, including their caregiver, if applicable, to establish the best possible medication history (BPMH) [31]. The BPMH is a complete documentation of medication therapy, including the name, dose, administration route, and medication administration frequency. To this end, medication information will be validated with at least 1 other reliable data source (eg, community pharmacy records) and documented in the patient's chart. The pharmacist will then detect medication-related problems [32] by analyzing this information and clinical data using their own judgment or validated criteria [33]. They will establish a care plan and the follow-ups needed with the patient in collaboration with the health care team and the community pharmacist. Pharmacists will also document the number and type of interventions and recommendations made to optimize patients' pharmacotherapy for 6 months following the medication review. We will offer training and mentoring support to these teams, including pharmacist support for more complex interventions and monthly web-based interdisciplinary meetings.

Study Setting

The study will comprise participants from an exposed group of approximately 5 FMGs with attending pharmacists who will implement the intervention and a control group composed of participants from 5 others FMGs without involved pharmacists. FMGs and home care teams will participate at their convenience within 2 Integrated (University) Health and Social Services Centers territories: (1) the *Centre intégré universitaire de santé et de services sociaux* (CIUSSS) *du Nord-de-l'Ile-de-Montréal* (NIM) in a metropolitan area and (2) the *Centre intégré de santé et de services sociaux* (CISSS) *de Chaudière-Appalaches* (CA) in a mixed—urban and rural—area. We used this selection process to facilitate implementation as the intervention teams need to be motivated toward its application and training and mentoring activities. To be eligible for participation, intervention FMGs must have at least 1 participating pharmacist, interested partner nurses, and physicians. Similarly, intervention home care teams must have access to a participating FMG pharmacist and a home care nurse. In contrast, in control FMGs and their home care teams, no FMG pharmacist will be systematically involved in the eligible patients' trajectory. However, the FMGs must be willing to allow data collection and delay implementing similar interventions within their teams.

Study Population

For the first step, the intervention targets 2 patient subgroups at turning points: (1) older adults undergoing cognitive evaluation or recently diagnosed with MNCDs in FMGs and (2) older adults with MNCDs followed at home by the home care teams.

For the second step, FMG professionals and home care teams implementing the intervention are also targeted.

Step 1: Quasi-experimental Controlled Trial

Inclusion and Exclusion Criteria for Older Adults

All older adults (aged ≥65 years) undergoing cognitive evaluation at the FMG OR referred to a memory clinic OR having been diagnosed with MNCDs at the FMG within the last year OR followed up at home for a MNCD AND referred to the pharmacist in the intervention FMGs will be invited. We will exclude older adults in palliative care or those who do not understand French or English (without a caregiver who could assist them).

Sampling Method, Recruitment, and Data Collection Procedure

We will conduct a quasi-experimental (ie, rather than a randomized) study given that our intervention will depend on whether an older adult's FMG includes a participating pharmacist (intervention group) or not (control group).

Sample Size Calculation

According to prior estimates provided by the CI(U)SSS, about 50 older adults may be targeted for participation per FMG per year. Considering that the on-site presence of FMG pharmacists is on average 2 to 3 days a week [11,12], it should be feasible to include approximately 40 older adults per FMG. By setting our intercluster correlation coefficient at 0.005 (conservative), the number of clusters (FMGs) at 5 intervention and 5 control FMGs, and at 40 older adults per FMG, we expect to be able to detect a difference of 1 medication per older adults between the beginning and the end of the intervention, between the 2 groups, with a power of 83%. Therefore, we have planned a 12-month inclusion period, corresponding to recruiting approximately 1 person per week per FMG. The inclusion date will be when the reference to the pharmacist was made. For control FMGs, we will consult electronic medical records and FMG health care professionals to identify all older adults who meet the inclusion criteria. Since there will be no reference to the pharmacist for these individuals, the inclusion date will be the date of identification by the FMG. For those receiving home care services, the inclusion date will be the first home visit following the start of the study.

Outcomes Measures

The primary outcome measure is the change in the number of prescribed medications. Specifically, (1) the total number of prescribed medications and (2) the number of potentially inappropriate medications according to the Beers criteria [33] will be measured in the intervention and control groups. We will obtain data from patients' medical records at the beginning (baseline) and 6 months after inclusion in the study.

We will assess several secondary outcome measures. First, a change in the treatment burden level will be measured with the 13-item MTBQ [26,27] in the intervention and control groups at baseline and 6 months follow-up. We will score each item as follows: 0 (not difficult/does not apply), 1 (a little difficult), 2 (quite difficult), 3 (very difficult), and 4 (extremely difficult). We will interpret the scores as suggested by the authors of the original MTBQ instrument: no burden (score 0), low burden (score <10), medium burden (score 10-22), and high burden (score ≥22) [26].

Second, we will measure the quality of life in the intervention and control groups at baseline and 6 months follow-up with the EQ-5D-5L [28]. The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. Responses are coded as single-digit numbers expressing the severity level selected in each dimension [28]. The last study outcome is the satisfaction with the care received and access to care. To measure this outcome, the PESQ, validated in Quebec primary care settings, will be used [29]. We have adapted the questions with the author's approval to consider not only the physician but the whole FMG team.

Step 2: Semistructured Interviews—Recruitment and Information-Gathering Procedures

The research team will invite all intervention FMG and home care professionals involved in the GPS intervention (pharmacists, nurses, and physicians) to an individual telephone interview at the end of the implementation period (ie, 18 months after inclusion of the first older adults). We will obtain verbal consent from the health care professionals before conducting the interview, which will last 30 to 45 minutes. We will aim for a total of approximately 30 interviews—that is, at least 1 pharmacist, 2 FMG nurses, and 2 physicians per FMG (n=25) and 6 nurses or nursing assistants from the home care team. This number should be sufficient to gather all the various health care professionals' experiences while being feasible in the context of FMGs. A qualified interviewer will conduct the interviews using a semistructured interview guide to explore their views on the intervention. The interview will cover categories proposed by Patton's Theoretical Model of Change [34]: (1) resources required for support, training, and coaching; (2) activities required by the model; (3) participation in the model's implementation; (4) reactions to and satisfaction with the model; (5) changes in knowledge, attitudes, and skills; (6) change in practice; and (7) perceived results of the model. We will also invite professionals to complete the pretested French version of the web-based NoMAD instrument [35,36] derived from the Normalization Process Theory [37] after the end of the implementation period.

Data Analysis

In step 1, we will use an intention-to-treat approach to assess the GPS intervention's effectiveness. The principal analysis will compare the difference (1) in the average number of medications per person between the unexposed and exposed groups according to the study period (baseline and 6 months) and (2) the average number of potentially inappropriate medications per person between the 2 groups, according to the study period, by mixed Poisson repeated measures regression. This type of analysis considers intra-FMG and intraindividual correlations. Contrasts will be built to determine if the average number of medications per person over time differs between the exposed and the unexposed group. Secondary results will be analyzed similarly to compare the MTBQ, PESQ, and EQ-5D-5L scores between the groups exposed and unexposed to the GPS intervention.

Medication data missing at measurement time periods after the initial data collection will be imputed using the last-observation-carried-forward method. Using this method, the potential benefits of the intervention should be underestimated. For participants lost to follow-up regarding the questionnaires, no measures will be imputed at follow-up, but sensitivity analyses may be used in which baseline questionnaires scores could be imputed for follow-up scores. We will perform all analyses with SAS statistical software (SAS Institute Inc).

In step 2, we will record the interviews and transcribe them verbatim to then perform qualitative thematic content analysis. The first stage of this analysis consists of coding the data using NVivo qualitative analysis software (QSR International). We

will develop a codebook based on Patton's Theoretical Model of Change [34] for this purpose. Two research agents will independently test the first version of the codebook by coding excerpts of a few interviews. They will discuss and improve this version and test it again by coding excerpts of other interviews. This procedure aims to obtain a rigorous coding of the interviews and an accurate description of the experiences. The final sequential analysis will allow the integration of the quantitative results on the intervention's impacts with the qualitative results describing the experiences of the FMG and home care teams. We will build and present an integration matrix and discuss it with the members of the research team and the stakeholders with whom the project was initiated, as well as with patient partners. This process will identify crucial elements for improving the intervention for future implementation.

According to mixed methods research methodology, the quantitative results obtained at step 1 will be interpreted and discussed in the light of information obtained from step 2, so that lessons can be learned on how to best implement such an interdisciplinary practice change, including the increased roles of some of the players [38].

Ethics Approval

Ethical approval was obtained from the Ethics review board of the CISSS CA and CIUSSS NIM (project number: MP-23-2020-732; latest amendments approved in January 2022).

Safety Consideration

The participant's consent to participate in the study will be obtained in writing or verbally, recorded using an audio device. All participants will be able to withdraw from the study at any time without giving reasons. All patient data will be collected and recorded into REDCap, a secure and confidential data entry software. Nominal patient data will be entered into a data collection sheet and confidentially stored in an ongoing computer database of the research center (*CHU de Québec*).

Results

All study materials (questionnaires, patients' recruitment tools, and training documents) have been developed in collaboration with clinicians and patient partners. As of September 2022, 13 FMGs have agreed to participate in the GPS project (11 implementing the intervention and 2 as controls). We have yet to recruit more FMGs that will be part of the control group. Recruitment of older adults began in September 2021, when the project was launched. We had planned 12 months for the inclusion of eligible older adults. As of September 2022, a total of 100 participants had been enrolled and the follow-up was completed for 23 of them. Data collection will take approximately 18 months, and data analysis and synthesis of the results will take another 9 months. Knowledge transfer/mentoring sessions will be organized regularly during the implementation period (ten 1-hour meetings in each CI[U]SSS have been realized as of September 2022) and are also planned after the end of the GPS study (approximatively 6 months). These sessions are open to FMG pharmacists, physicians, mentors (physicians and pharmacists with geriatric expertise), and research team members and comprise short presentations of specific clinical interest, summaries of issues surrounding the study methods and procedures, as well as an occasion for an exchange between all these persons on clinical and research questions.

Discussion

Our hypothesis is that the GPS intervention will improve pharmaceutical care for older adults undergoing cognitive assessment or with MNCDs and facilitate access to care. This research will add new knowledge on the impact of a systematic involvement of pharmacists in FMGs and their home care teams for older adults with MNCDs. In fact, despite growing recognition of the urgent need to address the "epidemic of polypharmacy in geriatric patients," this study is one of the first to evaluate the impact of an interdisciplinary care model involving FMG pharmacists on the pharmacotherapy of older adults with MNCDs. It will also evaluate the processes required to implement the GPS intervention and develop tools, procedures, and guidelines that could be transposed to other care settings to improve care and its continuity for these patients.

This study received financing as a "living laboratory," meaning that the proposed intervention will be adapted by the participating FMGs or home care teams and may thus vary slightly according to the different contexts of practice environments. This variability could influence the internal validity of the results, which is a possibility common in such strategies. Additionally, the COVID-19 pandemic has caused delays in deploying the project across the FMGs and brought some difficulties in patient recruitment. It might also be more challenging to recruit further FMGs because health care professionals must be willing to invest some time in implementing the intervention or for recruiting participants. Moreover, the characteristics of participants at risk or with a MNCD (eg, fatigue, memory loss, attention difficulties, anxiety, etc) may affect their level of understanding of their involvement in the project and possibly complicate data collection. Adjustments will be made in the methodology to account for the characteristics of the study population if necessary.

Acknowledgments

We thank the persons who will take the time to participate in the study. In advance, we also thank the family medicine groups who will agree to implement the project and the professionals who will offer energy and time to ensure its success. We are also grateful to the clinicians and patient-partners who contributed to improving measurement and training tools and study procedures. We also thank Mylène Chartrand and Lise Poisblaud, who were involved in the study from March 2021 to March 2022. The project is funded by the *Fonds de recherche du Québec*.

Data Availability

The data sets generated and analyzed during the current study are not publicly available due to data access and research ethics laws applicable in Quebec but are available from the corresponding author on reasonable request.

Authors' Contributions

LG, EK, and AM developed the initial intervention and study protocol in collaboration with coauthors. All authors collaborated on later versions of the study protocol and this paper’s writing.

Conflicts of Interest

None declared.

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Abbreviations

BPMH: best possible medication history
CA: Chaudière-Appalaches
CISSS: Centre intégré de santé et de services sociaux
CIUSSS: Centre intégré universitaire de santé et de services sociaux
FMG: family medicine group
MNCD: major neurocognitive disorder
MTBQ: Multimorbidity Treatment Burden Questionnaire
NIM: Nord-de-l'Ile-de-Montréal
PESQ: Physician Enabling Skill Questionnaire

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Protocol

Intimate Partner Violence and HIV Prevention Among Sexual Minority Men: Protocol for a Prospective Mixed Methods Cohort Study

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Abstract

Background: Sexual minority men experience intimate partner violence (IPV) at rates similar to those reported by heterosexual women in the United States. Previous studies linked both IPV victimization and perpetration to HIV risk and seroconversion; however, less is known about the impact of IPV on HIV testing, sexually transmitted infection (STI) testing, pre-exposure prophylaxis (PrEP) uptake, and the persistence of PrEP use among sexual minority men experiencing IPV. Although prior work suggests that IPV may influence HIV prevention behavior, experiences of IPV are so highly varied among sexual minority men (eg, forms, frequency, and severity; steady vs casual partnerships; perpetration vs receipt; and sexual vs physical vs psychological violence) that additional research is needed to better understand the impact that IPV has on HIV risk and protective behaviors to develop more effective interventions for sexual minority men.

Objective: This study aims to contribute to our understanding of the antecedents of IPV and the direct and indirect pathways between perpetration and receipt of IPV and HIV or STI risk behavior, STIs, and use of PrEP among sexual minority men experiencing IPV.

Methods: This mixed methods study has 2 phases: phase 1 involved formative qualitative interviews with 23 sexual minority men experiencing IPV and 10 key stakeholders or providers of services to sexual minority men experiencing IPV to inform the content of a subsequent web-based cohort study, and phase 2 involves the recruitment of a web-based cohort study of 500 currently partnered HIV-negative sexual minority men who reside in Centers for Disease Control and Prevention–identified Ending the HIV Epidemic priority jurisdictions across the United States. Participants will be followed for 24 months. They will be assessed through a full survey and asked to self-collect and return biospecimen kits assessing HIV, STIs, and PrEP use at 0, 6, 12, 18, and 24 months. They will also be asked to complete abbreviated surveys to assess for self-reported changes in key study variables at 3, 9, 15, and 21 months.

Results: Phase 1 was launched in May 2021, and the phase 1 qualitative interviews began in December 2021 and were concluded in March 2022 after a diversity of experiences and perceptions were gathered and no new ideas emerged in the interviews. Rapid analysis of the qualitative interviews took place between March 2022 and June 2022. Phase 2 recruitment of the full cohort began in August 2022 and is planned to continue through February 2024.

Conclusions: This mixed methods study will contribute valuable insights into the association that IPV has with HIV risk and protective behaviors among sexual minority men. The findings from this study will be used to inform the development or adaptation of HIV and IPV prevention interventions for sexual minority men experiencing IPV.

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KEYWORDS

intimate partner violence; cohort study; sexual minority men; HIV; sexually transmitted infections; pre-exposure prophylaxis; PrEP

Introduction

Background

Sexual minority cisgender men experience alarming rates of intimate partner violence (IPV). Rates of IPV victimization or perpetration range from 1 in 4 to 1 in 2 sexual minority men [1-4]. In the 2011 National Intimate Partner Violence Survey, 25% of sexual minority men reported lifetime physical victimization and 60% reported lifetime psychological victimization from intimate partners [5]. These rates are similar to those in other large samples of sexual minority men [6-12]. Estimated lifetime prevalence for receipt of IPV among sexual minority men ranges from 12% [13] to 45% [14] for physical forms, 2% [15,16] to 33% [14] for sexual forms, 28% [17] to 64% [15,16] for psychological forms, and 32% [18] to 78% [19] for any form of IPV. Perpetration of IPV is less studied and ranges from 8% [1] to 35% [20]. Among sexual minority men, IPV has been associated with minority race or ethnicity [18,21-23], less education [10], positive HIV status [10, 23,24], and being aged 15 to 24 years [6,25-27].

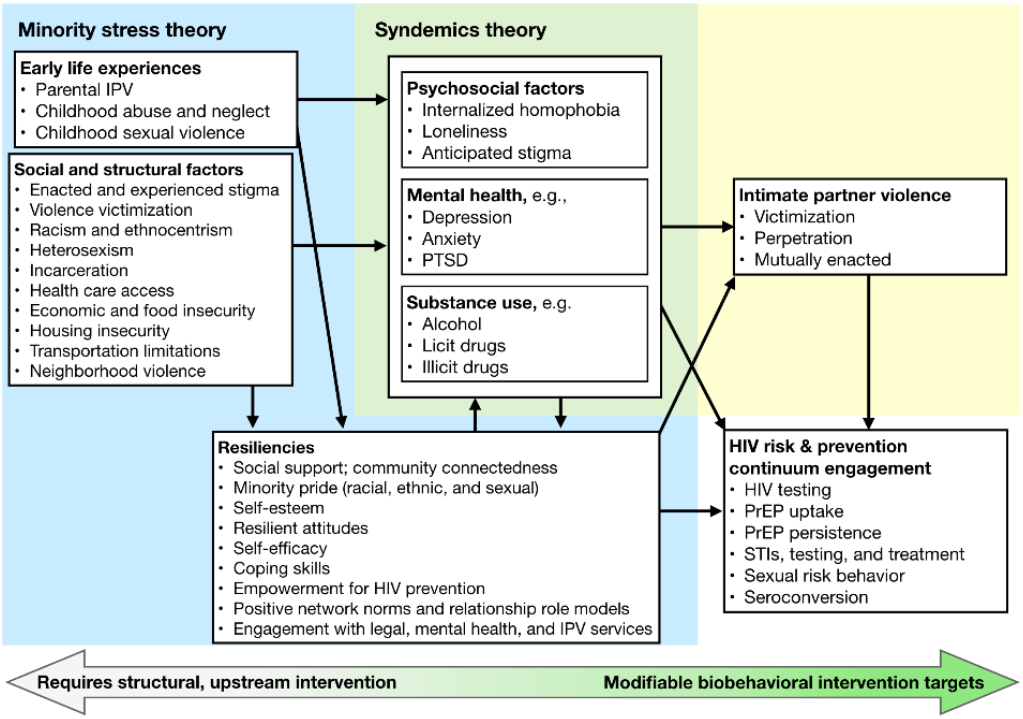
The overarching goal of the proposed study is to examine how IPV influences HIV risk behavior and contributes to gaps in engagement in the HIV prevention continuum at 3 specific points: HIV testing (awareness), pre-exposure prophylaxis (PrEP) uptake (uptake), and PrEP persistence (adherence or retention [28]). A recent cross-sectional study found associations between the use of PrEP and specific dimensions of IPV victimization and speaks to the need for greater attention to the multidimensional aspects of IPV as they relate to HIV prevention continuum engagement [29]. Forced sex and emotional forms of IPV were negatively associated with PrEP use; however, controlling forms of IPV were positively associated with PrEP use. The authors asserted the need for longitudinal research to better assess causality and understand the fluctuations that are likely to occur in IPV, HIV risk, and PrEP use over time [29].

Research has linked both IPV victimization and perpetration to HIV risk and seroconversion. A large longitudinal study of Latinx sexual minority men in Los Angeles, California, United States, found that any lifetime experience of IPV (perpetration or victimization) doubled the odds of HIV seroconversion during the study period [30]. In a meta-analysis of 17 studies with a cumulative total of 13,797 sexual minority men, experience of IPV was associated with being HIV positive and doubled the odds of having condomless anal sex [31]. Studies have also found both victimization and perpetration of IPV to be associated with condomless anal sex [4] among both casual and main sex partners [32-34]. IPV perpetration has also been associated with doubling the odds of condomless anal sex among sexual minority men [11]. There is preliminary evidence to suggest that IPV is associated with substance use among sexual minority men and that substance use in combination with IPV increases HIV risk. A study of 7844 sexual minority men found that IPV increased with stimulant and popper use, and substance use strengthened the association between IPV and being HIV positive [35].

Theoretical Framework

Minority stress theory [36,37] and syndemics theory [38,39] provide lenses through which the cumulative effects of structural, social, and individual-level stressors on sexual minority men, including factors that increase the risk for IPV and HIV, can be examined. Both theories are widely used to understand antecedents of HIV disparities among sexual minority men and how health disparities overlap with potential synergistic effects [40-50]. A recent analysis of syndemics among Black sexual minority men showed an association between stress and depression symptoms, sexual compulsiveness, and experiencing IPV [51]. Several studies have identified correlations between internalized homophobia and perpetration of physical [15,16,51,52], sexual [52], and emotional or psychological IPV [52]. Homophobic discrimination and sexual orientation concealment are correlates of physical IPV perpetration [53]. Stephenson and Finneran [54] found that internalized homophobia, the experience of homophobia, and the experience of racism were positively correlated with the experience and perpetration of IPV among sexual minority men. Minority stress theory maintains that individuals who have marginalized identities, such as sexual minority men and racial or ethnic minorities, experience disproportionately burdensome degrees of stigma, discrimination, and victimization. These distal stressors occur alongside more proximal stressors such as anticipated rejection, shame, and negatively appraised experiences. As a result, sexual minority men are at risk for depression, substance use, and risk behaviors that may put them at risk for HIV [36,37,55]. Syndemics theory suggests that co-occurring psychosocial health conditions such as substance use, mental health problems, and violence are mutually reinforcing among marginalized minority populations [38,39,56]. Combined, the theories provide a framework (Figure 1) to understand IPV, HIV risk, and protective factors among sexual minority men, as well as potential intervention targets.

Figure 1. Theoretical framework. IPV: intimate partner violence; PrEP: pre-exposure prophylaxis; PTSD: posttraumatic stress disorder; STI: sexually transmitted infection.



Although recent literature reveals IPV to be common and to have grave implications for sexual minority men's health, there are critical methodological limitations and gaps in knowledge. Of the limited studies of IPV among sexual minority men, heterogeneous definitions and measures of IPV have led to unreliable and widely varied prevalence estimates [11,57]. Few studies have assessed psychological or emotional forms of abuse. Researchers have tended to use modified IPV measures developed for women without formal assessment of their appropriateness and psychometric characteristics among men or sexual minority men more specifically [11]. For bisexual sexual minority men, studies have poorly differentiated violence perpetrated by female partners versus male partners [58]. Recognizing that the IPV measure used in many studies, the Conflict Tactics Scale, was never validated for use with sexual minority men, Stephenson and Finneran [59] developed and validated a new scale, the IPV–Gay and Bisexual Men scale, to capture IPV, as experienced by men in same-sex relationships, in a large sexual minority men sample, which assesses IPV victimization and perpetration [60].

Very few studies have examined IPV perpetration among sexual minority men; most have focused on the receipt of IPV [11]. Little research has assessed mutually enacted or reciprocal IPV and associations with HIV risk and prevention outcomes among sexual minority men. Studies have neglected to differentiate IPV-like behaviors (eg, physical fights) that may in fact be self-defense. In addition, the preponderance of cross-sectional data (there are no published longitudinal studies of IPV among sexual minority men) and use of inconsistent recall periods (eg, 3 months to lifetime) greatly limit causal inferences about factors contributing to IPV and how IPV influences HIV risk behaviors.

These shortcomings have hampered the field's basic understanding of the etiology, chronicity, severity, and escalation of IPV among sexual minority men, with consideration of the multiple forms of violence that exist (physical, sexual, and psychological). Together, this presents a knowledge gap regarding the 3 multidimensional aspects of IPV among sexual minority men (forms of violence, directionality of victimization, and frequency) and longitudinal trends among individuals or dyads. These 3 aspects are critical to intervention development.

Little is known about the mechanisms underlying the associations between IPV and the HIV prevention continuum, which undermines our ability to develop evidence-based interventions. Few studies have delved into the experiences and correlates of IPV for male-male couples. Previous, limited research suggests that stressors and triggers commonly acknowledged in the literature regarding heterosexual couples and IPV are also relevant to male-male couples (eg, substance use, jealousy, and financial stress) [58,61,62]. In addition to these, there are potentially distinct correlates among sexual minority men; for example, Finneran and Stephenson [58] found that these included discordance in HIV status, sexual disagreements (eg, positioning), a lack of sexual orientation outness, and competition to be the "alpha male" in a male-male relationship. Similarly, in their analysis of data from 403 sexual minority men in Atlanta, Georgia, United States, with main partners, Stephenson et al [63] found that IPV was less common among men with social networks that contained more gay-identified friends, highlighting the potential role of social support and peer modeling of healthy same-sex relationships. IPV in male dyads, while influenced by factors that are common to dyads of all genders and all types of couples, is shaped by factors specifically related to sexual orientation and the experience of being in a same-sex relationship.

Objectives

The overall aim of the proposed study is to provide new knowledge of how perpetration and receipt of various forms of IPV (eg, physical, sexual, and psychological, as well as in the context of steady or casual intimate relationships) contribute to HIV risk, sexually transmitted infections (STIs), and HIV PrEP use among sexual minority men in the United States. Longitudinal research must unpack the global negative association of IPV with HIV risk, as well as how specific types of IPV may be associated with HIV risk and HIV prevention continuum engagement. This research is critical to the development of appropriate and effective HIV and IPV interventions for sexual minority men.

Methods

Study Design

This study represents a collaboration between researchers and staff at the San Diego State University, the University of Michigan, and the RAND Corporation. All survey assessments will be programmed and administered by the RAND Survey Research Group (SRG). Phase 1 research activities involved formative qualitative interviews with 23 sexual minority men who reported experienced or perpetrated IPV during the 12 months before the interviews and an additional 10 interviews with key stakeholders and providers of IPV-related services to sexual minority men to inform the subsequent cohort study to be completed in phase 2.

Phase 1 Qualitative Data Collection

In phase 1, we conducted formative, in-depth interviews with 23 racially and ethnically diverse sexual minority men experiencing or perpetrating IPV in the past 12 months and 10 key stakeholders with experience providing services to sexual minority men experiencing or perpetrating IPV. The general purpose of these interviews was to inform the selection of measures and the development of additional questions for the phase 2 surveys and also inform methods and materials to be used for participant recruitment. To recruit a diverse sample of sexual minority men in terms of age and racial or ethnic identity, we used a combination of recruitment sources. We received direct referrals for participation from clinicians working directly with sexual minority men as part of an IPV prevention program for sexual and gender minorities. We also advertised the study through the social media page of a large urban lesbian, gay, bisexual, transgender, and queer service provider and by passing out flyers for the study in community spaces that sexual minority men were known to frequently visit (eg, gay bars, stores, and events). All phase 1 study activities took place in Los Angeles.

Interviews were conducted via video teleconference (through Zoom videoconferencing; Zoom Video Communications, Inc) with sexual minority men and focused on examining how participants' lived experiences of IPV, both victimization and perpetration, may have directly or indirectly influenced their risk for HIV and STIs, their engagement in HIV testing, and their use of PrEP among other sexual health behaviors. For the stakeholder interviews, we purposely recruited participants from a wide range of professional roles interacting with and serving sexual minority men experiencing or perpetrating IPV, including counselors and program directors from an IPV-focused program, as well as additional mental and sexual health providers who work with sexual and gender minorities who have experienced IPV. Interviews with key stakeholders focused on the experiences of IPV victimization and perpetration that may be unique to sexual minority men, as well as any ways that they have noticed IPV affecting the sexual health of the sexual minority men they were working with. Interview probes specifically assessed for any relationships noticed between IPV and HIV and STI risks or engagement in prevention behaviors, including HIV and STI testing, PrEP uptake, and PrEP persistence, and elicited suggestions for what may be beneficial for future IPV and HIV prevention interventions focused on sexual minority men. Providers were also asked to provide feedback on the proposed recruitment methods and materials to be used in the recruitment of sexual minority men in the cohort study. All interviews were audio recorded and transcribed verbatim with identifying information removed to prepare for analysis. The phase 1 qualitative data analysis plan and how the data are being used to inform phase 2 study activities are described in the *Data Analysis Plan* section.

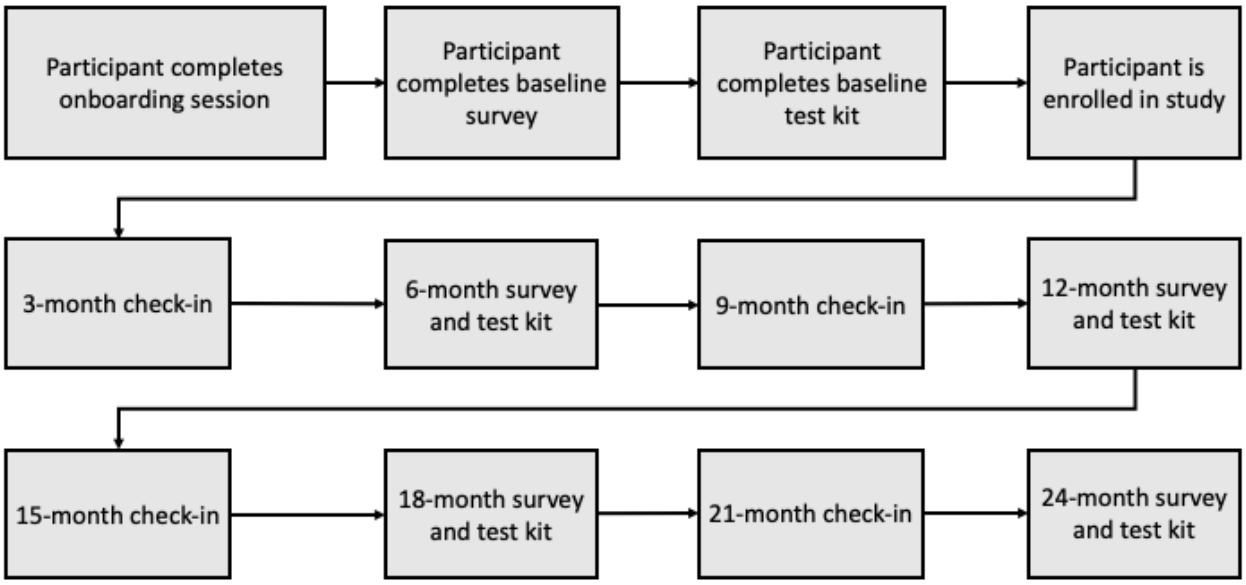
Phase 2 Longitudinal Cohort Data Collection

Each of the 500 participants who enroll in the prospective cohort study will be followed for 24 months. Each laboratory-confirmed HIV-negative cisgender sexual minority men participant will need to report being in a relationship with another cisgender sexual minority man for a minimum of 3 months at baseline and will also need to report residing in one of the Centers for Disease Control and Prevention (CDC)–identified Ending the HIV Epidemic (EHE) jurisdictions across the United States to be eligible for participation. Participants will be recruited through web-based advertising from across all the CDC-identified EHE jurisdictions. Figure 2 reflects the flow of each phase 2 study activity.

Participants will be followed for 24 months, with full study assessments at 0, 6, 12, 18, and 24 months and mini "check-in" assessments at 3, 9, 15, and 21 months to assess for changes in key study outcomes (IPV and engagement in HIV prevention). Participants will also submit self-collected dried blood spot (DBS) samples at 0, 6, 12, 18, and 24 months to test for the use of PrEP and for HIV seroconversion through mailed home test kits. Participants will also submit self-collected urine samples and self-collected rectal and pharyngeal swabs for the culture of gonorrhea and chlamydia at 0, 12, and 24 months through the same mailed home test kits. At each assessment, participants will receive up to 3 reminders based on their preference (either email or SMS text message, provided participants have consented to both) containing a link to the baseline survey at regular (eg, weekly) intervals during the survey window period. We currently plan to use a 28-day window but may expand or contract this window based on real-world completion rates.

This is a nonintervention cohort study. We will enroll 500 sexual minority men, allowing for 20% attrition, for a final sample of 400 sexual minority men at month 24. The eligibility criteria are listed in Textbox 1.

Figure 2. Phase 2 study flow diagram.



Textbox 1. Cohort study eligibility criteria.

Inclusion criteria

- Assigned male sex at birth and currently identifying as man (cisgender male)
- Aged 18 to 45 years
- Reporting currently being in a relationship with a cisgender man lasting at least 3 months; a relationship is defined as "Do you have a primary male partner, that is, someone you feel emotionally, romantically committed to above others?"
- Residing in one of the Centers for Disease Control and Prevention Ending the Epidemic priority jurisdictions
- Able to provide at least two means of contact for follow-up
- Not currently enrolled in an HIV prevention study
- Having self-reported HIV-negative serostatus at baseline (status confirmed via home test kit mailed to laboratory)
- We may stratify eligibility as needed to ensure that at least 60% of participants report past-year intimate partner violence at baseline
- We will stratify as needed to ensure at least 35% of the sample identifies as Black or African American and at least 35% identifies as Hispanic or Latinx

Exclusion criteria

- Not assigned male sex at birth
- Aged <18 years or >45 years at enrollment
- Partnered <3 months or currently unpartnered
- Living outside of the Centers for Disease Control and Prevention Ending the Epidemic priority jurisdictions
- Self-reporting HIV-positive status or is laboratory determined to be HIV positive at baseline
- Expressing unwillingness to complete regular surveys during informed consent
- Expressing unwillingness to provide biospecimens with home testing kits during informed consent
- Expressing unwillingness to provide partner contact information (to allow us to screen for dyads)
- Individual's romantic partner is already enrolled in the study (we will not enroll dyads)

Recruitment

Investigators and research staff from San Diego State University and the University of Michigan will be responsible for all recruitment activities. The study will enroll participants who reside in one of the CDC-defined EHE priority jurisdictions. The "Ending the HIV Epidemic: A Plan for America" was launched by the US Department of Health and Human Services to reduce new HIV infections by 90% by 2030 by leveraging critical scientific prevention strategies in specified high-incident geographic locations [64]. The proposed activities will recruit participants from the counties, territories, and states included

in the EHE plan. To recruit a sample from the CDC-identified EHE jurisdictions, we will use paid advertising on social media and dating or hook-up apps targeted to end users in the specified EHE locations (Textbox 2).

Figure 3 illustrates 2 sample advertisements for the study. We will use a combination of advertisements on the social networking websites Facebook and Instagram, as well as on mobile gay dating or hook-up apps (eg, Scruff, BarebackRT, Jack'd, and Grindr) to promote the study and recruit study participants. Web-based advertisements will show a variety of institutional review board–approved visual representations of sexual minority men across a range of races or ethnicities or will just feature institutional review board–approved call-to-action text and the study logo. Recruitment materials will highlight the eligibility criteria for currently being in a relationship and will state that this is a study focused on men's health and relationships. Importantly, recruitment materials will not mention IPV for participant confidentiality and safety. The websites or apps we recruit from will not have access to the screener data.

Advertisements will be targeted at adult (aged 18-45 years) sexual minority men in the EHE jurisdictions. We will be using the social media platforms Facebook and Instagram, as well as the sexual networking apps mentioned above. Men with partners may have relationship agreements that allow for outside sex partners, hence, the decision to enroll through sex-seeking apps.

Men who click on the web-based or app-based advertisements will be shown a brief introduction script that describes the study. They will then be directed to a consent form (to be screened for eligibility) and complete a short demographic and behavioral eligibility survey form. Screening data will be accessible to study staff only.

Participants who are eligible based on the screener survey will be contacted by a study research coordinator to schedule their 30-minute virtual onboarding orientation session, during which the research coordinator will provide a thorough overview of all research activities and timelines, go over the biological specimen collection instructions, review an informed consent form, and collect the participant's consent (through electronic signature) to participate in the cohort study.

Textbox 2. Centers for Disease Control and Prevention–identified Ending the HIV Epidemic states, counties, and territories.

States

- Alabama, Arkansas, Kentucky, Mississippi, Missouri, Oklahoma, and South Carolina

Counties

- [Arizona] Maricopa; [California] Alameda, Los Angeles, Orange, Riverside, Sacramento, San Bernardino, San Diego, and San Francisco; [Florida] Broward, Duval, Hillsborough, Miami-Dade, Orange, Palm Beach, and Pinellas; [Georgia] Cobb, DeKalb, Fulton, and Gwinnett; [Illinois] Cook; [Indiana] Marion; [Louisiana] East Baton Rouge Parish and Orleans Parish; [Maryland] Baltimore City, Montgomery, and Prince George's; [Massachusetts] Suffolk; [Michigan] Wayne; [Nevada] Clark; [New Jersey] Essex and Hudson; [New York] the Bronx, Kings, New York, and Queens; [North Carolina] Mecklenburg; [Ohio] Cuyahoga, Franklin, and Hamilton; [Pennsylvania] Philadelphia; [Tennessee] Shelby; [Texas] Bexar, Dallas, Harris, Tarrant, and Travis; and [Washington] King

Territories

- Puerto Rico's San Juan Municipio and Washington DC

Figure 3. Sample cohort study advertisements. STI: sexually transmitted infection.

Baseline Survey

Once a participant has completed the onboarding interview and consented to participate in the cohort study, the research coordinator will complete a study enrollment form to import the participant's contact information and key data elements into the RAND SRG–developed Record Management System, which will then trigger a unique link to the baseline survey (programmed in Forsta) to be sent to the participant's email address. The baseline survey has been informed by the phase 1 qualitative interview data and will include questions from the following domains: demographic characteristics; IPV, including *physical*, *sexual*, *emotional*, *financial*, *monitoring*, *stalking*, and *HIV prevention–specific* forms of IPV; mental health; relationship and partner; sexual behavior and agreements; experiences of stigma and discrimination; structural vulnerabilities; social support; spirituality and religiosity; HIV testing; PrEP uptake; PrEP persistence; STIs; and sexual risk behavior. Baseline measures are presented in Textbox 3.

Participants who do not complete the baseline survey during the survey open window will be removed from the study unless they contact the study team to request more time.

Textbox 3. Baseline survey measures.

Intimate partner violence (IPV)

- Modified IPV–Gay and Bisexual Men scale (62 items assessing IPV among sexual minority men, including physical, sexual, psychological, and monitoring or stalking IPV) [59] and adapted financial control items [65]
- Disclosure of IPV experiences to or by others [66-68] (some questions adapted from the original version)
- Help-seeking behaviors and receipt of IPV services (some questions adapted from the original version)
- IPV victimization stigma and shame [69]
- IPV perpetration stigma and shame [70]
- Perceived prevalence of IPV [66-68] (some questions adapted from the original version)

HIV prevention engagement

- HIV testing [71] (self-report and medical record confirmation)
- Sexually transmitted infections testing and diagnosis [71] (self-report and biomarker)
- Sexual behavior and condomless sex (self-report)
- HIV status (self-report, medical record confirmation, and biomarker)
- Pre-exposure prophylaxis (PrEP) uptake and PrEP persistence (self-report and biomarker)
- Perceived PrEP adherence (self-report)
- Reasons for not using PrEP or stopping PrEP [66-68] (self-report)
- PrEP modality acceptability [72] (self-report)
- Long-acting injectable PrEP acceptability
- PrEP stigma [73] (self-report)
- PrEP use [71]

Demographics

- Age
- Race
- Ethnicity
- Nativity (United States–born)
- Employment status [74]
- Employment precarity [75]
- Financial well-being [76]
- Educational attainment [74]
- Food insecurity [77]
- Sexual orientation [74]
- Housing status and housing instability [78]
- Recent homelessness [79]
- Housing precarity [74]
- Gender identity [75] (planned for 6-month follow-up assessment)

Health status and health care

- Self-rated health [80]
- Insurance coverage [81]
- Physical health care use [82]
- Behavioral health care use and perceived unmet need [83]
- Current health conditions (planned for 6-month follow-up assessment)

Partner and relationship characteristics (reported by index participant)

- Relationship status
- Relationship characteristics (type; duration and history of separations)
- Marital status
- Cohabitation
- Partner demographics (race, ethnicity, gender, sexual orientation, educational attainment, age, and HIV status)
- Financial reliance
- Partner PrEP use or HIV treatment status or viral suppression
- PrEP conversations [66-68] (some questions adapted from the original version)
- Partner support for taking PrEP [66-68] (some questions adapted from the original version)
- Inclusion of other in self [84]
- Sexual agreements (type and adherence)
- Relationship power balance and decision-making [85]
- Communication patterns [86]
- Social support from partner [87]
- Relationship role models (regardless of relationship status)

Early-life and childhood experiences

- Childhood violence and abuse and mistreatment by adults [88] (planned for 6-month follow-up assessment)
- Victimization and bullying [89] (planned for 6-month follow-up assessment)

Social and structural factors

- Incarceration (lifetime and recent) [71]
- Experienced discrimination (racial or ethnic, sexual orientation, gender expression, and other characteristics) [90]
- Perceived neighborhood safety [91]
- Recent exchange or transactional sex [71]

Mental health

- Depressive symptoms [92]
- Loneliness [93] (planned for 6-month follow-up assessment)
- Posttraumatic stress disorder [94]
- Nonsuicidal self-injury [95] (planned for 6-month follow-up assessment)

Substance use and abuse

- Alcohol use [96]
- Illicit and licit substance use [97]

Psychosocial factors

- Internalized homophobia [98,99]
- Gay-related stigma [100]
- Racial and ethnic identity devaluation [101]
- Masculinity ideals and attainment
- Conformity to hegemonic male norms [102]
- Anticipated stigma (global demographics) [103] (some questions adapted from the original version)

Resiliency factors

- Lesbian, gay, bisexual, transgender, and other community affiliation [104]
- Global resiliency traits [105]

- Perceived social support (eg, emotional and instrumental) [87]
- Coping self-efficacy [106]
- Global self-esteem [107] (planned for 6-month follow-up assessment)

Miscellaneous

- Willingness to be contacted for future studies
- Survey satisfaction [108]
- Enrollment in other sexual minority men's health studies

Baseline Biospecimen Sample Collection

After the baseline survey has been completed, the participant's provided mailing information is transferred to Molecular Testing Labs (MTL) through MTL's application programming interface. The RAND SRG will assign a unique order ID to each specimen collection kit to inform MTL to mail the participant the specimen collection kit through US Postal Service Priority Mail. The collection kit will contain instructions and materials for collecting and returning the biospecimen samples. Packaging will be plain and discreet. After the participant has received their kit and collected their sample, they will return the samples using a prepaid mailer. Participants will be given 2 weeks from the date of kit delivery to collect their samples and return them in the mail for processing. They will receive up to 6 reminders through SMS text messages or email. After 4 weeks, participants who have not returned their baseline samples will be designated as having decided to not collect their samples and will be stopped from further study participation. In addition, those who screen HIV positive (at baseline) will not be enrolled in the full cohort study.

Biospecimen Sample Collection Procedures

DBS specimens will be collected to detect the presence of HIV at baseline and 12- and 24-month assessments. DBS specimens will also be used to confirm reported use of PrEP at 0-, 6-, 12-, 18-, and 24-month assessment points when participants self-report taking PrEP (survey). The DBS procedure involves using a lancet to prick one's fingertip, and 3 to 6 drops of blood are applied to each of the 5 circles on a DBS collection paper card. We will also collect self-administered urethral gonorrhea and chlamydia testing at baseline and 12- and 24-month assessment visits through the nucleic acid probe of urine specimens. Participants will provide a urine sample of 30 mL to 50 mL from the initial urine stream in a collection cup.

To complement the urine-based urethral samples, we will also collect self-administered rectal and pharyngeal swabs for gonorrhea and chlamydia testing at baseline and 12- and 24-month assessment visits. Briefly, participants will swab each site using provided collection swabs and place the swabs into transport tubes for processing. All survey and biospecimen procedures will take place according to the schedule presented in Table 1.

Table 1. Schedule of survey and biospecimen collection by time point[a].

Outcome	Baseline- assessment	6-month assessment	12-month assessment	18-month assessment	24-month assessment
Primary					
HIV testing behavior	Survey	Survey	Survey	Survey	Survey
PrEP[b] uptake	Survey+DBS[c]	Survey+DBS	Survey+DBS	Survey+DBS	Survey+DBS
PrEP persistence	Survey+DBS	Survey+DBS	Survey+DBS	Survey+DBS	Survey+DBS
STIs[d] (CT[e] and GC[f])	Survey+culture	Survey	Survey+culture	Survey	Survey+culture
Secondary					
Sexual risk behavior	Survey	Survey	Survey	Survey	Survey
HIV seroconversion	Survey+DBS	Survey	Survey+DBS	Survey	Survey+DBS

[a]Brief assessments of relationship changes, intimate partner violence exposure, and self-reported HIV prevention continuum and STI outcomes at 3, 9, 15, and 21 months (not shown).

[b]PrEP: pre-exposure prophylaxis.

[c]DBS: dried blood spot.

[d]STIs: sexually transmitted infections.

[e]CT: chlamydia.

[f]GC: gonorrhea.

Laboratory Testing and Follow-up

Samples will be tested by MTL for HIV, PrEP, and STIs (gonorrhea and chlamydia). In the event that MTL finds the quality of the sample to be insufficient, participants will be contacted by their preferred method of communication (either email or SMS text message) by the study team to request a second sample collection. MTL will mail a second kit, and the participant will re-collect the sample and mail it back to MTL.

Participants who have a reactive HIV or STI test will be contacted by study staff to let them know that they have received a preliminary positive test result and will be told that they need to schedule a visit with a local provider to confirm the result and be linked to care for treatment. Participants will be instructed that the laboratory test is for research purposes and that they should seek confirmation from their physician. Study staff will offer to help participants locate a local provider or clinic should they request assistance.

Study Task Reminders and Participant Retention

The study will use multiple platforms to maintain the participant database, program the web surveys, and circulate email and SMS text message communications. Participant information, survey response data, test results, and other administrative data are maintained in a secure, encrypted database. Most email-based and SMS text message–based study communications (eg, survey notifications, reminders to complete a survey, and reminders to return a biospecimen kit) are automated, using scheduling criteria and prewritten templates that use a conversational tone and accessible reading level. For participants in danger of missing a study task (ie, within 7 days of a task deadline, such as a survey window closing), study staff will contact participants individually by telephone, email, or SMS text message.

Compensation

Participants will have the potential to earn up to US $340 as remuneration (in the form of e-gift certificates) for participation in this study. Each survey time point includes US $25 as remuneration, each returned biospecimen kit includes US $25 as remuneration, and check-in surveys include US $10 as remuneration. Participants who complete all primary study tasks (full survey time points and biospecimen kits) will also receive a US $50 bonus at the conclusion of their follow-up.

Data Analysis Plan

The analyses described in the following sections describe the analyses for phase 1 and our preliminary analysis plan for phase 2, specified in advance. Although the focal outcomes will remain the same, the specific analytic methods may change based on data (eg, feasibility of a proposed model, given the data distributions), evolution of the research questions (eg, based on advances in the field during the 2-3 years of data collection), and statistician input. We may also pursue additional analyses on secondary outcomes of interest.

Phase 1 Qualitative Data Analysis

To inform the selection of measures, development of any additional items, and inform the development of recruitment materials and methods for phase 2 of the study, members of the study team reviewed and discussed analytic memos written by interviewers after each interview and memos written by coders upon reading the verbatim transcripts [109,110]. This resulted in the identification of preliminary thematic patterns that informed the baseline survey so that the phase 2 cohort study was able to launch in August 2022.

In June 2022, we began the process of rigorously confirming the preliminary findings that informed the baseline survey using an applied thematic analysis approach to identify all key patterns across our 2 sources of qualitative data [111]. This process will lead to the publication of our qualitative findings and will further inform future survey assessments (eg, 6-month assessments and 12-month assessments). Data (transcripts) are being organized and coded in NVivo qualitative data analysis software (QSR International) [112] using a codebook of deductive (ie, a priori, codes), as well as inductive codes grounded in the data. Coders tested iterations of the codebook on a series of transcripts over time to identify needed updates (ie, adding new codes, deleting redundant codes, and refining code definitions). To formally assess intercoder agreement, the coders double-coded >10% of the transcripts, discussing coding discrepancies and updating the codebook in real time. After multiple rounds of intercoder agreement assessment (final Cohen κ>0.80, suggesting sufficient reliability in coding), the codebook was finalized, and the coders began independently coding the transcripts [113].

Once all qualitative data have been coded, we will develop code summaries (high-level summaries of excerpts for individual codes), which will be reviewed and discussed by members of the research team with attention to repetition, frequency, salience of ideas, and meaning within context across interviews. Multiple rounds of group-level discussion, rereading of code summaries and specific coded excerpts, visually mapping relationships between key themes and subthemes, and triangulation across the sexual minority men and key stakeholder interviews [114] will inform final theme development [111,115] (Felner, JK, unpublished data, March 2022) and, in turn, the remaining phase 2 study activities.

Phase 2 Quantitative Data Analyses

Phase 2 analyses will examine the robustness of our measures and our sample. First, we will assess the psychometric properties of all measures. Second, Wilcoxon rank sum and chi-square tests will be performed on baseline and follow-up variables to test for differences between dropouts and completers. Statistical adjustments will be used to correct for effects of attrition [116]. Standard multiple imputation techniques [117] could be used to account for missing data, such as imputing covariates using sequential Bayesian additive regression trees (using the R package *sbart*), which is nonparametric and avoids assuming that covariates are related [118]. Before building more elaborate latent curve models (LCMs), we will first explore relationships among our measures using correlations, regressions, and simple structural equation models (SEMs).

In phase 2, we will model multiple developmental trajectories of 5 waves of data using LCMs. We will examine three developmental trajectories: (1) the trajectory of the predictor, IPV; (2) the trajectory of the primary outcomes, HIV prevention continuum engagement and STI diagnoses; and (3) the trajectory

of the secondary outcomes, risky sexual behavior (condomless anal sex) and seroconversion. The predictor trajectory is defined by repeated measures of IPV. As LCM allows for the estimation of multiple trajectories at the same time, we are also modeling a parallel process of HIV prevention continuum engagement. These primary outcomes are based on repeated measures of 3 binary indicators: HIV testing, PrEP uptake, and PrEP persistence. Although engagement in these HIV prevention continuum indicators has been described as discrete steps [28], the approach we propose is innovative as we will build measurement models based on these 3 indicators. From a factor analytic perspective, these are dichotomous indicators used to define a single latent HIV prevention continuum factor (*f*). With 5 waves of data, the repeated measures of the same latent variable are represented by *f1* to *f5* in the LCM. The developmental trajectory of HIV prevention continuum engagement will then be based on the latent variables *f1* to *f5*. In a similar fashion, we can model the relationship between the predictor trajectory and the trajectory for STI diagnoses (primary outcome) and condomless anal sex and seroconversion (secondary outcomes).

We will explore trajectory patterns to assess whether growth is linear or nonlinear. If it is nonlinear, we will explore quadratic effects or piecewise developmental patterns. To our knowledge, modeling the developmental trajectory of a latent HIV prevention continuum factor using multiple indicators is novel. Furthermore, we have multiple parallel developmental processes (IPV, prevention continuum, STIs, condomless sex, and seroconversion) in the same growth model.

We hypothesize that resilience factors (eg, coping skills, greater social support, and positive role models) will mediate (or moderate) the relationship between IPV and HIV risk and strengthen the association between IPV and HIV prevention continuum outcomes. We also hypothesize mediating effects of potential risk factors (eg, substance use, poorer mental health, and incarceration, as well as partner- and relationship-level factors). Such potential mediating effects can easily be incorporated into SEMs. Given the complicated LCM setup with multiple developmental trajectories, we anticipate challenges in adding moderators directly into the growth model.

A way of overcoming these challenges is to use multiple group analysis. By comparing relationships between the predictor trajectory and the outcomes trajectories across different groups, multiple group analysis allows us to (1) test different assumptions about group equality [119] and (2) build appropriate models for different, heterogeneous subpopulations. Given the diversity of life experiences in our sample, the relationships between IPV and HIV prevention continuum engagement may vary based on these diverse behaviors and psychosocial states. Moreover, our inclusion of resilience lends itself to the development of strength-based interventions where the buffering effect of resilience is evidenced in sexual minority men, according to Storholm et al [120]. Various time-varying and invariant covariates can also be added to the LCM to explore the effects of the characteristics of sexual minority men, their intimate partners, and their relationship dynamics. We will use Mplus (Muthén and Muthén) for these analyses [121]. We will test different moderating and mediating effects, focusing on the different risk and protective factors, while controlling for demographic and socioeconomic characteristics. Alternative models will be compared using a set of model fit indices, including root mean square error of approximation, Tucker-Lewis index, and various fit statistics, as described by Jöreskog and Sörbom [122].

Ethics Approval

All study protocols and procedures have been approved by the San Diego State University Institutional Review Board (phase 1 protocol number HS-2021-0054 and phase 2 protocol number HS-2022-0094). All procedures are in accordance with the ethical standards of the institutional and national research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was or will be obtained from all participants included in the study.

Data Sharing Plan

This project does not exceed the US $500,000 cap set by the National Institutes of Health in any project year. However, based on the importance of the data, we encourage collaborations with interested investigators. Data will be made publicly available through publication in peer-reviewed journals, public seminars, and invited lectures and conference presentations. After 2 years of publication of the main findings of the study, we will consult with the San Diego State University's Human Research Protection Program about how to securely make data available in the form of an electronic database for researchers who successfully complete a registration process. Any shared data will be deidentified and will not contain any direct or indirect identifiers. As part of the registration process, users must complete a data sharing agreement that outlines the conditions of use governing access to the public release data, including restrictions against attempting to identify study participants, destruction of the data after analyses are completed, reporting responsibilities, restrictions on redistribution of the data to third parties, and proper acknowledgment of the data resource. The data sharing agreement will include a commitment to using the data only for research purposes, a commitment to securing the data using appropriate computer technology, and a commitment to destroying or returning the data after analyses are completed. Users must submit brief proposals regarding the intended use of the data; the study team will determine the scientific soundness of the proposal as part of the decision to allow the researchers to access the public use data set. Users must be monitored by an approved human subjects board.

Results

This study was funded in March 2021 by the National Institute of Mental Health (R01MH126762). The study was launched in May 2021, and phase 1 interviews began in December 2021 and concluded in March 2022. Rapid analysis of the qualitative interviews took place between March 2022 and June 2022. Phase 2 recruitment of the full cohort began in August 2022 and is planned to continue through February 2024.

Discussion

Principal Findings

This study seeks to conduct a multidimensional, longitudinal assessment of IPV and HIV prevention continuum outcomes among sexual minority men. Unlike most studies that have only focused on physical contact forms of abuse, we will also assess forms of IPV that involve coercive control and psychological abuse. We hypothesize that IPV will have a deleterious overall impact on HIV prevention continuum engagement and that the pathways between IPV and HIV prevention continuum engagement will be mediated by individual (eg, internalized homophobia, mental health, and substance use), interpersonal (eg, social support, relationship characteristics, and gender norms), and structural-level (eg, poverty, incarceration, health care access, and neighborhood violence) factors. Our measurement of IPV will include measurement of both the receipt and perpetration of IPV among sexual minority men, unlike prior research that has largely neglected IPV perpetration. Our assessment of the chronicity of IPV is also novel, as is the type of relationships in which it occurs. Most of the research has assessed either lifetime or recent (eg, past-year) experiences of IPV, which precludes analysis of chronicity, spacing of episodes, or escalation or waning of IPV.

We will use a longitudinal design for temporality to better understand the potential mechanisms between IPV and HIV risk and protective factors. We will use SEM to assess the intersectionality of multiple syndemic factors made possible with methods that we have refined over several previous studies of sexual minority men. This will allow us to explore the unique and common effects of different kinds of stigmas and supportive factors on HIV risk and HIV prevention outcomes. A longitudinal approach allows us to assess temporality with regard to associations between IPV and HIV prevention continuum engagement and heterogeneous phenotypes therein; for example, we will be able to differentiate sexual minority men who experience simultaneous IPV and poor HIV prevention continuum engagement from men whose IPV experiences precede worsening HIV prevention continuum engagement or HIV risk behaviors. We will also be able to assess whether HIV prevention continuum engagement is associated with waning IPV over time, perhaps as sexual minority men avail themselves of wraparound services linked to HIV prevention continuum services. Longitudinal assessment also allows us to assess how mediators and moderators such as mental health problems, psychosocial factors, and resiliency factors change over time in this context. Although a longitudinal design is critical, it is also necessary to have a large enough sample (for statistical power) and a long enough follow-up period to adequately examine the complexity of the dynamics in play with IPV and HIV risk among sexual minority men in multiple types of relationships, all of which necessitates and is accomplished by the proposed research.

In addition, we will examine resiliencies and risk factors to better understand underlying mechanisms and identify modifiable intervention targets. Most studies have focused on risk factors. Much less is known regarding the vitality of protective factors in the health of sexual minority men. To design IPV and HIV prevention interventions for sexual minority men, it is vital that we also examine protective factors. Our study may be the first to elucidate the potential effects of resiliencies such as coping skills, social support, and sexual minority pride in the constellation of risk factors between IPV and poor HIV prevention continuum engagement. Understanding the important role of these protective factors is vital to the development of innovative strengths-based interventions.

Limitations and Strengths

A handful of limitations could affect this study and are important to acknowledge. First, documentation of IPV, both in terms of victimization and perpetration, will rely on self-report. As such, there may be underreporting of perpetration because of fear of possible legal consequences. There may also be underreporting of victimization because of potentially socially desirable responding and social norms that shame male survivors of IPV. To minimize these concerns, in-depth interviews will provide insights into how best to assess both victimization and perpetration in the context of same-sex male relationships. In addition, by conducting a prospective investigation, we will be uniquely positioned to examine how current experiences of IPV influence gaps in HIV prevention continuum outcomes prospectively. Second, the measurement of perceived social support, a potential buffer between IPV and IPV-associated HIV prevention continuum gaps, is based on the egocentric assessment of the degree to which individuals perceive receiving social support from a range of social network members (eg, peers, family members, and coworkers). However, obtaining egocentric-level data on multiple forms of perceived social support using a validated measure is a common and widely accepted approach.

The proposed study will be designed and implemented with a high degree of scientific rigor and has the potential for significant public health impact. First, we have a core team with expertise in the design and conduct of prospective cohort studies in IPV, HIV risk, and HIV prevention continuum outcomes among sexual minority men, as well as in advanced statistical analyses. Second, we will measure exposures, moderators, and outcomes at multiple time points in this prospective cohort study. Third, we will be conducting this study in the EHE-identified HIV high-incidence jurisdictions.

Dissemination Plan

The research team will collaborate with key community stakeholders to review and validate the data and findings and make recommendations for intervention development or adaptation. We will also review interventions from the CDC compendium of evidence-based interventions to examine where content that addresses IPV may be integrated. The aim is not necessarily to develop an intervention in the time frame of this study but rather to use the data to provide strong evidence for the forms, types, and content of new interventions or adaptations to existing interventions. It is likely that this planning phase will lead to the development of an intervention that we will test in the next phase of our ongoing research program. Dissemination of findings will take place primarily through the publication of scientific manuscripts and stakeholder-oriented

research briefs; professional conference presentations; and community-focused meetings and presentations with stakeholder groups at local, regional, state, and national levels. We will maximize the impact of our dissemination efforts through best-practice approaches such as framing the presentation of results in ways that highlight the relevance to various stakeholder audiences and by working with trusted intermediary organizations.

Conclusions

This longitudinal cohort study will provide the data needed to better understand the direct and indirect ways in which IPV affects HIV risk and prevention behaviors. With the goal of providing concrete recommendations for intervention development, we believe that this is the first study to provide the needed science to develop and promote interventions to reduce the harms associated with both IPV and HIV risk or HIV prevention continuum outcomes. These findings will fill a critical gap in our efforts to reduce HIV-related disparities as part of the National Institutes of Health Strategic Plan for HIV and HIV-Related Research.

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Conflicts of Interest

None declared.

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Abbreviations

CDC: Centers for Disease Control and Prevention
DBS: dried blood spot
EHE: Ending the HIV Epidemic
IPV: intimate partner violence
LCM: latent curve model
MTL: Molecular Testing Labs
PrEP: pre-exposure prophylaxis
SEM: structural equation model
SRG: Survey Research Group
STI: sexually transmitted infection

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Protocol

Relationships and Sex Education Outcomes for Students With Intellectual Disability: Protocol for the Development of a Core Outcome Set

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Abstract

Background: People with intellectual disability are twice as likely to experience sexual abuse, unintended pregnancies, and sexually transmitted diseases as people in the general population. Despite this, very little is known about how to deliver relationships and sex education effectively to this vulnerable population, how to measure the impact of its delivery in schools, and what stakeholders perceive as important outcomes of this education.

Objective: To address these urgent issues, this study aims to develop a stakeholder consensus–based core outcome set of relationships and sex education for use in research and educational settings with students with intellectual disability.

Methods: The study will use a 2-stage mixed methods design. The first stage will involve a systematic review of relationships and sex education outcomes reported in the literature, followed by qualitative exploration with caregivers, teachers and school staff, policy makers, and researchers to investigate their perspectives of meaningful outcomes of this education. Students with intellectual disability will be enabled to take part to express their views on outcomes of importance to them. The second stage will use findings from stage 1 in a 2-round web-based Delphi study with caregivers, teachers and school staff, policy makers, and researchers to develop consensus on proposed outcomes for the evaluation of relationships and sex education with this population.

Results: As of September 2022, we have completed a systematic review and recruited 56 stakeholders (n=53, 95%, adults and n=3, 5%, students with intellectual disability) for the first stage of the study. We are still recruiting students with intellectual disability. Data analysis has not started yet. Recruitment for the second stage will commence in November 2022. We expect to complete the study by October 2023 and publish the results by the end of 2024.

Conclusions: The development of a core outcome set of relationships and sex education will provide a significant first step to assist the implementation, delivery, evaluation, and sustainability of relationships and sex education for students with intellectual disability. Key audiences will be teachers, researchers, policy makers, and decision makers.

Trial Registration: Core Outcome Measures in Effectiveness Trials 1787; https://www.comet-initiative.org/Studies/Details/1787

International Registered Report Identifier (IRRID): PRR1-10.2196/39921

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KEYWORDS

core outcome set; relationships and sex education; intellectual disability; students

Introduction

Background

Approximately 2% of the children in the world have intellectual disability (ID), which is defined as a lifelong neurodevelopmental condition characterized by limitations in cognitive and adaptive skills [1,2]. Children and young people with ID are among the most disadvantaged and vulnerable people in our society [3,4]. They have between 4 and 6 times higher risk of being sexually abused than children without ID [3-5]. Young people with ID are also 2 times more likely to practice unsafe sex and experience sexually transmitted diseases and unintended pregnancies than their peers from the general population matched by age, sex, and exposure to other sociodemographic variables [6]. Although young people with ID are more likely to be experience bullying, some young people with ID can also be bullying perpetrators, possibly because of lack of social skills, difficulties with emotion regulation, or inability to recognize bullying behaviors and other people's verbal and nonverbal communication cues [7,8]. One potential route to reduce these higher risks is through effective relationships and sex education (RSE) delivered in schools. Despite its importance, little is known about how to deliver RSE effectively to this population; what students with ID should achieve in, and from, RSE lessons; and what students with ID, their caregivers, and teachers perceive as important outcomes of this education.

Evidence from systematic reviews carried out on RSE content, delivery, and effectiveness for people with ID of any age indicates that existing RSE programs do not have clear outcome goals, and the outcomes measured lack consistency [9-12]. Heterogeneity in RSE outcome reporting makes it challenging to compare the effectiveness of RSE across studies, and this affects the development of appropriate evidence-based RSE for this vulnerable population. Furthermore, these reviews highlight that people with ID are not involved in the development of RSE programs, and thus the content delivered and outcomes measured do not reflect their views [9-12]. This might possibly lead to ineffective or even harmful RSE programs delivered to students with ID—for example, if there are unexpected adverse outcomes that could have been anticipated by working with them—and research waste.

The development of a core outcome set (COS) could help to address these limitations in the current evidence base. The COS involves identifying *what* to measure and includes a consensus of stakeholders' opinions on what could constitute meaningful outcomes [13]. The COS provides a minimum standard of outcomes that all randomized controlled trials, evaluation studies, and practice-based audits should measure and report within a specific health or social care area [14]. This standardization of outcomes improves research utility by involving stakeholders' perspectives as well as reducing inconsistency, reporting bias (when only preferred outcomes are reported instead of all outcomes assessed), and research waste [14]. The Core Outcome Measures in Effectiveness Trials (COMET) Initiative has developed a standardized methodology that has been successfully used to develop a COS across a wide range of health and social care areas [14]. However, there is no published COS of RSE for students with ID. The development of such a COS will not only help to demonstrate different perspectives and develop much needed consensus in this sensitive area but also provide, for the first time, a standardized set of outcomes to be used in research and educational practice to assess RSE delivery and help to design and develop the curriculum or evaluation studies.

Aim and Objectives

The aim of this project is to develop a stakeholder consensus–based COS of RSE for students with ID. The specific objectives of the study are as follows:

- Develop a comprehensive list of potential outcomes through (1) existing evidence on RSE outcomes for students with ID reported in the literature and (2) data collected from key stakeholders, including students with ID, caregivers, teachers and school staff, policy makers, and expert researchers.
- Finalize a COS using a structured consensus-based approach.

Methods

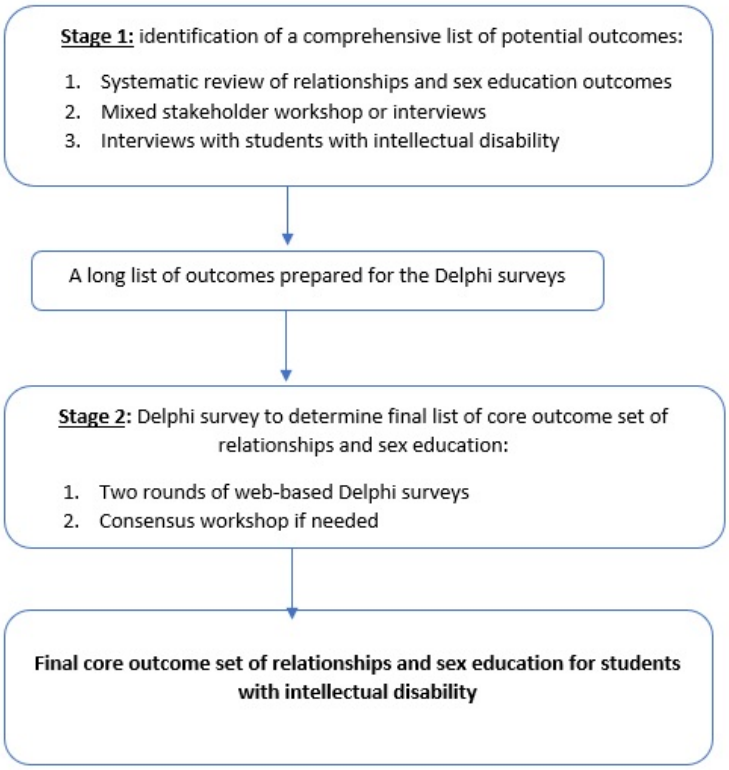
Ethics Approval

Ethics approval for the study was received from the research ethics committee of the Institute of Education, University College London (REC 1565).

Design

The COMET handbook for COS development [14] will guide the methodology of this study. The study protocol has been written following the Core Outcome Set–Standardized Protocol Items guidelines for reporting protocols of COS development [15]. The study will use a 2-stage mixed methods design that involves a systematic review, stakeholders' workshops and interviews, a Delphi web-based survey, and, if needed, a subsequent consensus workshop (Figure 1).

Figure 1. Study design.



Scope of the COS

Population

The COS of RSE for students with ID will be developed for use in English educational settings and research evaluations primarily in Western countries, with a potential extension to non-Western countries after adaptations that reflect their cultural, socioeconomic, and policy characteristics.

Our target population is students aged 5 to 25 years with any level of ID (mild, moderate, severe, or profound) and verbal ability (verbal, minimally verbal, or nonverbal). Children with ID are a heterogeneous group with a wide range of abilities and additional needs. ID is a neurodevelopmental condition characterized by significant limitations in intellectual functioning and adaptive skills present from the developmental period (0-18 years) [2]. Intellectual functioning involves activities such as learning and abstract thinking. Adaptive skills refer to conceptual, social, and practical skills used in everyday activities such as socializing or feeding oneself. ID is diagnosed by a score of 2 SDs below the general population mean on standardized tests of cognitive skills—for example, IQ <70—*and* adaptive skills score <70 [2]. ID can be classified into 4 levels depending on severity: mild, moderate, severe, and profound. Children with mild ID may have subtle developmental delays (eg, they may have school learning problems and delays in communication abilities), whereas children with severe or profound ID will have severe developmental delays (eg, they may be nonverbal and require significant support with basic needs such as using a toilet or feeding) [2]. ID can be caused by genetic and chromosomal abnormalities (eg, Down syndrome and Fragile X syndrome, which can be associated with having more severe ID) or problems during pregnancy and birth (eg, infection or maternal substance abuse) [2]. Many children with ID also have co-occurring conditions such as autism and sensory processing difficulties as well as mental and physical health problems [16,17]. Therefore, students with any level of ID and co-occurring conditions will be eligible to take part in the study, ensuring that this COS is applicable across the ID spectrum.

In England, the term *intellectual disability* is synonymous with *learning disability or difficulty*, which is a term that some study participants might recognize more easily. Our target population will include students who have a formal ID diagnosis as well as students whose ID is administratively defined (eg, those who receive special education or other services because they have ID). The age range was selected to include all school students with ID who are receiving RSE. In England, RSE was made compulsory in all schools in 2020 [18]. RSE begins in primary schools (when students are aged 5-11 years) and continues through to secondary schools (when students are aged 11-16 years) [18]. However, the upper age limit of 25 years was selected because some students with ID in England remain in school education until the age of 25 years [19].

Intervention

Our target intervention is RSE that is a curriculum delivered directly to students in schools or other educational settings. Different terms across countries globally are used to refer to RSE (eg, *sex education* or *reproductive health education* or *life skills education*) [20]. RSE terminology, delivery, content, and policy also differ across the United Kingdom. We use *RSE* because it is the preferred term in England, the setting of the study. The statutory guidance on RSE delivery in England indicates that students in primary schools must receive education on topics regarding positive and unhealthy relationships, and in secondary schools, they must receive information on sexual

relationships, sexuality, and safeguarding (eg, exploitation and female genital mutilation) [19]. The RSE content delivered to students with ID can be adapted to their developmental levels [19].

RSE can be delivered as a stand-alone subject or integrated into other subjects [21]; for example, in England, RSE is usually delivered within the wider curriculum of personal, social, health, and economic education [21]. RSE can be delivered by teachers, school-based nurses, or external specialists [22]. It is often delivered to a whole classroom, but for students with ID, RSE may be provided in small groups or on a one-to-one basis in social care settings (eg, at day centers or group homes) and at students' homes (eg, after-school activities delivered by caregivers at home) in addition to being delivered at schools [23].

Stakeholders and Setting

We will involve 5 groups of stakeholders in the development of this COS: (1) students with ID; (2) caregivers of students with ID (eg, parents or other unpaid individuals who are responsible for providing care to the students); (3) teachers and school staff who are involved in the delivery of RSE to this population; (4) policy makers such as people from government agencies, parliamentary committees, third sector organizations, and charities that support families of children with ID and specialize in special education policy in England, as well as those who were also involved in formulating the RSE policy in England; and (5) researchers who have authored key papers on RSE for people with ID or specialize in research on the sexuality and relationships of people with ID or education for people with ID. Students with ID and their caregivers as well as teachers and school staff will be approached via established mainstream and special school networks that serve students with ID in England. We will aim to recruit stakeholders from mainstream and special schools because both settings serve students with ID in England, which might allow us to capture a variety of opinions on important outcomes. Expert researchers (from England and internationally) will be identified from the systematic review (refer to the Systematic Review section), internet searches, and snowball recruitment. Policy makers will be identified through special education charities and policy networks in England, internet searches, and snowball sampling.

We will recruit 10 to 15 participants in each of the four stakeholder groups (caregivers, teachers and school staff, researchers, and policy makers) for the data collection from adults using 2 data collection methods (ie, for both the workshop and interviews combined) and 10 to 15 students with ID for the interviews. For the Delphi web-based survey, we will recruit 10 to 15 participants in each of the 4 stakeholder groups (caregivers, teachers and school staff, researchers, and policy makers). There is no *gold standard* number of stakeholders to involve in the COS development and Delphi surveys [13]. However, consensus approaches with 15 participants are considered to be effective [24]. We will pilot study materials to check clarity and ambiguity with stakeholders who are not taking part in the study where possible.

Stage 1: Identifying a Comprehensive List of Potential Outcomes

In stage 1, potential outcomes will be identified through a systematic review, a mixed stakeholder workshop, interviews with adults, and interviews with students with ID.

Systematic Review

The review protocol was registered prospectively with PROSPERO (CRD42021243176), and the findings were published elsewhere [25] before our primary data collection. The objectives of the review were to (1) identify outcomes of RSE for students with ID reported in existing studies, (2) identify the measurement instruments used to measure RSE outcomes, and (3) evaluate the identified instruments' measurement properties (validity, reliability, and responsiveness) using the Consensus - Based Standards for the Selection of Health Measurement Instruments criteria [26] that were developed for evaluating the quality of COS measurement instruments.

The search consisted of 2 parts. The first part of the search was carried out in March 2021 to identify all RSE outcomes and their measurement instruments published in any language using 9 electronic databases (eg, MEDLINE, Embase, and PsycINFO) and gray sources (eg, ResearchGate and Google Scholar). The second part of the search was carried out in August 2021 to retrieve studies on the identified instruments' measurement properties using the same databases and gray sources as in the first part [25]. Outcomes identified through the review were extracted verbatim from the text and grouped into 3 separate lists based on the students' age. These lists of potential outcomes will be incorporated into the data collection methods (the workshop, interviews, and Delphi survey) with key stakeholders for their consideration.

A Mixed Stakeholder Workshop

The process of a priority setting partnership based on the James Lind Alliance principles [27] will be adapted to carry out a mixed stakeholder workshop (carried out either face to face or remotely depending on participants' preferences and the extant COVID-19–related regulations) with caregivers, teachers and school staff, policy makers, and researchers to gather information on what outcomes they perceive as necessary and important for RSE. The priority setting partnership is a structured consensus-based approach that involves mixed stakeholder groups working together to produce a prioritized list of outcomes [27]. Before stakeholders are invited to attend the workshops, we will obtain informed consent for participation. Demographic information (such as participants' ethnicity and religious affiliations) will be collected and used when analyzing the results because research indicates that people from different cultural and religious backgrounds hold different attitudes toward the sexuality of people with ID as well as different beliefs on what topics are appropriate to deliver to students with ID in RSE [28-31].

At the workshops, stakeholders will be split into smaller groups (6-8 in each group; there will be a caregivers' group, teachers' group, etc). Each group will be asked to discuss a list of possible outcomes of RSE. Prompts (eg, pictures) will be provided to

facilitate the discussion among the groups, if needed. Each group will be asked to come up with the top 3 outcomes of RSE, which will be written down on a board or flip chart for everyone to see. When presenting their top 3 outcomes each group will be asked why they have chosen these outcomes and how important they are to the group, and this will be discussed with the wider group. The lists of outcomes extracted from the systematic review will also be available for participants to see. The workshops will be audio recorded, transcribed in full, and analyzed. The recording of the smaller group discussions might provide additional outcomes that were discussed in the smaller groups but were not presented for the whole group discussion, perhaps because the outcome was mistakenly not thought feasible and measurable by the smaller group. This method will allow us to explore differences among the subgroups (eg, what outcomes the caregivers perceive as the most important) while unpacking their different understandings together and also achieving a consensus-based list of outcomes at 1 workshop, thus reducing the demand on participants.

Because of the research topic that may be perceived by some participants as sensitive or uncomfortable for a discussion in a group format, we will be offering to these participants the opportunity to express their views on RSE outcomes in a one-to-one semistructured interview. The interviews will follow the same procedure as described for the workshop, but they will be conducted individually and will be of shorter duration than the workshop.

Interviews With Students With ID

Overview

The views of students with ID on RSE outcomes (identified through the systematic review, workshop, and interviews with adults) will be explored using individual face-to-face interviews conducted by the main researcher (LP). Interviews were selected because many students with ID have complex needs and differences in their communication profiles. Face-to-face sessions have been chosen because research conducted on remote sessions with children with ID during the COVID-19 pandemic indicates that the children found it very challenging or impossible to engage in web-based sessions [32]. Moreover, teachers at special schools reported that approximately 30% of the families of children with ID had no access to a computer or the internet during the pandemic [32]; thus, a remote approach would exclude many voices.

The interviews will use 1 of 3 promising visual qualitative data collection methods catering to different student communication profiles and abilities: (1) a picture-sorting activity based on the Talking Mats framework, (2) an art-based session, or (3) a diamond ranking activity (for more details, refer to the sections that follow and Multimedia Appendix 1 [33-35]). The choice of method for a specific student will be based on their prior experience of using a similar method and preferences. Three data collection methods will be offered because the literature indicates that a *one-size-fits-all* method for exploring the views of this heterogeneous population is not effective [36,37]. Preparatory sessions with the participating students' caregivers or teachers before the interviews will be conducted by the main researcher (LP) to discuss prior familiarity with the proposed measures, proposed adaptations to the interview to accommodate students' needs, and likely cultural restrictions regarding the topics selected. The interviews will be piloted with a small group of students who will not be taking part in the study. All interviews with study participants will be audio recorded because students with verbal abilities might provide their views of RSE outcomes or might suggest additional outcomes. Students' teachers or caregivers will be present (if the child does not object) at the interview with the main researcher (LP). Pictures will be taken of completed activities (eg, sorted mats of RSE outcomes). Details of the 3 visual data collection methods have been provided in the following sections.

A Picture-Sorting Activity Using Talking Mats

Talking Mats have been shown to be effective in enabling people with different levels of ID and verbal communication abilities to express their views [33,38,39]. Talking Mats is a visual, structured, symbol-based communication framework that allows a person with verbal difficulties to express their views by using symbols [33]. In this activity, students will be introduced to the RSE topic (eg, "We are going to talk about what you learn at school. Tell me which topic you like.") and asked to place pictorial RSE outcomes under categories of the visual scale (eg, *OK* or *Do not know*) adapted for each student. The ranking of outcomes will start with practice rounds of sorting neutral topics, making sure that the students understand the task, and building up toward RSE outcomes. At the end of the sorted RSE mat, the interviewer will discuss the placements of pictures to double-check that the sorted pictures correspond to the students' views and were not sorted randomly.

Art-Based Session

Art-based methods (eg, drawings and posters) have been used in educational and therapeutic settings to explore the views of people with ID who struggle to express themselves verbally [34,40]. This method was selected because students do not need to have good expressive language or understand a visual scale (eg, *OK* or *Do not know*) to take part. In this activity, students will be presented with art and craft material of different textures (eg, pictures of RSE outcomes coproduced with students with ID, sticky notes, and water paint) as well as a large piece of paper and asked to make a *what I want to learn about growing up* poster (adapted to each student's comprehension and RSE level). An example of how to perform this activity will be presented, and students will be guided through the process whenever needed. Students with verbal abilities will be asked simple questions about what they selected and why. Carers of students with limited or no verbal abilities will be asked to comment on what the student selected and what they think are the reasons for the student's choice.

A Diamond Ranking Activity

A diamond ranking activity involves ranking items from most important to least important in a diamond shape [35] and has been used successfully previously with young people with ID and complex communication profiles [41-43]. This activity might be particularly suitable for students with ID who do not like direct questioning because the emphasis in this activity is on sorting items in the diamond shape, and questions can be asked while students complete the task [41]. In this activity,

students will be presented with pictures of RSE outcomes that will have short verbal descriptions at the bottom of each picture. Students will be asked to sort the pictures of RSE outcomes by placing pictures on a piece of paper in a diamond shape with examples provided as needed. They will be told to place outcomes of RSE that they like at the top, the outcomes that they are unsure about in the middle row, and the outcomes that they do not like at the bottom. Students will be asked questions about their rating choices and their views on outcomes.

Coproduction of Pictorial RSE Outcomes

In this study the pictorial RSE outcomes (identified in the systematic review, workshop, and interviews with adults), coproduced with students with mild ID (n=5) who are not taking part in the interviews, will be used with participating students with ID in the interviews (eg, diamond ranking activity). The main researcher (LP) will present different pictures to the students (selected from pictorial databases designed for people with ID, such as Photosymbols [44], and pictures taken by the main researcher of RSE teaching materials that schools use). The main researcher will ask the students to select the most accurate pictures to represent RSE outcomes using the Talking Mats framework. The coproduction of material with people with ID using Talking Mats has been undertaken successfully previously [45]. This coproduction of pictorial RSE outcomes has the aim of ensuring that the symbols chosen to represent RSE topics are appropriate and are not confusing for students with ID; thus, they do not lead to misinterpretations.

Data Analysis

Qualitative data collected from the mixed stakeholder workshop, interviews with adults, and interviews with students with ID will be analyzed by the main researcher (LP) using the reflective thematic analysis approach described by Braun and Clarke [46]. Precisely 20% of the data will be second-coded by another researcher for dependability and confirmability. Interrater reliability will be measured using the Cohen κ coefficient and based on the parameters proposed by Landis and Koch [47]. Quantitative data—for example, diamond ranking activity—will be analyzed using descriptive statistics such as medians and percentages.

Outcome Generation

We will follow the COMET guidelines [14] for organizing the outcomes identified in stage 1 of the project. All outcomes identified from the systematic review, workshop, interviews with adults, and interviews with students with ID will be extracted verbatim, compiled by the main researcher (LP) into three long lists based on students' age (eg, RSE outcomes for primary education reported for, or by, students with ID aged 5-11 years; RSE outcomes for secondary education reported for, or by, students with ID aged 11-16 years; and RSE outcomes for further education reported for, or by, students with ID aged 16-25 years). In these 3 lists, outcomes that are overlapping will be deduplicated by the main researcher (LP), and outcomes considered semantically related by the main researcher (LP) will be presented to the senior research team (CR and VT) and, after a discussion, merged into outcome domains. The senior research team will review outcomes that were categorized into 3 lists. These 3 long lists of possible RSE outcomes will be presented in stage 2 of the project, the Delphi survey to reach consensus on the final COS. The list of outcomes identified from the systematic review, workshop, and interviews with adults and students will be incorporated into the web-based survey.

Stage 2: Delphi Survey to Determine Final List of COS of RSE

Web-Based Delphi Survey

The web-based Delphi process will be used to reach consensus on the COS. The process involves completion of web-based questionnaires answered anonymously by a panel of stakeholders (caregivers, teachers and school staff, policy makers, and expert researchers) [48]. The web-based survey will be first piloted with a small number of caregivers, teachers, or other professionals who are not taking part in the project to assess clarity and readability before being sent to the Delphi survey participants. Before they take part in the survey, participants will receive information about the study, explaining how to rate the outcomes and the importance of completing surveys in both rounds. Participants will also be offered support from the research team if they have difficulties completing the survey. The survey will be administered using the Qualtrics web-based survey tool [49], and participants will receive individual invitations to the survey via email. When participants click on the survey link, they will be asked to provide informed consent to take part in the survey and answer demographic questions embedded in the survey.

In round 1, stakeholders will be presented with the outcomes (identified through the systematic review, workshop, and interviews with adults and students) and asked to score anonymously the importance of including a particular outcome in a COS on a 9-point Likert scale using a scoring framework recommended by the Grading of Recommendations Assessment, Development, and Evaluation [50]. On the basis of this framework, outcomes scored 1 to 3 will indicate *not important* outcomes, 4 to 6 will indicate *important but not critical* outcomes, and 7 to 9 will indicate *critical* outcomes. Participants will also have an option to choose *unable to score* for items and provide comments and feedback in free-text boxes for each rating question.

The plan is for all outcomes from round 1 to be retained in round 2 to allow stakeholders to see each group's ratings and then make a final decision regarding the importance of including this outcome in the COS. However, we will consider dropping outcomes after round 1 to reduce participant burden and attrition rates in round 2 if the piloting of the survey indicates that the initial list of potential outcomes is considered by stakeholders to be too long. In this case, an outcome from round 1 will be retained in round 2 if ≥50% of the participants rate it with a score of 7 to 9 and <15% of the participants rate it with a score of 1 to 3. An outcome will be dropped if ≥50% of the participants rate it as 1 to 3 points and <15% of the participants rate it as 7 to 9 points. New outcomes suggested by participants in the comments sections will be included in round 2.

Participants who complete at least 75% of the survey in round 1 will be invited to participate in round 2. In round 2,

stakeholders will be able to see a summary of scores of each stakeholder group presented separately as a median score. Each person will be asked to think about the group results and decide whether they want to change their responses. Outcomes will be analyzed using descriptive statistics in Excel (Microsoft Corporation). Consensus to retain an outcome in the final COS list will be determined to have occurred if ≥70% of the respondents score it as 7 to 9 points and <15% of the respondents score it as 1 to 3 points. Outcomes that are scored by ≥70% of the respondents as 1 to 3 points and by <15% of the respondents as 7 to 9 points will not be included in the final COS list. Attrition bias will be assessed by comparing the average scores of each outcome rating of participants in each stakeholder group who complete only round 1 with the average scores of the participants who complete both rounds to see whether this affects the final COS list.

In both rounds, participants will have 2 weeks to complete the survey, and participants who have not completed the survey and have not declined to participate will receive 2 email reminders during this period.

Optional Final Workshop

Stakeholders from the Delphi survey will be invited to a final workshop (which will either be held face to face or on the web depending on participants' preferences and the extant COVID-19–related regulations) if all outcomes identified as critical by students with ID (as they will not take part in the Delphi survey) did not end up being included in the final COS or if there are a large number of outcomes that participants are unable to reach consensus on. In this final workshop, stakeholders will be presented with these omitted outcomes as well as outcomes on which there was no consensus and asked to discuss and reconsider them. If, even after the final workshop, all outcomes identified by students with ID as critical do not end up being included in the final COS, we will report these outcomes as well as an overview of the workshop discussion and recommend that users of a COS of RSE add at least one outcome from the list identified by students with ID.

Dissemination Plan

The findings will be published in academic journals (eg, *American Journal on Intellectual and Developmental Disabilities* and *Journal of Intellectual Disability Research*), registered at the open-access COMET database, presented at special schools using links that the team has with special schools and research networks, and presented at conferences. An easy read summary of findings will be disseminated to the different stakeholder groups involved. Through these dissemination events, we will encourage schools that serve students with ID to adopt the COS to evaluate their current delivery or to work with researchers to achieve this. We will publish a policy briefing on the final COS so that the findings reach a wider policy maker audience. We will contact relevant journals and funding bodies so that they may include the COS in their guidelines for researchers and authors.

Results

As of September 2022, we have completed a systematic review and recruited 56 stakeholders (n=53, 95%, adults and n=3, 5%, students with ID). We are still recruiting students with ID for the interviews. Data analysis has not started yet. Recruitment for the Delphi survey will commence in November 2022, and recruitment for the additional workshop (if needed) will be carried out in January 2023. We expect to complete the study by October 2023 and publish the results by the end of 2024.

Discussion

Anticipated Findings and Potential Impact

This protocol describes a study that aims to develop the first COS of RSE with, and for, students with ID aged 5 to 25 years. The findings from the study have the potential to have immediate application in English educational practice and policy because it is little known what students with ID should achieve in compulsory RSE lessons and how to obtain caregivers' support for RSE's aims and objectives. It will provide information of importance to researchers by proposing a standardized set of outcomes that should be measured in all RSE evaluation studies; this will enable the building of an evidence base for RSE programs for students with ID in Western countries.

This study will also provide theoretical and conceptual developments in the engagement and perspectives of a range of stakeholders, including students with ID, their caregivers, teachers, researchers, and other experts. A flexible approach will be used to engage students with ID of varying communication needs and ID severity level to ensure that they are included in the study and that their opinions are incorporated.

Comparison With Prior Work

Previous systematic reviews on RSE programs delivered to people with ID indicate inconsistent outcome measurement in evaluation studies and a lack of involvement of people with ID in the development of such programs [9-12]. Therefore, our work will address these gaps in the evidence. The proposed COS will include the views of students with ID and other key stakeholders and will be based on consensus across groups. Crucially, this will be the first COS of RSE for students with ID and, to our knowledge, the first COS on any topic developed for, and with, people with ID. This COS is also one of a few COS lists developed for children and young people that involves them in the development as participants and uses data collection methods adapted to the population [51,52].

Strengths and Limitations

The key strength of the study is the aim to involve different stakeholders in the process and, most importantly, students with ID, which has never been done before in COS development. We will also use multiple data collection methods (eg, systematic review, workshop, interviews, and Delphi survey) to gather different perspectives on this topic. Three data collection methods will be used with students with ID to support research participation by students with different abilities.

Although the empirical work supporting this COS will be limited to a specific geographical and cultural context (England) and to the specific group of students with ID to be recruited (aged 5-25 years), the systematic review supporting this COS considered the international literature [25]. Thus, although the COS findings will be mostly generalizable to this area and this population, we are incorporating evidence from all available international studies in the first step toward building this COS.

This COS of RSE will be developed with, and for, students with ID, who make up a heterogeneous population with varied abilities, needs, and copresenting problems. Our inclusion criteria for the students and other key stakeholders to take part in the study are wide. We are not excluding students based on their level of ability or other co-occurring conditions (eg, autism) because an inclusive group of participants is more representative of the group of students with ID currently being educated in English special and mainstream schools. We are also including other stakeholders (eg, caregivers, teachers, and researchers) who support students with a range of abilities because each of them will bring a unique and valuable perspective. However, the empirical work supporting this COS will be based on convenience sampling and will not be generalizable to all students with ID in all areas. Therefore, the outcomes included in this COS will need to be adapted when applied in practice in different contexts to take into account a student's location, culture, developmental level, and current RSE knowledge. Adaptation of RSE measurement will be important in future applications of this COS to better reflect the profile and needs of the population being measured. However, it is also extremely important that the selection of outcomes is not based on a selector's individual beliefs and societal attitudes. The outcomes excluded from measurement for a particular student at a particular point in time will need to have comprehensive justification, making sure that a student's level of ID (which determines intellectual functioning and adaptive skills, not their sexual and relationship needs) is not the sole reason for the omission of outcomes.

In the course of the proposed study, it is likely that our inclusive recruitment plans might face difficulties; for example, we might struggle to engage directly with a specific subgroup of students such as those with severe ID and stakeholders from diverse cultural and religious backgrounds. Past research indicates that recruitment to the studies on this topic can be challenging because of the topic being perceived as sensitive or taboo [53-55]. Studies also indicate that in some cultures it is shameful to talk about the sexuality of people with disabilities [31,55-57] and that some stakeholders hold beliefs that people with severe ID do not need to receive RSE [58]. These attitudes may affect recruitment to the study. Our data collection methods might also fail to enable all students with ID to express their views. The COVID-19 pandemic might also affect the availability of school staff and caregivers to take part in the study. Therefore, we might fail to capture perspectives of specific subgroups of stakeholders in this COS, and future work might be needed to address these gaps if this occurs.

Conclusions

There is a high need for a COS of RSE to guide the development and provision of RSE curricula in special and mainstream education for students with ID. This COS of RSE aims to engage different stakeholders in the process of its development and achieve a consensus on the core RSE outcomes that are important for this population. The findings have the potential to improve current RSE practice in English educational settings, harmonize RSE outcome measurement in research, and support the development of effective RSE programs for students with ID in Western countries.

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Data Availability

Data sharing will not be available because this study considers sensitive information. It was not a requirement by the funder to deposit data in a publicly available repository for studies undertaken by PhD students, and participants' consents for data sharing were not obtained in this study.

Authors' Contributions

The study protocol was designed with input from all authors (LP, CR, and VT). LP wrote the manuscript, CR and VT provided revisions and edits, and all authors approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Summary of methods to be used with students with intellectual disability.

[DOCX File , 435 KB - resprot_v11i11e39921_app1.docx]

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Abbreviations

COMET: Core Outcome Measures in Effectiveness Trials
COS: core outcome set
ID: intellectual disability
RSE: relationships and sex education

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Corrigenda and Addenda

Correction: Development and Application of a Metaverse-Based Social Skills Training Program for Children With Autism Spectrum Disorder to Improve Social Interaction: Protocol for a Randomized Controlled Trial

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In "Development and Application of a Metaverse-Based Social Skills Training Program for Children with Autism Spectrum Disorder to Improve Social Interaction: Protocol for a Randomized Controlled Trial" (JMIR Res Protoc 2022;11(6):e35960) the authors made one addition.

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The Acknowledgments section has been corrected to:

> *This work was supported by Institute of Information & communications Technology Planning & Evaluation (IITP) grant funded by the Korea government(MSIT) (No. 2022-0-00234, Development of digital therapeutics (DTx) on social interaction skills of patients with Autism Spectrum Disorder)*

The correction will appear in the online version of the paper on the JMIR Publications website on November 14, 2022, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Original Paper

Using Semistructured Telephone Interviews to Collect Qualitative Data From People With HIV Who Are Not in Medical Care: Implementation Study

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Abstract

Background: The Medical Monitoring Qualitative (MMP-Qual) Project was designed to collect qualitative data from people with HIV not engaged in medical care that would complement quantitative data collected by the Medical Monitoring Project (MMP)—a national surveillance system—and inform the MMP's recruitment and data collection methods.

Objective: Our objectives were to describe the methodology of this project, reflect on the challenges and lessons learned from conducting qualitative telephone interviews at a national level, and describe how we used and plan to use the qualitative data to evaluate our recruitment procedures and quantitative data collection instrument as well as knowledge of HIV care engagement.

Methods: We used stratified purposive sampling to identify and recruit participants who had participated in the structured MMP interview into the MMP-Qual Project. To be eligible, participants must have had an HIV diagnosis, be aged ≥18 years, have lived in an MMP jurisdiction, and have not been engaged in HIV medical care. From August 1, 2018, to May 31, 2019, we conducted semistructured telephone interviews with 36 people with HIV across the United States about several topics (eg, facilitators and barriers to care and experience with surveys). Four trained interviewers conducted semistructured 60-minute telephone interviews with 36 participants. Data collection lasted from August 1, 2018, to May 31, 2019.

Results: From 2018 to 2019, 113 people were eligible to participate in the MMP-Qual Project. Of the people recruited, 28% (22/79) refused to participate. Of those who agreed to participate, 63% (36/57) were interviewed, and 37% (21/57) were no-shows. Of the 34 participants for whom we had complete data, 15 (44%) were aged ≥50 years, 26 (76%) identified as male, 22 (65%) were Black or African American, and 12 (35%) lived in the Southern United States.

Conclusions: We learned that it is possible to obtain rich qualitative data from people with HIV who are not in care via telephone interviews and that this mode might be conducive to talking about sensitive topics. We also learned the importance of flexibility, communication, and coordination because we relied on health department staff to perform recruitment and had difficulty implementing our original sampling strategy. We hope that other projects will learn from our experience conducting qualitative telephone interviews with people with HIV on a national level.

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KEYWORDS

qualitative research; methods; telephone interviews; HIV; semistructured interviews; recruitment

Introduction

Background

Qualitative data can improve and inform quantitative data collection instruments, study recruitment procedures, and our understanding of complex phenomena such as facilitators and barriers to HIV care engagement. According to a systematic review, the practice of using qualitative data for questionnaire development has increased over time, with individual interviews and focus groups being the most common ways to generate questionnaire items [1]. Quantitative data collection instruments that are developed using qualitative methods have survey items that are acceptable, understandable, and relevant and often reflect the perspectives and experiences of the population of interest [2]. Qualitative studies have also been used to inform the recruitment of people with HIV into clinical trials [3,4]. In a qualitative study of facilitators and barriers to recruitment and enrollment of people with HIV with opioid use disorders into a clinical trial, the study staff listed stigma; fear of research; and structural factors such as housing, communication, and transportation as barriers [4]. In another qualitative study, women noted that peer pressure, monetary compensation, and a desire to learn and reflect on their hazardous drinking behavior were reasons for participating in a clinical trial [3]. However, to our knowledge, few qualitative studies have been used to inform the recruitment of people with HIV who are not engaged in care into cross-sectional surveys. Understanding what motivates people with HIV who are out of care to participate in cross-sectional surveys is important because people with HIV who are not retained in care or are unaware of their HIV diagnosis transmit approximately 80% of the annual HIV infections [5]. In addition, qualitative studies have improved our understanding of facilitators and barriers to HIV care engagement. However, most qualitative studies on the subject tend to focus on a single sociodemographic group of people with HIV, are conducted locally, or recruit people from service organizations or infectious disease organizations, thus excluding people with HIV who are not engaged in medical care.

Objectives

We conducted a qualitative project that would inform and improve the data collection instrument and recruitment procedures of the Medical Monitoring Project (MMP) while also providing rich data on sensitive topics such as HIV care engagement and sexual behaviors. This qualitative project sought to answer the following questions:

1. What facilitators and barriers to HIV care engagement exist among people with HIV who are not in care?
2. How do these facilitators and barriers to HIV care engagement vary by race, region of residence, and length of time for someone who has not been in care?
3. What are the reasons for participating in survey activities for people with HIV who are not in care?

In this paper, we describe our experience implementing this qualitative project in the hopes that others might learn from our experience. In addition, we hope to add to the body of work on experiences using telephone interviews to collect qualitative data. Thus, our objectives were to (1) describe the methodology of this project; (2) reflect on the challenges and lessons learned from conducting qualitative telephone interviews at a national level; and (3) describe how we used, and plan to use, the qualitative data to evaluate our recruitment procedures and quantitative data collection instrument, as well as knowledge of HIV care engagement. Our objectives do not include the discussion of findings from our project because they are reported elsewhere [6]. We felt that doing so would detract from our main objectives.

Methods

Overview

The MMP is an annual cross-sectional survey designed to produce nationally representative estimates of the sociodemographic, behavioral, and clinical characteristics of adults with diagnosed HIV in the United States [7]. Sociodemographic and behavioral data are collected through telephone or in-person structured interviews conducted across 23 jurisdictions, and clinical data are collected through medical record abstraction. Since 2015, the MMP has collected quantitative data on people with HIV who are engaged in HIV care as well as those not engaged in HIV care. From 2018 to 2019, we conducted the Medical Monitoring Qualitative (MMP-Qual) Project, which was designed to collect qualitative data from people with HIV not engaged in HIV medical care that would complement quantitative data collected by the MMP and inform the MMP's recruitment methods and quantitative data collection instrument.

Sampling

The MMP-Qual Project sample was derived from participants in the MMP's 2018 data collection cycle: thus, some of the eligibility criteria mirror those of the MMP, including having an HIV diagnosis, being aged ≥18 years, and living in one of the 23 MMP jurisdictions on December 31, 2017. To be eligible to participate in the MMP-Qual Project, participants must have met additional eligibility criteria. Participants must have been out of HIV care for ≥12 months or never received HIV care based on their response to a question on the MMP structured interview. In addition, persons who did not speak English or were incarcerated at the time of the interview were ineligible for participation. We used a stratified purposive sampling strategy to recruit people who had participated in the MMP structured interview into the MMP-Qual Project. We chose this sampling strategy for 2 reasons. First, we wanted to identify differences and similarities in people's experiences with HIV care. Second, we wanted to ensure that people with certain characteristics were represented in the final sample of the project. A stratified purposive sampling strategy allowed us to do both. In a stratified purposive sampling strategy, the characteristics chosen for stratification are chosen based on the assumption that they offer a unique or important perspective for the phenomenon being investigated [8]. We selected 3 characteristics that we would purposively include in our final sample. These were race or ethnicity, length of time since the last receipt of HIV care, and region of residence at the time of the MMP structured interview. We dichotomized each characteristic into Black participants versus participants who

identified as American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, White, Hispanic or Latino, or multiracial; participants who were out of care for 12 to 23 months versus participants who were out of care for ≥24 months; and participants who lived in the Southern United States versus participants who did not live in the Southern United States. We chose these characteristics because these factors have been related to HIV disparities, and we expected there to be relevant variations in the experiences of people not in HIV care based on these characteristics [5,9-11]. We also reviewed MMP quantitative data (which are nationally representative data of adults diagnosed with HIV in the United States) from prior data collection cycles to determine whether we would have enough participants to interview if we created strata using these 3 characteristics. The data showed that there would be enough participants to interview considering our inclusion and exclusion criteria and these 3 characteristics.

After we decided upon the 3 characteristics that would be included in the final sample, we divided or stratified our sample according to these characteristics. We created a blank nested table with the 3 dichotomized characteristics. This table had 8 cells. The next step was to set a quota for the size of each cell, that is, the number of participants to allocate to each cell or stratum. To do so, we consulted the literature and considered practical realities and concerns. Before we set the quota for each stratum, we discussed what approximate size our final sample should be. According to a study, data saturation had occurred at 12 qualitative interviews [12]. Thus, we wanted a sample size of >12 participants. As we had 8 strata, we wanted to ensure that each stratum had enough participants to generate meaningful data. However, we did not want to select too many participants in each stratum because we had limited resources (eg, time, budget, and staffing). We also used data from past MMP data collection cycles to determine the number of people not engaged in HIV care who were Black versus those who identified as American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, White, Hispanic or Latino, or multiracial; who lived in the Southern United States versus those who did not live in the Southern United States; and who were out of care for 12 to 23 months versus those who were out of care for ≥24 months. We settled on a quota of 5 participants per stratum after taking all the aforementioned factors into account (Table 1).

As we progressed through the project, we realized that it was becoming increasingly difficult to recruit participants in some of these strata; for example, by December 2018 (ie, 4 months into the project), we had not interviewed any non-Black participant living in the Southern United States who was out of care for 12 to 23 months and any non-Black participant who did not live in the Southern United States who was out of care for ≥24 months. We realized that trying to fill each of these strata—and not interviewing people in strata that had exceeded 5 participants—was impeding our ability to interview enough participants. Thus, halfway through the project (sometime in January 2019) and during data collection, we stopped trying to reach the quota we set for each stratum and simply interviewed whoever was eligible and agreed to participate in the project.

Table 1. The stratified purposive sampling strategy for the Medical Monitoring Qualitative Project.

	Length of time without care, months							
	≥12 to ≤23				≥24 or never in care			
Race or ethnicity	Black, non-Hispanic		American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, White, Hispanic or Latino, or multiracial		Black, non-Hispanic		American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, White, Hispanic or Latino, or multiracial	
Region	South[a]	Other[b]	South[a]	Other[b]	South[a]	Other[b]	South[a]	Other[b]
Quota (number of participants to interview)	5	5	5	5	5	5	5	5

[a]On the basis of United States Census Bureau classifications: Delaware; Florida; Georgia; Houston, Texas; Mississippi; North Carolina; Texas; and Virginia.

[b]On the basis of United States Census Bureau classifications: California; Chicago, Illinois; Illinois; Indiana; Los Angeles, California; Michigan; New Jersey; New York City, New York; New York; Oregon; Pennsylvania; Philadelphia, Pennsylvania; Puerto Rico; San Francisco, California; and Washington.

Recruitment

Throughout this paper, the term *interviewers* will refer to staff members in the 23 MMP jurisdictions. They conducted the MMP structured interview with participants and recruited participants into the MMP-Qual Project. The term *CDC* (Centers for Disease Control and Prevention) *interviewers* will refer to CDC staff members who interviewed participants using a semistructured interview guide for the MMP-Qual Project. The CDC interviewers did not have access to participants' personal information (eg, telephone numbers, addresses, and names); thus, the recruitment strategy for this project relied heavily on interviewers in the 23 jurisdictions who had access to the personal information of the participants who were eligible for the MMP-Qual Project.

At the end of the MMP structured interview, a pop-up message appeared in the computer-assisted personal interview software program notifying the interviewers that a participant was eligible for the MMP-Qual Project based on their responses to a question. After receiving this pop-up message, the interviewers introduced the MMP-Qual Project to eligible participants using a standardized recruitment script. If participants agreed, the interviewers scheduled appointments for the participants to

complete a semistructured telephone interview with a CDC interviewer. As CDC interviewers were unable to access participants' personal information for privacy and confidentiality reasons, interviewers in the jurisdictions were responsible for scheduling interviews, providing appointment reminders, and maintaining the contact information of persons sampled for the MMP-Qual Project. While scheduling interview appointments, the interviewers gave participants a unique code as well as the telephone number to call for the semistructured interview with CDC interviewers. This telephone number was secure and could not be traced to the CDC. Likewise, the CDC interviewers could not see the caller's telephone number or any other identifying information. The interviewers in the jurisdictions instructed participants to give their unique code to the CDC interviewer upon first contact. This code allowed us to link the data from the semistructured interviews with the MMP quantitative interview and medical record abstraction data.

Ethical Considerations and Informed Consent

In accordance with the federal human participant protection regulations and guidelines for defining public health research, the MMP was determined to be a nonresearch, public health surveillance activity used for disease control program or policy purposes [13,14]. As this project was determined to not be research, it was not subject to human participant protection regulations, including federal institutional review board review and approval. However, all federal, state, and local MMP staff members adhere to ethical principles and standards by respecting and protecting the privacy, confidentiality, and autonomy of participants. MMP jurisdictions follow their state or local procedures to determine whether the project is subject to state or local human participant protection regulations. Furthermore, MMP data are subject to the CDC's data security and confidentiality guidelines for HIV, viral hepatitis, sexually transmitted disease, and tuberculosis programs [15]. The security of our data systems meets all Federal Information Systems Management Act, Office of Management and Budget, Department of Health and Human Services, and CDC IT security requirements, which ensure the confidentiality, integrity, and availability of data on federal information systems. Verbal informed consent was obtained from all participants in this project.

Data Collection

Four trained CDC interviewers conducted semistructured 60-minute telephone interviews with 36 participants. Data collection lasted from August 2018 to May 2019. The interview guide contained 22 questions and prompts that asked about facilitators and barriers to accessing or engaging in HIV medical care, knowledge of HIV treatment as prevention, the preferred method of contact for participation in surveys, and the reason for participation in the MMP. We used information from literature reviews, existing quantitative data from the MMP, and results from the Never in Care Pilot Project to inform the interview guide questions [16]. In addition, community advisory board members for the MMP provided input on interview guide questions and prompts. The community advisory board members are community representatives who are concerned about the well-being of people with HIV in their community and the quality of care that people with HIV are receiving in their jurisdictions. They provide input on the project, including reviewing procedures and methods, ensuring that recruitment methods are effective, providing input on data collection instruments, and ensuring that data collected are helpful to the local community. At the end of every interview, the CDC interviewers asked participants whether they needed additional resources such as referrals to ancillary services or medical care. If participants expressed a need for additional resources, the CDC interviewers informed interviewers in the jurisdictions concerned. The interviewers were then tasked with providing local resources to participants because the CDC interviewers did not have access to local resources or the participants' contact information.

Data Analysis

All interviews were audio recorded and transcribed verbatim by 6 trained CDC staff members following a transcription protocol. Data quality checks were performed on all transcripts; for instance, a CDC team member who did not transcribe the transcript under review read the transcript while listening to the audio recording of the interview, ensuring accuracy of transcription and fidelity to the transcription protocol. Five team members independently read 2 interview transcripts and assigned a list of codes that were used to develop the initial codebook. The team applied the initial codebook to 2 more interview transcripts and continued until they reached consensus. The team performed intercoder reliability on 21% (7/34) of the transcripts, reviewing and discussing codes with κ coefficients <0.61 until reaching agreement on code application. The team also established trustworthiness (eg, credibility and dependability) and rigor through various means; for instance, we kept records of interview notes; created thorough documentation of all project processes, including notes of code and theme generation and chronology of activities; maintained documentation of team meetings; and stored data and notes in well-organized archives. In addition, we engaged in reflexivity—documenting and discussing how our understanding might have affected the data analysis process—and peer debriefing after the interviews [17,18]. We used applied thematic analysis as the primary qualitative data analysis method [19].

Results

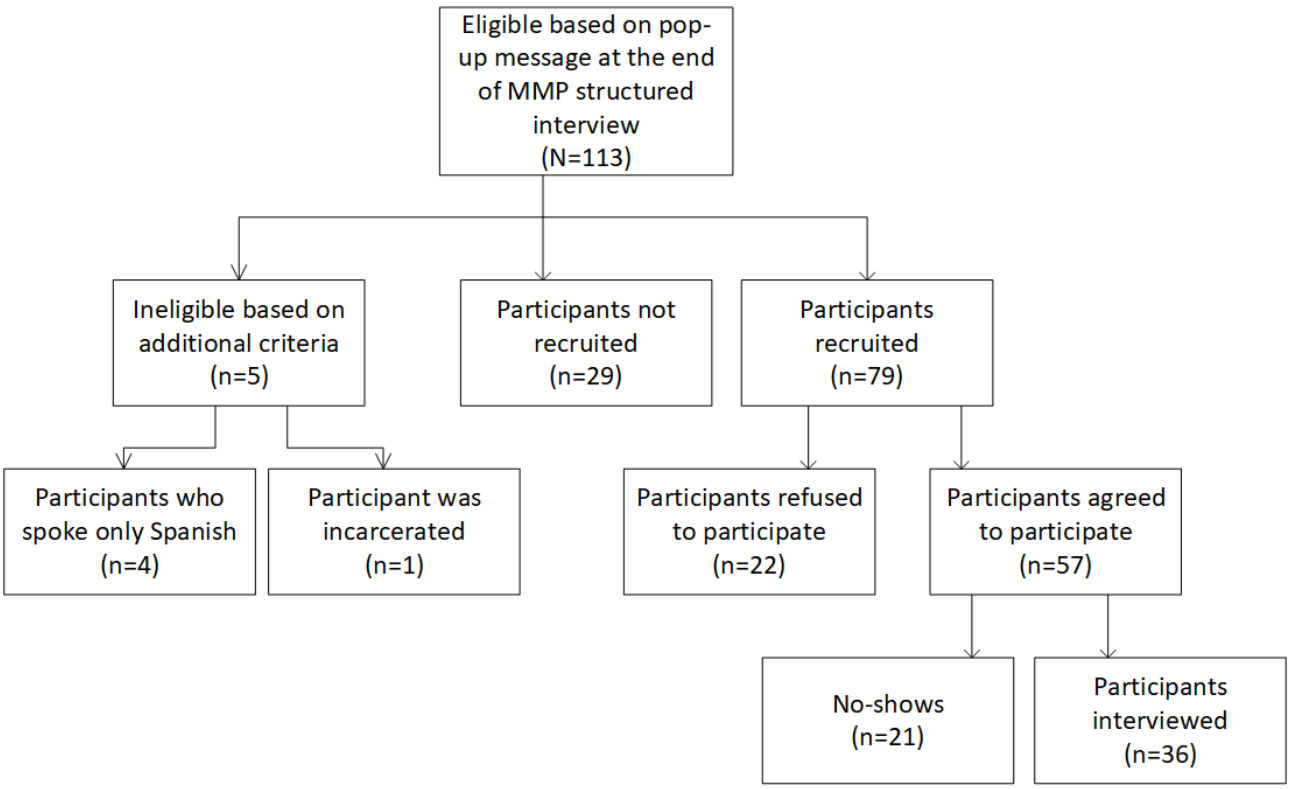
Interview Data

From 2018 to 2019, a total of 113 MMP participants were eligible for participation in the MMP-Qual Project based on their responses to a question on the MMP structured interview. Of the 113 people, 5 (4.4%) were ineligible because they were incarcerated (n=1, 20%) or spoke only Spanish (n=4, 80%). Of the 113 people, 29 (25.7%) were not recruited: in most of these cases, the interviewers missed the pop-up message at the end of the structured interview and thus failed to recruit the participant, whereas some people were not recruited for reasons not given. Of the 113 people, 79 (69.9%) were recruited, of whom 22 (28%) refused to participate, and 57 (72%) agreed to participate. However, of the 57 people who agreed to participate, 21 (37%) were no-shows, that is, they never called the CDC to do the interview and would be considered soft refusals. Thus,

of the 57 people who agreed to participate, 36 (63%) were interviewed. Of these 36 interviewees, we had complete data for 34 (94%); of the 36 interviewees, 1 (3%) stated that they were HIV negative, which meant we had to end the interview, and the interview with 1 (3%) participant was never audio recorded (Figure 1).

Of the 23 jurisdictions participating in the MMP-Qual Project, 16 (70%) completed interviews, whereas 7 (30%) did not complete any interviews. The jurisdictions that did not complete interviews were Illinois; Los Angeles, California; Mississippi; New York; Pennsylvania; Puerto Rico; and Texas. Among these jurisdictions, Illinois and Mississippi only had refusals; Los Angeles, California, and Pennsylvania did not recruit participants; Puerto Rico had participants who were ineligible because of language; and New York and Texas had participants who were no-shows.

Figure 1. Flow diagram of participant enrollment. MMP: Medical Monitoring Project.



Demographic Data

Of the 34 participants with complete interviews, 15 (44%) were aged ≥50 years, 10 (29%) were aged 18 to 39 years, and 9 (26%) were aged 40 to 49 years. Of the 34 participants, 26 (76%) identified as male (both sex assigned at birth and gender identity were male), and 7 (21%) identified as female (both sex assigned at birth and gender identity were female). We had missing gender identity data for 3% (1/34) of the participants (we had data related to the sex assigned at birth but no gender identity data). Of the 34 participants, 22 (65%) were Black or African American, and 7 (21%) were non-Hispanic White. We classified 8% (3/34) of the participants as another race or ethnicity, which included American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or multiracial, and 6% (2/34) identified as Hispanic or Latino. Of the 34 participants, 12 (35%) lived in the South, 8 (24%) lived in the Midwest, 7 (21%) lived in the West, and 7 (21%) lived in the Northeast (Table 2).

Of the 34 participants, 12 (35%) requested linkage to care or referrals to ancillary services at the end of the qualitative interview; 4 (12%) requested financial assistance such as social security disability insurance, supplemental security income, and financial assistance for copays and medications; 2 (6%) requested housing and food or meal services; 4 (12%) requested referrals to an HIV medical provider; and 5 (15%) requested other medical care, including referrals to a dentist, optometrist, and psychiatrist.

Table 2. Demographic characteristics of participants in the Medical Monitoring Qualitative Project (N=34).

Characteristics[a]	Values, n (%)
Age (years)	
18 to 39	10 (29)
40 to 49	9 (26)
≥50	15 (44)
Gender[b]	
Male	26 (76)
Female	7 (21)
Transgender	0 (0)
Missing[c]	1 (3)
Race and ethnicity	
Non-Hispanic Black or African American	22 (65)
Hispanic or Latino[d]	2 (6)
Non-Hispanic White	7 (21)
Another race or ethnicity[e]	3 (8)
Current US region of residence[f]	
West	7 (21)
Midwest	8 (24)
Northeast	7 (21)
South	12 (35)

[a]Participant demographic data were obtained from the Medical Monitoring Project structured interview.

[b]Gender was based on gender identity and sex assigned at birth. Transgender persons were defined as those who self-identified as transgender or who reported a gender identity different from sex assigned at birth.

[c]Data were coded as missing because participants refused to answer.

[d]Hispanic or Latino persons may be of any race. Persons are classified into only 1 race or ethnicity category.

[e]Includes American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, or multiracial.

[f]Regions based on classification by United States Census Bureau and limited to Medical Monitoring Project jurisdictions: West (California, Oregon, and Washington), Midwest (Indiana, Illinois, and Michigan), Northeast (New Jersey, New York, and Pennsylvania), and South (Delaware, Florida, Georgia, North Carolina, Virginia, and Texas).

Discussion

Overview

This paper describes the methodology of the MMP-Qual Project in the hopes that others might learn from our experience. We experienced several challenges along the way: our initial sampling strategy was difficult to implement, given our practical realities; our recruitment strategy relied on our health department colleagues (who were geographically dispersed); and our mode of data collection (ie, telephone interviews), although practical, might have created barriers to forming trust and building rapport with the participants. Despite these challenges, we were able to collect data from a diverse group of people with HIV. We have used some of these data to report on facilitators and barriers to HIV care engagement, improve our MMP data collection instrument, and inform MMP recruitment procedures [6]. In the following sections, we describe in more detail the challenges we faced and the lessons we learned.

Challenges During Recruitment and Data Collection

Although our goal was to interview 20 Black and 20 non-Black participants, we were only able to interview 12 non-Black participants. Although our goal was to interview 20 people who lived in the Southern United States and 20 people who did not live in the Southern United States, we were only able to interview 12 people who lived in the Southern United States. Finally, although our goal was to interview 20 people who were out of care for 12 to 23 months and 20 people who were out of care for ≥24 months, we only interviewed 14 people who were out of care for ≥24 months. Upon reflection, we believe that there were several reasons why we were not able to meet our goals. First, although we chose our sampling strategy partly because of practical reasons (such as how much time and money we had), it was only during recruitment and data collection that other practical realities came to light, including a delayed project start because of technical issues with scheduling. Furthermore, we realized that we selected many stratification criteria. The more stratification criteria one includes in one's sample frame,

the more difficult recruitment becomes and the longer it takes to find participants [20]. Thus, we might have found more success if we had selected fewer (ie, 1 or 2) stratification criteria. We also believe that we might have overestimated people's interest in participating in the MMP-Qual Project. We assumed that if participants had taken part in the MMP structured interview, they probably would participate in an additional qualitative component of the project. However, the 2 activities (the MMP structured interview and the MMP-Qual Project) were different, including data collection being conducted by 2 different institutions (the local jurisdiction vs the CDC). Participants might have felt skeptical about being interviewed by CDC interviewers and thus declined to participate in the qualitative project; for instance, during a qualitative interview, a participant said they were hesitant and concerned about being interviewed by a CDC staff member. Despite these challenges, we felt that we obtained data from a diverse array of participants with regard to age, gender, race and ethnicity, and region of residence.

Another challenge we faced was being unable to recruit people into the MMP-Qual Project ourselves, leading to our having to rely on staff in the 23 jurisdictions to recruit participants and schedule interviews. Interviews had to be scheduled in advance, and participants could not complete the qualitative interviews on the same day as, or right after, the MMP structured interview; thus, participants had to be flexible to meet our schedules as much as we had to be flexible to meet theirs. Sometimes CDC interviewers and health department interviewers were in different time zones. If a participant lived on the west coast and wanted to schedule an interview late in the day (eg, after 9 PM), that would not be possible for CDC interviewers who were on the east coast and did not have access to their offices during certain hours (eg, after midnight). Thus, interview slots were sometimes limited because of time zone differences and limited resources (eg, available CDC interviewers). In addition, before CDC interviewers could interview a participant, they needed the participant's unique code, which interviewers in the jurisdictions had assigned to participants during recruitment. Because of strict data security and confidentiality procedures, interviewers in the jurisdictions needed to send this code to the CDC through a secure system, a process that sometimes took several hours. Another option that interviewers in the jurisdictions had was to call the CDC to verbally provide the unique code. If we did not receive the code, we could not interview the participant because we had no way of confirming their identity. This was challenging because it required consistent communication and coordination with interviewers in the jurisdictions who had other competing priorities. To address these challenges, we conducted training with all interviewers across the 23 jurisdictions on recruitment procedures for the MMP-Qual Project, which included being aware of the pop-up message indicating eligibility, assigning eligible participants a unique code that would be linked to the quantitative data, scheduling interviews, and the importance of sending the unique code promptly to the CDC. If we were to conduct a similar project again, we would dedicate more time to developing a more efficient electronic scheduling system that would allow interviewers in the jurisdictions to share the participant's unique code during scheduling.

CDC interviewers did not have access to participants' personal information such as names and telephone numbers. Although this was key to ensuring and maintaining anonymity during the interview process, it also brought on several challenges. For one, if a person failed to call the CDC for their scheduled interview, CDC interviewers could not contact them to reschedule. This required continual communication with interviewers in local jurisdictions who performed the recruitment because they were responsible for rescheduling interviews and maintaining contact with eligible participants. In addition, it was challenging to establish rapport with the participant if we could not address them by name. We stressed that they should not reveal their name, location, health care provider's name, or any personally identifiable information. Despite these challenges, we believe that the anonymous nature of the interview allowed participants to disclose sensitive information about topics that many of them discussed feeling stigmatized by. Furthermore, because the telephone we used had minimal technology (this was done to safeguard the confidentiality of participants), we could not directly record the interviews using the telephone. Thus, we used an audio recorder to record the interview, which required the use of the speaker option on the telephone. This made the audio quality of interview recordings suboptimal at times. When audio quality was poor, and we could not discern what the participant was saying, we transcribed segments of text from the interview as inaudible, which meant the loss of these data.

Finally, we realize that the interview guide we used was lengthy. The interview guide covered 4 main topics and included an opening and closing question. It covered 22 questions, not including probes, in 60 minutes. If we were to conduct a project like this again, we might ask fewer semistructured interview questions because participants might have felt fatigued or had insufficient time to provide robust responses to some questions (especially those posed toward the end). We also could have modified the interview guide halfway through the project to reduce the number of questions and thereby participant burden. However, we felt that the interview length issue was mitigated because the questions on each topic were similar—and sometimes participants naturally answered questions that were about to be asked. Furthermore, CDC interviewers received training on what to do if an interview was not moving at the pace required to ask all 22 questions and how to determine whether a participant had adequately addressed questions that had not been posed yet; for instance, sometimes, interviewers skipped questions that had already been addressed in some form during prior questions. For the most part, CDC interviewers did not feel rushed during the interviews and obtained robust data from the participants.

Reflections

We described the methodology of the MMP-Qual Project and described the recruitment and data collection challenges. We learned several lessons from our experience. One of the first challenges we faced was having to pivot from our original sampling strategy. We needed to be flexible based on how recruitment was progressing in the field and cognizant of timelines and resource constraints. Although we did not meet our initial sampling goals, we obtained perspectives from a

diverse group of people with HIV who nonetheless shared common experiences relating to not being engaged in HIV care.

In addition, recruitment and interviews were being conducted by different staff in different states: interviewers in local jurisdictions recruited participants, whereas CDC interviewers conducted the semistructured interviews. To ensure successful recruitment, communication, coordination, and training were key. We trained interviewers on how to recruit and checked with staff in the jurisdictions about recruitment progress regularly. Interviewers who recruited eligible participants for the MMP-Qual Project were typically the same interviewers who had conducted the structured MMP interview with the participant. Thus, interviewers in the jurisdictions had already established rapport with participants during the structured interview. At the end of the qualitative interviews, participants expressed having been more open to participating in the MMP-Qual Project based on their experience with the structured interview. Other qualitative projects attempting to sample participants from a cross-sectional survey might also experience this benefit.

This was also the first time we conducted telephone qualitative interviews for the MMP. As a mode of qualitative in-depth data collection, the telephone has become a practical option for qualitative research: telephone interviews allow for data collection among geographically dispersed participants, reduce cost compared with in-person interviews, and increase privacy for participants [21,22]. In addition, telephone interviews give participants greater anonymity than in-person interviews, which increases feelings of privacy, and this may be particularly important when sensitive questions are asked and the need for anonymity is high, which is often the case for people with HIV [21,23]. By contrast, researchers posit that it is difficult to form trust and build rapport during qualitative telephone interviews because of the physical separation between participant and interviewer, which may compromise the richness and quality of the data. However, there is minimal evidence to indicate that data quality is compromised when using telephone interviews [24]. In a study using qualitative telephone interviews to understand hazardous drinking among sexual minority women who had participated in the population-based National Alcohol Survey, participants provided rich narrative data over the telephone about sensitive topics such as sexual identity, traumatic experiences, and alcohol or drug use [22]. We similarly collected rich data from our participants. We believe that the anonymous nature of the interviews allowed participants to disclose sensitive information about a topic that many participants discussed feeling stigmatized by (Textbox 1). The telephone as a mode of qualitative data collection was also an affordable option for our project and reduced participant burden because participants did not have to travel to a specific location to be interviewed.

We were able to obtain rich data by completing training with CDC interviewers who conducted the qualitative interviews, which included mock interviews, and by using strategies to build rapport, such as those detailed by Drabble et al [22]. Throughout the qualitative interviews, interviewers used orienting statements to let participants know what to expect during the process and emphasized the voluntary nature of their participation (eg, they did not have to answer any question they did not want to answer). Interviewers could only respond to auditory cues (such as tone of voice or background noise) and the content of the answers; thus, their active listening skills were heightened. In addition, interviewers used neutral words such as “sure,” “okay,” “I see,” or “yeah” to vocalize that they understood and were listening. Finally, interviewers communicated their appreciation to the participants and maintained an accepting and nonjudgmental tone, which is key when discussing HIV.

In the MMP quantitative data collection instrument, we ask participants about facilitators and barriers to HIV care. We used the data from the qualitative interviews to evaluate whether our current questions on facilitators and barriers to care adequately capture the most salient barriers in the lives of participants who are not in care. On the basis of the qualitative data, we confirmed that the most salient barriers, including stigma, patient-provider relationships, and mental health issues, were captured in our data collection instrument. Thus, the MMP data collection instrument reflects the perspectives and experiences of people with HIV who are not engaged in care. Other cross-sectional surveys might be interested in conducting qualitative projects to understand the extent to which their data collection instruments reflect the experiences of their populations of interest. In the qualitative interviews, we also asked participants about their preferred method (eg, telephone call, letter, email, or in person) of contact for participation in surveys, concerns about participation in the MMP, the reason for participation in the MMP, and whether they would complete the MMP quantitative interview on the web. We are using these data to inform recruitment procedures and materials (eg, recruitment scripts, recruitment letters, and website materials).

Textbox 1. Challenges and lessons learned from conducting the Medical Monitoring Qualitative Project.

- Recruitment of participants to fill each quota in our stratified purposive sampling strategy
  - Pivoting from your original sampling strategy based on how recruitment progresses in the field as well as on timelines and resource constraints
  - Reviewing incoming data throughout data collection to ensure that you are obtaining data from a diverse array of participants as it relates to characteristics important to your evaluation and research questions
  - Selecting fewer stratification criteria if there are limited resources
- Being unable to recruit participants ourselves and relying on health department staff across the country
  - Maintaining consistent communication and coordination with staff who perform recruitment
  - Training staff who perform recruitment on eligibility criteria, security, confidentiality, and scheduling interviews
  - Creating an efficient electronic scheduling system when scheduling interviews across different geographic locations
  - Tapping into any existing relationship with staff: participants may be more open to participating in a qualitative project after having built rapport with local staff during recruitment and previous participation in a survey
- No access to participants' personal information (eg, names and telephone numbers)
  - Recognizing that the anonymous nature of interviews may allow participants to disclose sensitive information, as they might feel stigmatized by the condition
- Being unable to directly record interviews using the telephone (requiring the use of an audio recorder and speakerphone, which made audio quality suboptimal at times)
  - Investigating telephone technology that would allow you to record telephone interviews without obtaining any personal information (eg, names and phone numbers)
- The first time we used telephone interviews to collect qualitative data for the Medical Monitoring Project
  - Training interviewers who conduct qualitative interviews to navigate the different sets of challenges and nuances posed by telephone interviews
  - Using strategies to build rapport during telephone interviews (including orienting participants to the interview process, emphasizing the voluntary nature of participation, using neutral words to vocalize understanding, and maintaining an accepting and nonjudgmental tone)

Conclusions

The MMP-Qual Project was conducted to complement quantitative data collected in the MMP and to inform and improve the MMP's recruitment procedures and data collection instrument. We experienced several challenges during our project, but we also learned many lessons. We learned to be flexible based on recruitment progress in the field, to use live web-based training to train interviewers on participant recruitment into a qualitative project, to build rapport during qualitative telephone interviews, and to safeguard the privacy and confidentiality of our participants. We learned that it is possible to obtain rich qualitative data over the telephone from people with HIV who are not engaged in HIV medical care and that this mode might be particularly helpful for such a sensitive topic.

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Data Availability

National Medical Monitoring Project (MMP) data are not publicly available because of the need for specialized technical assistance for working with the large and complex data sets and the security and confidentiality guidelines for the release of HIV surveillance data. However, the Centers for Disease Control and Prevention (CDC) will grant access to MMP data in accordance with security and confidentiality guidelines on a case-by-case basis. Researchers may submit analysis concept proposals that are reviewed and

prioritized based on their importance for public health, their scientific merit, and on the needs and current workload of the team that oversees the MMP at the CDC. There are currently no fees associated with accessing or receiving MMP data, but the release of data is subject to the availability of CDC resources to complete such requests. More information on the appropriate procedures for concept proposals can be obtained by contacting the CDC [25].

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Authors' Contributions

MP was responsible for writing the paper (editing [equal] and original draft [lead]) and conceptualization (lead). MG was responsible for writing the paper (review and editing [equal] and original draft [supporting]). JF was responsible for writing the paper (review and editing [equal] and original draft [supporting]), methodology (lead), and conceptualization (lead).

Conflicts of Interest

None declared.

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Abbreviations

CDC: Centers for Disease Control and Prevention
MMP: Medical Monitoring Project
MMP-Qual: Medical Monitoring Qualitative

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Protocol

Use of the Maslach Burnout Inventory Among Public Health Care Professionals: Protocol for a Scoping Review

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Abstract

Background: Burnout syndrome is a chronic response to stressors in the workplace. It is characterized by emotional exhaustion and physical and mental burnout and may lead to high employee turnover, work absenteeism, and increased occupational accidents. Most studies use the Maslach Burnout Inventory (MBI) to identify burnout and implement preventive actions and treatments.

Objective: This study presents a scoping review protocol to identify and map studies that used MBI to assess burnout syndrome in health care professionals working in public health services.

Methods: This scoping review protocol follows the Joanna Briggs Institute reviewers' manual, and this protocol consists of 6 stages: identifying the research question, identifying relevant studies, study selection, data extraction and coding, analysis and interpretation of results, and consultation with stakeholders. We will conduct searches in Embase, LILACS, PubMed/MEDLINE, PsycINFO, Scopus, Web of Science databases, and gray literature. The main research question is as follows: how is MBI used to identify burnout syndrome in health care professionals working in public health services? Inclusion criteria will comprise qualitative and quantitative studies using MBI to identify burnout syndrome in health care professionals working in public health services and no restrictions in language and publication dates. Data will be extracted using a spreadsheet adapted from the Joanna Briggs Institute model. Quantitative and qualitative data will be analyzed using descriptive statistics and thematic analysis, respectively. The consultation with stakeholders will be essential for increasing the knowledge about MBI, identifying new evidence, and developing future strategies to guide public policies preventing burnout syndrome in health care professionals working in public services.

Results: This protocol will guide a scoping review to identify and map studies that used MBI to identify burnout syndrome in health care professionals working in public health services. The results of this review may be useful to public health care professionals, managers, policymakers, and the general population because these findings will help understand the validated, translated, and adapted versions of MBI and domains, number of items, Likert scales, and cutoff points or the latent profile analysis most used in the literature. Furthermore, possible research gaps may be identified to guide future studies. All information regarding the stages of the scoping review favor its transparency and allow it to be methodologically replicated according to the principles of open science, thereby reducing the risk of bias and data duplication.

Conclusions: This study may reveal the multiplicity of scales described in the literature and the different forms of assessing burnout syndrome in health care professionals. This study may help to standardize the assessment of burnout syndrome in health care professionals working in public health services and contribute to the discussion and knowledge dissemination about burnout syndrome and mental health in this population.

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KEYWORDS

health care personnel; health care workers; public health services; Maslach burnout inventory; burnout, health care professional; workplace stress; mental health; occupational health; psychological well-being; policymaker

Introduction

Burnout syndrome is a work-related psychological syndrome included in the International Classification of Diseases 11th Revision (code QD85) [1]. Herbert Freudenberger described this syndrome in 1974 [2,3], and it is characterized by a chronic response to interpersonal stressors in the workplace that may be related to work organization and environment [4,5]. The protocol in our study will guide a scoping review to identify and map studies that used the Maslach Burnout Inventory (MBI) to identify burnout syndrome in health care professionals working in public health services. The results of this review may be useful to public health care professionals, managers, policymakers, and the general population since these findings will help understand the validated, translated, and adapted versions of MBI and domains, number of items, Likert scales, and cutoff points or the latent profile analysis most used in the literature. Furthermore, possible research gaps may be identified to guide future studies. All information regarding the stages of the scoping review favor its transparency and allow it to be methodologically replicated according to the principles of open science, thereby reducing the risk of bias and data duplication [3].

Different definitions of the burnout syndrome consider many etiological factors; thus, literature lacks a consensus about its definition and diagnostic criteria [6,7]. Some authors define burnout syndrome as fatigue and emotional exhaustion [8], whereas others consider it as emotional exhaustion and depersonalization [9]. Gil-Monte [10] defines burnout syndrome according to 4 dimensions: enthusiasm toward the job, psychological exhaustion, indolence, and guilt. Bakker et al [11] define the syndrome as mental distance from the job and emotional, physical, and cognitive exhaustion. One of the most used definitions of burnout syndrome was proposed by Maslach and Jackson who considered this syndrome as emotional exhaustion, depersonalization, and personal accomplishment associated with physical and psychological symptoms. Thus, this scoping review protocol used this definition to map the use of MBI [5].

The main characteristics of burnout syndrome are emotional exhaustion, resulting in fatigue; depersonalization, associated with negative behaviors and cynicism in work relationships; and low scores in personal accomplishment, with feelings of incompetence and low productivity [12-14]. Individuals with burnout syndrome see work as a source of misery and unpleasurable [3], leading to high employee turnover, work absenteeism, decreased quantity and quality of work, and increased occupational accidents, thereby representing institutional consequences [15,16]. People working with the general public are more prone to develop the burnout syndrome. Studies have shown burnout in several work fields; however, the most affected were teachers, police officers, and health care professionals (especially physicians and nurses) [6,17-19]. The burnout syndrome affects approximately 10%-70% of nurses and 30%-50% of physicians, nurse practitioners, and physician assistants [20] and is highly prevalent among health care professionals [21-24], especially among those working in public health services [25,26].

Many aspects of burnout syndrome have already been established, and more than 90% of the studies used MBI [27] to identify and implement preventive interventions and treatments [12,28]. MBI is a self-report questionnaire developed by Christina Maslach and Susan Jackson to obtain a multidimensional view of burnout and comprises 22 items divided into 3 sections: emotional exhaustion (9 items), depersonalization (5 items), and personal accomplishment (8 items). The original version uses a 7-point Likert scale (0 corresponds to “never” and 6 to “every day”) [5,29] that assesses burnout according to scores in each dimension: high levels of burnout are characterized by high scores in emotional exhaustion and depersonalization and low scores in personal accomplishment. According to studies, MBI must be used in a 3D approach to enhance the comprehension of the burnout syndrome, since all 3 dimensions are considered important for identifying burnout and the individual dimensions alone do not sufficiently define the construct [21,30-32].

MBI is also intended to investigate the syndrome in other work settings. The MBI-Educators Survey is intended for education professionals, and the MBI-General Survey measures the syndrome in any professional category. For health care professionals, there is a specific version called the MBI Human Services Survey [5,29]. The MBI-Student Survey is designed to identify burnout in students [33]. The literature shows different translated, validated, and adapted versions of MBI. This diversity constitutes a challenge for the development of research using the instrument, since it can impact the interpretation of data and make comparisons between studies impossible, as well as hinder the identification of workers at risk for developing the syndrome because there is no standardization in its use.

The choice of the setting in our study was due to evidence in the literature that professionals working in public health services are more exposed to stress, thereby causing burnout [34]. In these services, there is usually wage-related dissatisfaction on the part of professionals, the need for better planning of actions and work processes [35,36], the difficulty in operationalizing actions, underfunding, and poor infrastructure [35-37]. The evidence of the aforementioned factors in public health services should be considered and will help us in terms of understanding that the development of burnout syndrome in health care professionals may be related to the organization and development of the work process in these services, which reflects the importance of conducting this study in the current context. Considering the global importance of MBI for

identifying burnout syndrome [38], we conducted a preliminary search in the Joanna Briggs Institute (JBI) evidence synthesis, the international Prospective Register of Systematic Reviews (PROSPERO), Cochrane Library, and PubMed/MEDLINE databases by using the descriptors "health care professionals," "public health services," "Maslach Burnout Inventory," and "burnout syndrome." We found only 1 integrative review synthesizing the use of MBI in Brazil; however, this study was not directed to public health care professionals [39]. No studies or protocols were found when expanding the search to other continents.

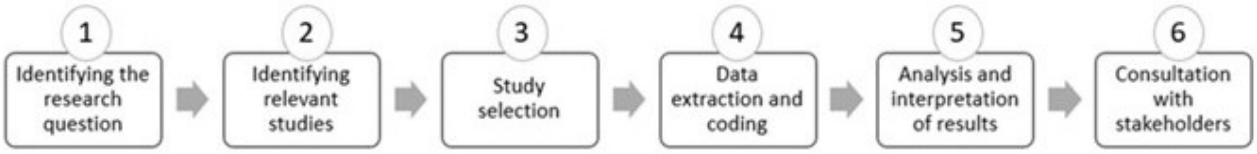
Therefore, this scoping review protocol will identify and map studies that used MBI to assess burnout syndrome in health care professionals working in public health services. It will allow us to map the evidence describing different translated and validated versions of MBI and assess the consistency in frequencies and cutoff points of the scale and its application in different countries, aiming to guide a possible standardization in its use. We will also evaluate possible research gaps regarding the use of MBI among health care professionals working in public health services.

Methods

Overview

This scoping review protocol follows the JBI reviewers' manual [40] and is guided by the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [41]. This protocol is registered in the Open Science Framework [42]. Our review will follow 6 stages [43,44], as shown in Figure 1.

Figure 1. Stages of the scoping review.



First Stage: Identifying the Research Question

The research question was formulated using the Population, Concept, Context mnemonic [40] (Table 1). The Population, Concept, Context mnemonic maps information to identify knowledge gaps, present key concepts, quantify aspects of interest, and identify practices and evidence in the thematic area [45].

In this context, the questions of this scoping review protocol were defined as follows: "How is MBI used to identify burnout syndrome in health care professionals working in public health services?", "What is the most studied professional category using MBI?", "What are the main results of MBI in health care professionals working in public health service?", and "What are the recommendations for clinical practice arising from the use of MBI?"

Table 1. Definition of concepts used in the review.

Research question theme	Definition
Population: health care professionals in public services	
Health care professionals	Workers of health care services, with or without professional qualification, working or not in health programs and institutions, and subjected or not to government regulation
Public health services	Responsibilities of the state government regarding health care. It includes responsibilities for executing activities and specific actions in public health, or mobilization, promotion, orientation, and articulation of social agents [46]
Concept: use of the Maslach Burnout Inventory	
Maslach Burnout Inventory	Instrument used to investigate burnout syndrome in workers [29]
Context: health care professionals with burnout syndrome	
Burnout syndrome	Psychological syndrome characterized by emotional exhaustion, depersonalization, and reduced personal accomplishment and present in individuals working with the public [29]

Second Stage: Identifying Relevant Studies

The search strategy was based on 4 controlled vocabularies in health: health sciences descriptors, medical subject headings, Emtree, and the American Psychological Association thesaurus. Natural language processing was used to increase sensitivity and expand the search results [47,48]. A librarian also refined the search strategy to increase the number of results in all the databases. The strategy was built using a high sensitivity model composed of extraction, conversion, combination, construction, and use [47]. Table 2 shows the conversion of the mnemonics into descriptors.

Table 2. Conversion of mnemonics.

Mnemonic	Extraction	Conversion
Population	Health care professionals working in public health services	Health care personnel Public health services
Concept	Use of the Maslach Burnout Inventory	Maslach Burnout Inventory
Context	Health care professionals with burnout syndrome	Burnout

A description of the complete search strategy for PubMed/MEDLINE is shown in Multimedia Appendix 1. An initial exploratory search was performed in PubMed/MEDLINE to identify the main medical subject headings related to the topic. The search strategy combined the Boolean operators AND and OR and will be further adjusted to each database (Embase, LILACS, PubMed/MEDLINE, PsycINFO, Scopus, and Web of Science). The grey literature will be explored in ProQuest Dissertations & Theses Global, Google Scholar, Brazilian Digital Library of Theses and Dissertations, and Open Access Theses and Dissertations. Additional sources will also be manually retrieved from reference lists. If needed, authors will be contacted for additional information.

Third Stage: Study Selection

The following inclusion criteria will be adopted: quantitative and qualitative full-text studies using MBI among health care professionals working in public health services and no language restriction and no publication date restriction. Duplicated studies, literature reviews, letters, editorials, theoretical essays, opinion articles, and studies analyzing burnout syndrome in non–health care professionals or private services will be excluded. Relevant studies will be retrieved and exported to a spreadsheet. Duplicated studies will be manually excluded. Two independent researchers will read titles and abstracts, and a third reviewer will be consulted in case of disagreement. Texts will be analyzed according to inclusion criteria, and reasons for exclusion will be registered and reported. Following the JBI manual, a pilot test with a random sample of 25 studies (title and abstract) will be conducted to assess eligibility criteria and agreement among the researchers enrolled (it must reach at least 75% of agreement before proceeding with independent assessment) [40]. Details regarding study selection (identification, screening, eligibility, and inclusion) will be presented in a flowchart [41].

Fourth Stage: Data Extraction and Coding

Two independent reviewers will chart data by using an adapted data extraction form based on the JBI model [35] (Table 3).

Table 3. Instrument for data extraction.[a]

Variable	Standardization
Study type	Article, dissertation, or thesis
Publication date	Year of publication
Publication context	Where the study was conducted/published
Journal	In which journal the study was published
Author qualification	Major degree of the first author
Aim/purpose	Aim or purpose of the study
Research type	Research type described by authors
Data collection	Methods for data collection
Study population	Health care professionals and sample size
Sample	Number of participants
Maslach Burnout Inventory	Version of the Maslach Burnout Inventory used
Maslach Burnout Inventory domains used	Emotional exhaustion, depersonalization, and personal accomplishment
Items and Likert scale	Number of items and Likert score
Cutoff points or Latent profile analysis	Cutoff points to identify burnout syndrome or Alternative methods for identifying burnout
Results	Main results of the study
Challenges and limitations	Description of challenges and limitations in using the scale
Recommendations for practice	How the study contributes to improving the mental health of health care professionals
Administration method	In-person or using digital tools

[a]Source: Adapted from Joanna Briggs Institute model [41].

Fifth Stage: Analysis and Interpretation of Results

Quantitative data will be analyzed using descriptive statistics and presented in absolute or relative frequency, whereas qualitative analysis will identify meanings and patterns by using thematic analysis [49].

Sixth Stage: Consultation With Stakeholders

Preliminary results will be presented to 5 researchers in the field of burnout syndrome to contribute to knowledge dissemination, disclosure of findings, and identification of gaps in the use of MBI, frequencies, and cutoff points adopted worldwide. This step will be essential to increase knowledge about MBI, identify new evidence, and develop future strategies to guide public policies preventing burnout syndrome in health care professionals from public services [45]. An email containing the written informed consent and an electronic form with preliminary results will be sent to stakeholders. Interested parties will not be identified, and authors will ask for an analysis of the results.

Ethics Approval

This study followed the ethical principles in human research and was approved by the research ethics committee of the Onofre Lopes University Hospital (4.952.319 and CAAE 46284921.4.0000.5292) on September 3, 2021.

Results

This protocol will guide a scoping review to identify and map studies that used MBI to identify burnout syndrome in health care professionals working in public health services. The results of this review may be useful to public health care professionals, managers, policymakers, and the general population since the findings will help understand the validated, translated, and adapted versions of MBI and domains, number of items, Likert scales, and cutoff points or the latent profile analysis most used in the literature. Furthermore, possible research gaps may be identified to guide future studies. All information regarding the stages of the scoping review favor its transparency and allow it to be methodologically replicated according to the principles of open science, thereby reducing the risk of bias and data duplication.

Discussion

Principal Findings

This protocol will guide a scoping review to identify and map studies that used MBI to identify burnout syndrome in health care professionals working in public health services. This is one of the most important instruments used to identify burnout syndrome and is used worldwide, especially among health care professionals. In addition to the classification by cutoff points, this study advances the consideration of alternative methods for identifying burnout (latent profile analysis) to highlight significant associations and guide the identification of the number of profiles for a given construct. Through this analysis, it will be possible to explore whether the identified profiles differ from the clustering of MBI scores [50,51]. The protocol was developed by a research team with knowledge and experience in scoping reviews and by applying MBI to identify the burnout syndrome. A librarian helped develop a high-sensitivity search strategy based on the combination of 4 vocabularies and no date or language limitations to expand the results and allow a broad access to the literature. All information regarding the stages of the scoping review favor its transparency and allow it to be methodologically replicated according to the principles of open science, thereby reducing the risk of bias and data duplication.

Limitations

As a limitation of the study, we emphasize that the multiplicity of MBI scales that can be found may reveal possible biases regarding the correct use of the instrument. In this sense, we will summarize the results according to the version of MBI most applied in each country and the populations studied. Although this protocol will guide the searches and development of the scoping review, it may not cover the entire literature; thus, studies indexed in different databases may not be found. Although we did not impose a language limitation for inclusion of the studies, the use of descriptors and search terms in English and Portuguese languages may be a limitation for this study.

Conclusions

This study protocol presents the main methodological steps that will guide the scoping review and identify and map studies that used the MBI scale to identify the burnout syndrome in health care professionals working in public health services. This study may reveal the multiplicity of scales described in the literature and the different forms of assessing burnout syndrome in health care professionals. The results of our study may also help to standardize the assessment of burnout syndrome in health care professionals working in public health services and promote knowledge dissemination about burnout syndrome and mental health in this population.

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Authors' Contributions

JPS conceptualized this study. JPS, RHL, PBdSM, CRDVS, CCFMR, and JLdC devised the methodology, wrote the original draft of the paper, and reviewed and edited this paper. JPS, RHL, and PBdSM performed data curation and formal analysis. JLdC performed study administration and supervision. All authors have read and agree with the publication of this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Complete strategy for the search in MEDLINE/PubMed.
[DOCX File , 16 KB - resprot_v11i11e42338_app1.docx]

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Abbreviations

JBI: Joanna Briggs Institute
MBI: Maslach Burnout Inventory
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses-Extension for Scoping Reviews
PROSPERO: International Prospective Register of Systematic Reviews

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