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Self-reported Subjective Effects of Analytically Confirmed New Psychoactive Substances Consumed by e-Psychonauts: Protocol for a Longitudinal Study Using a New Internet-Based Methodology

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Abstract

Background: During the last few years, the continuous emergence of new psychoactive substances (NPS) has become an important public health challenge. The use of NPS has been rising in two different ways: buying and consuming NPS knowingly and the presence of NPS in traditional drugs as adulterants. The rise of NPS use is increasing the number of different substances in the market to an extent impossible to study with current scientific methodologies. This has caused a remarkable absence of necessary information about newer drug effects on people who use drugs, mental health professionals, and policy makers. Current scientific methodologies have failed to provide enough data in the timeframe when critical decisions must be made, being not only too slow but also too square. Last but not least, they dramatically lack the high resolution of phenomenological details.

Objective: This study aims to characterize a population of e-psychonauts and the subjective effects of the NPS they used during the study period using a new, internet-based, fast, and inexpensive methodology. This will allow bridging an evidence gap between online surveys, which do not provide substance confirmation, and clinical trials, which are too slow and expensive to keep up with the new substances appearing every week.

Methods: To cover this purpose, we designed a highly personalized, observational longitudinal study methodology. Participants will be recruited from online communities of people who use NPS, and they will be followed online by means of a continuous objective and qualitative evaluation lasting for at least 1 year. In addition, participants will send samples of the substances they intend to use during that period, so they can be analyzed and matched with the effects they report on the questionnaires.

Results: The research protocol was approved by the Institutional Review Board of the Hospital del Mar Research Institute on December 11, 2018. Data collection started in August 2019 and was still ongoing when the protocol was submitted (September 2020). The first data collection period of the study ended in October 2020. Data analysis began in November 2020, and it is still ongoing. The authors expect to submit the first results for publication by the end of 2021. A preliminary analysis was conducted when the manuscript was submitted and was reviewed after it was accepted in February 2021.

Conclusions: It is possible to conduct an institutional review board–approved study using this new methodology and collect the expected data. However, the meaning and usefulness of these data are still unknown.

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KEYWORDS

psychotropic; psychoactive; psychonautic; longitudinal; observational; pharmacology; psychopharmacology; subjective effects; sentinel; mental health; public health; internet; eHealth; cathinones; drugs of abuse; psychedelics; mobile phone; smart phone; online recruitment; online forums

Introduction

Importance of New Psychoactive Substances

To date, new psychoactive substances (NPS) still represent a very important challenge to legislate, monitor, study, and develop health interventions. The understanding of use patterns remains poor, with most information being based on populations and settings where problems have already occurred [1].

The ever-increasing number of psychoactive substances used nowadays represents a new challenge for psychiatry, as the pharmacodynamics and pharmacokinetics of many NPS are not yet thoroughly understood [2]. In addition, NPS consumption rarely occurs in isolation from other habits but, on the contrary, is placed within a kaleidoscopic range of poly drug use trajectories. There seems to be no differential risk for NPS use compared with the use of traditional psychoactive substances such as alcohol, cannabis, or cocaine [1].

This new phenomenon represents an unprecedented challenge in the field of drug use as well as a fast-growing problem from social, cultural, legal, and political perspectives [3].

NPS: Definition

NPS are substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances but which may pose a public health threat. It is important to note that different authors have previously referred to them as *designer drugs*, *legal highs*, *herbal highs*, *bath salts* and *research chemicals*. Moreover, the term *new* does not necessarily refer to new inventions but to substances that have recently emerged on the market [4]. Hence, *new* can include a failed pharmaceutical or an old patent that has been *rediscovered* for *recreational* substance [2].

Another distinction being made is between NPS and emerging psychoactive substances, where the latter term captures all NPS as well as drugs that may not be newly invented but have recently experienced a resurgence of, or increase in, use [2]. However, to simplify this work, only the term NPS will be used, also including all emerging psychoactive substances. Most NPS are the result of minor changes to the molecular structure of well-known legal or illegal drugs, such as opioids, ecstasy, or stimulants [5].

Between 2009 and 2017, 803 NPS were reported in 111 countries or territories [2,6]. In the European Union, by the end of 2017, the number of NPS was over 670, of which 632 were notified after 2004 [2,7]. However, evidence suggests that the NPS scenario could be much larger than that formally identified by international agencies. In a recent publication, Schifano et al [2] used a web search engine to identify NPS discussed online by NPS enthusiasts. Using this methodology, they identified a few thousand NPS, a number which is about 4-fold higher than the figures suggested by European and international drug agencies.

There is an ongoing debate on the scale of challenges posed by NPS, as the evidence on the prevalence of NPS use is scarce. For example, general population surveys suggest that the prevalence of NPS use is relatively low, with the best estimates found in the scientific literature being between 1% and 2% in the United Kingdom. However, the speed of technological innovation and the ease of synthesizing NPS present substantial challenges to regulatory authorities, researchers, and clinicians [5,8].

NPS: Challenges

NPS may now pose a big challenge due to several factors:

1. NPS consist of several different classes of substances, which vary in their psychological and physiological effects. Treatment is often difficult because of the young age of most users and the possibility of concurrent polysubstance use. The pattern of use is often intermittent in social settings, so it may be perceived as less of a problem [9].
2. NPS appear into—and sometimes disappear from—the market very quickly, and as such, they are not significantly impacted by regulatory efforts. Currently, new substances are identified in Europe at a rate of one or more per week [10]. Several key studies have shown the continued use and popularity of mephedrone, a popular NPS, among specific drug-using populations after it was brought under control. The scheduling of new substances could even increase the speed at which manufacturers innovate, to bypass the law [11].

3. NPS are mainly distributed through the internet in a transnational market without solid information about their effects and risks [11]. During recent years, the widespread availability of internet access has led to a gradual, although only partial, shift from a *street* to a *web* market [12]. The increased web-based distribution has been seen in both the surface web and *dark net* [13].
4. NPS can substitute traditional drugs in times when their availability is restricted [8]. This could be problematic, as this substitution happens both by introducing new substances in the market as well as by selling NPS as traditional drugs, exposing large populations, unknowingly, to the effects of a new unstudied substance without previous experiences. This is especially dangerous, combined with the rapid turnover of NPS, as they change before we can obtain research data using conventional methodologies [5].
5. There is a concerted effort to grapple with the challenges of researching NPS, as traditional methodologies are too slow and expensive to generate relevant and timely data on the effects of NPS [5].
6. Clinicians are not usually able to identify a potential NPS user, and NPS usually produce negative results to traditional drug tests, which are designed to assess a very limited number of traditional substances [6]. On the other hand, NPS users rarely search for professional help linked exclusively to this problem, and clinicians are not trained to screen or identify NPS use.

What Has Been Done and What Is Needed in NPS Research?

Despite the high number of publications about NPS during the last 20 years, especially after a sharp increase in 2010, there are still concerning *gaps in our understanding* of the phenomena. From the evidence map about the NPS research performed by Mdege et al [8], 2 things appear quite striking:

- First, most of the studies were performed in a general hospital population (118/294, 40.1%) or specialist settings (24/134, 18.2%), with relatively *low rates of studies coming from the internet population (*5/59, 8%). In addition, these studies mainly reported severe intoxication or other acute NPS-related problems.
- Second, the most frequent study design reported in the indexed peer-reviewed literature was case series and/or reports (n=367), followed by the literature review (n=243), the survey (n=130), and the secondary quantitative data analysis (n=99), with only 13 existing randomized controlled trials, 6 prospective cohort studies, and 1 case-control study [5,8].

There are also some *specific limitations* to the research performed till date. Although the most robust and representative data on NPS use are for mephedrone (surveys have been conducted in the United Kingdom since 2010), Mdege et al [8] acknowledge important limitations to this most robust research. For example, although participants may report using a substance, the names of NPS are sometimes used interchangeably, and *there is no analytical confirmation* of the true compound that was taken. Therefore, there is inherent uncertainty in the reported use of a particular NPS.

The same authors also reported that sentinel populations are likely to be at a greater risk of NPS use. However, it remains mostly limited to attendees of nightclubs where different sexual orientations are accepted. Other authors have also remarked that only a handful of studies have moved beyond prevalence to explore subjective user experiences and motivations [11].

Currently, the potential data sources that can provide some information on the acute effects of NPS consumption are as follows: (1) user self-reports on internet discussion forums, (2) surveys answered by users, and (3) fatal and nonfatal case reports.

Self-reports and surveys are mostly based on self-reported use rather than the analytical confirmation of the substances used. In contrast, case reports are usually generated from hospital settings in the context of an intoxication or overdose with multiple substances involved, so there is analytical confirmation of the substance but no self-reported effects. Unsurprisingly, the literature is dominated by studies investigating the problems associated with NPS (773/995, 77.7% of records). Therefore, caution is required when interpreting these data because of the following limitations:

- Users will report what they believe they have used, rather than whatever substance is actually taken [10].
- Intoxications with multiple substances in hospital settings do not target the information on psychopharmacological effects of a particular NPS [5,8].

In their empirical and conceptual review to produce research recommendations, Mdege et al [8] provide the following advice for research, among others:

1. The need to be aware of innovation opportunities, such as testing emerging NPS brands online as they become available.
2. Using cohort study designs to better understand the determinants of NPS use and related physical and mental health, psychosocial problems, and how patterns of involvement and consequences change over time.
3. What are the prevalence and patterns of NPS use in the general UK population and do they differ between subgroups of the population?
4. Are there sentinel populations capable of being monitored to provide early warnings of new trends?
5. Which acute intoxication problems are associated with NPS use?
6. Which promising approaches are currently available or can be made available in the United Kingdom for intervening with NPS use?

Finally, they concluded that there is a need for a major research effort to be directed at NPS, which should address NPS together with other forms of licit and illicit drug use [5,8].

The e-Psychonaut Population

Both the limitations and recommendations stated above lead to the *necessity of conducting a longitudinal study in a specific and potential sentinel population*, such as internet NPS–consuming communities. This would allow for early assessments of the effects of recently emerged drugs and to

study the patterns of consumption, harm reduction strategies, and long-term drug-related problems.

Available data on sentinel populations are growing. For example, several studies of attendees of gay-friendly night clubs suggest that the trend in reduction of mephedrone witnessed nationally may also occur in this subgroup. However, the study of this sentinel population has failed to predict future harms and trends in the global NPS market [5].

Conversely, data on another sentinel population, namely, e-psychonauts, have been able to predict future NPS-related harms occurring in more general settings [2].

In fact, the sentinel population of *e-psychonauts* has been considered by several authors as potentially useful in identifying NPS availability, market, and diffusion in advance. This population is believed to be responsible for shaping and influencing the drug scenarios of the future [13]. In addition, Corazza et al [3] provided evidence supporting the claim that the online NPS scenario predicts the real-life NPS scenario.

The term psychonaut was first described by Newcombe [14] as an adult user of psychoactive drugs who takes these substances in *normal, everyday settings* with the intention of subjectively exploring their effects.

Some years later, O'Brien et al [11] coined the term *cyber-psychonauts* to refer to their sample composed predominantly of NPS consumers. Cyber-psychonauts are further defined by their commitment to harm reduction, to using NPS safely and responsibly, and to purchasing chemicals online [8].

Tackett-Gibson [15] also documents the existence of online communities populated by self-defined *experts* in using NPS, providing a contrasting narrative around drug use and risk to that established by the scientific community. A brief perusal of relevant websites confirms the existence of a great number of NPS-related discussion threads, suggesting the existence of an online community of more discerning NPS users [15].

Orsolini et al [13] also refer to this population in their more recent study, identifying *educated and informed* users within web-based drug forum communities, who can provide reliable information on psychoactive compounds. They refer to these users as *e-psychonauts*, providing the best characterization of the population to date [13]. The e-psychonauts appear to be mainly young and unmarried White males, presenting good or excellent employment conditions and with a set of key skills, including awareness to their inner *soul*; high standards of knowledge about drugs' chemical and pharmacological issues; and high levels of both technology-related skills. They are meant to have a wide vocabulary to define their own *on drug* experiences in the most subtle and precise way possible.

Among this population, the frequency of NPS use is high, with one-third of the participants reporting its use in the last week. They view themselves as knowledgeable consumers who use the internet to accumulate information about NPS and share their own experiences, informing fellow users of potential harms. However, other studies [16] reported possible stimulant dependence (3 or more dependence symptoms) in 30% of mephedrone users. Mdege et al [8] also found that NPS users often report substance use disorder symptoms, especially craving.

This community may have some other distinct characteristics. A minority of the sample reported that an NPS was the first drug that they had ever taken. Of those who ceased using NPS, majority found it either easy or very easy to stop. Most commonly, cessation was due to the side effects of NPS [17]. They also perceived internet forums as an important channel through which to communicate information on new drugs, and retailers reported monitoring forums to determine which drugs to stock in their store [8]. These users also tend to post online warnings based on first-hand experiences about the potential harms of the substances consumed and are willing to avoid harm to their peers. Orsolini et al [13] even stated that posting online the *on drug* experience report is arguably the *trait d'union* of all e-psychonauts, considering the intention behind using a substance is the most significant difference between a psychonaut and a typical drug user. O'Brien et al [11] also identified the role of e-psychonauts in disseminating emerging information about NPS-related harm and considered them well equipped to make a valuable contribution to NPS policy debates in general, and e-psychonauts are ideally placed to report on the effects of recent policy changes on NPS-related harms in particular.

Several authors have tried to engage cyber-psychonauts as research participants. Mdege et al [8] found difficulties in involving NPS users throughout the project due to a lack of willingness on the part of NPS users to be contacted in ways other than email. In addition, working with this population has inherent sampling problems: internet research participants are, by definition, a nonrandom and self-selecting sample, and it is very difficult to know the characteristics of the overall pool from which the sample is drawn [18,19].

Different authors believe that these internet communities are a huge opportunity for researchers. The qualitative analysis of how different groups interact with online communities may help to systematize and codify needs, values, and preferences that are relevant to the group [20]. In internet communities, researchers can simply recruit participants or even go further and engage drug users more fully in dialog [21]. Some authors even state that the lack of physical presence and separate physical settings all reduce researcher control and power, thereby potentially leading to a more balanced relationship between researchers and participants [22,23]. In any case, e-psychonauts are a hidden, hard-to-reach population that may have a significant influence on future drug trends.

Some authors even consider cyber-psychonauts to be ideally placed to become involved in the actual implementation of innovative responses to the increasing prominence of NPS markets, as it is difficult to imagine a more efficient method for the rapid dissemination of new information about things such as the adverse effects of new products to consumers [24].

The recent alarm related to the growth of the NPS market and the gradual shift from the street to the cyber-drug market may call for the implementation of preventive tools and practices tailored to these new drug users' characteristics [13].

Finally, in their empirical and conceptual revision of the NPS research field, Mdege et al [8] concluded that there was a clear need to move beyond an expert-driven discourse on NPS and involve people who use NPS as active and valuable research collaborators and stakeholders instead of passive research participants.

It is clear then that this sentinel population might be difficult to reach and retain in a highly structured study protocol [5,8,18,21,25]. However, the collaboration of the Energy Control (EC) International Drug Checking Service might provide a critical opportunity for recruitment, offering a free chemical analysis of the substance they want to consume. This service is already being used by this population in the main internet communities of psychonauts, and it has a well-regarded institutional presence in most of them [26,27].

Relevance and Goals of This Study

In summary, NPS pose a public health threat at different levels, and there is a lack of research on the effects of the emerging substances as well as on which ones are appearing now. In addition, the research conducted to date has been unable to cover important gaps, such as studying relevant sentinel populations of e-psychonauts using new technologies, involving them in the research, and obtaining confirmatory analytical data of the substances studied. Old methodologies repeatedly fail to reach the skyrocketing turnover pace of newer NPS in the e-market. By the time old trials recruit the necessary drug *X* study participants and engage them in the old trial machinery, drug *X* has already become obsolete and has been replaced by *Y* and—possibly—even *Z* drugs.

This study aims to bridge the abovementioned evidence gaps. To do so, a naturalistic, observational, and longitudinal design has been adopted, recruiting e-psychonauts to gather information on their characteristics and the substances that they might be using before their popularization. This has been possible thanks to the development of a new online ad hoc tool designed for this project: an online platform thought to enhance communication with the e-psychonauts and allow community building. In addition, subjective effects on these substances have been studied, allowing the participants to send samples to a partner laboratory with gas chromatography (GC)/mass spectrometry (MS) in Barcelona and administering drug effect questionnaires in the most resembling way possible to the drug laboratory studies.

This design has resulted in the first internet-based, multinational study on a key sentinel population with laboratory confirmation on the composition of the reported samples.

Study Objectives and Hypothesis

The study has been designed to answer 3 main research questions:

1. Who are the people who first try the new substances when they emerge in the market?
2. What are the substances emerging right now and their subjective effects?
3. Is it possible to collect reliable data to answer these questions using a low-budget internet platform and the design used in this study?

The researchers' initial hypotheses are as follows:

1. The population of e-psychonauts will be made up of functional and educated people who use drugs mainly in a recreational way.
2. During the study period, we will be able to identify a wide variety of different substances, some of which have never been reported before in the scientific literature or by the organizations aimed at controlling illicit drug supply.
3. The study design and implementation will attract enough research participants with sufficient commitment to provide valuable, reliable, and meaningful data to generate quality evidence.

Methods

Overview

This study aims to discover the characteristics of the e-psychonaut population and the effects of the NPS they use, with a longitudinal design and no control group. The study is conducted online, recruiting participants using an innovative and specifically developed platform as part of the study project: Global Research and Analysis of New Substances Project (GRASP).

The study has been designed and will be reported using the Checklist for Reporting Results of Internet E-Surveys [28] and the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement checklist for observational studies [29], with the support of the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement checklist of 2013 [30].

The study protocol was submitted in October 2018 and was approved by the Clinical Research Ethics Committee (Parc de Salut Mar, Barcelona, Spain, ref. 2018/8283/I) in January 2019. The study was conducted according to the Declaration of Helsinki recommendations and the emerging recommendations for online research on sensible topics [21,25]. All data collected online on the participants were encrypted according to the European and Spanish data protection regulations (2016/679 European Parliament and 27/4/16 reglamento general de protección de datos [general law about data protection] Spanish Royal Decree).

Study Setting

The study is conducted mainly though internet, using 3 main tools:

1. The specifically designed GRASP platform
2. The *Qualtrics* survey service licensed though Columbia University
3. The Google Suite platform as an email service to contact candidates and attend to the private questions and concerns of the study participants.

In addition, the samples were received through traditional mail in the EC Headquarters in Barcelona, where they were initially

processed and identified. The samples were then transported to the EC laboratory at the Hospital del Mar Research Institute (IMIM), second floor, to be analyzed using the techniques described below. The research team worked at both the EC headquarters and the IMIM laboratories. During the COVID-related lockdown that was established in Spain in March 2020, the laboratory analysis was interrupted for 3 months.

The usability of the platform and the multiple automated processes, such as *sending an email with a specific link to a questionnaire*, and the logic pathways (adaptive questioning) and validation requirements used in the *Qualtrics* questionnaires were systematically tested by the research team. A checklist of all possible scenarios was devised, and they were all executed by a blind research team member and the principal investigator. Once errors were identified, they were corrected, and the process was repeated from the beginning. In addition, participants were encouraged to report any problems or ideas to improve the procedures, so changes could be implemented when needed during the study.

Participants

All the participants were correctly and fully informed by writing (refer to the participant information sheet in Multimedia Appendix 1) and prompted to ask any questions by email. In that case, answers were provided until the candidate confirmed that they had no more questions and were satisfied with the information received. All participants indicated their agreement to participate and signed an informed consent (IC) form (Multimedia Appendix 2) that was sent to the project email address and checked by the principal investigator before inclusion. It was not possible for candidates or participants to answer any online questionnaires without previously receiving the specific link, which was sent by the research team only when the participant met the criteria to fill the questionnaire. Participants were asked to sign with their online usernames to further protect their physical identity, as recommended by Barratt et al [21,25]. Participants received no monetary compensation for their participation, but instead, they were offered the possibility to get the NPS they reported on analytically tested for free in the EC laboratory, located in the *IMIM*, Barcelona. The cost of this service is US $110 if contracted independently through the EC International Drug Checking Service.

This study included e-psychonauts, who have been defined as people with the following characteristics:

1. Previous experience with at least three NPS 12 months before the study inclusion
2. Activity on online communities where NPS consumption is discussed.

The inclusion and exclusion criteria for participants are provided in Textbox 1.

Textbox 1. Inclusion and exclusion criteria for participants.

Inclusion Criteria

- Meeting the operational definition of e-psychonaut
- Being 18 years or older at the time of recruitment
- Self-reported plans of maintaining the use of new psychoactive substances for the following 18 months

Exclusion Criteria

- Difficulties in communicating in English
- Difficulties in using new technologies to participate in the study
- Potentially pregnant women
- Potential presence of severe psychopathological symptomatology

Note that there is no restriction on the geographical location of the participants, as the study will not collect such data to further protect the participants' physical identity. Therefore, participants from around the globe could participate in the study. Both inclusion and exclusion criteria have been mainly assessed by direct self-reporting in an initial screening questionnaire (Q0), except the following:

1. Previous participation in forums has been assessed by self-report and exclusive advertisement of the study on these forums.
2. Difficulties in using new technologies have been assessed by the steps required to complete the screening process, such as sending an IC form in a particular format, registering to the platform, and following the instructions there to introduce themselves to the research team and other participants.
3. Difficulties in communicating in English and the presence of potential psychopathological impairments have also been evaluated by the principal investigator, assessing the answers to long and elaborate open questions in the screening questionnaire (Q0) and in the written introductions to the online platform.
4. The potential of being pregnant was assessed by indirect questioning using the same screening questionnaire (Q0) questionnaire.

Recruitment

Recruitment ads were sent to the moderators of the selected online communities after establishing bilateral communication with them, mainly to ask permission and explain the goals of the project. To maximize interest in participating in the study, the only focus was on establishing rapport with community leaders, as if they share their interest in the study, they will be

able to transfer it to the rest of the community [31]. Each community moderator posted the research ad in the most appropriate way in their community after discussing it with the research team. Research ads were posted on all communities during the summer of 2019 (refer to Multimedia Appendix 3 for details). The recruitment was designed to be sequential until the designed sample size was reached or the study reached its duration limit.

The operational definition for online communities of people who use NPS has been adapted from the study by Barratt [21]:

1. Surface websites with at least 5 years of existence
2. Presence of participation forums dedicated to discussing the use of NPS
3. At least weekly activity on the community forum
4. The use of pseudo-anonymity by community members to identify themselves
5. The presence of official and analytical drug checking services in the community.

When the study design was completed (October 2018), there were 4 communities meeting the previously stated criteria [21]:

1. *Bluelight* [32]: Established in 1997, bluelight is probably the most prominent community of people who take illicit drugs, with approximately 250,000 members. Within the community, there is a subdivision in which the use of NPS is exclusively discussed. The community is known for its commitment to promoting risk management and harm reduction strategies among its participants as well as its formidable contributions to similar research projects [28]. Registration is required to access the content.
2. *Reddit* [33]: Established in 2010, this subreddit community allows almost any type of discussion regarding NPS. The community has approximately 90,000 members, but it is part of a broader community of people who use illicit drugs (not only NPS), with over 700,000 members. Both of these are part of the global reddit community, where all types of topics are discussed. The platform does not require registration to access the content.
3. *Drugs-forum* [34]: Established in 2003, this community also seems to have approximately 250,000 members. Registration is required to access the content.
4. *DNstarsVIP*: Established after discussing about NPS sources was banned on the *reddit* community, *DNstars* is a strongly emerging community with approximately 2000 users. Registration is required to access the content.

The main communities that were assessed and excluded were as follows:

1. *Legal-highs forum*: excluded because of the lack of weekly interactions, technical website problems, and impossibility to contact community managers.
2. *Erowid*: excluded because of the lack of an active forum.
3. *Psychonaut wiki*: excluded because of the lack of an active forum.
4. *Tripsit*: excluded because of the lack of an active forum, although there was an internet relay chat–supported chatroom.
5. *Dimethyltriptamine-nexus:* excluded because of the lack of a specific NPS subsection.
6. *Ecstasy data*: excluded because of the lack of an active forum and the lack of a specific NPS subsection.
7. *Shroomery:* Excluded because of the lack of a specific NPS subsection.

To the best of the authors' knowledge, the selected communities were the main ones at the moment when the selection occurred (October 2018), although it has to be acknowledged that this is a rapidly changing scenario; in a few years, this same process might produce different outcomes. At that moment, the authors were unable to find any contradicting information with that assumption. Soussan et al [35] referred to *bluelight*, drugs-forum, and legal-highs forum as the top 3 communities. However, they did not consider collaboration with drug checking organizations to be a relevant factor. Moreover, as stated above, these rankings are expected to change over relatively short periods [35].

The GRASP platform, which allowed for interaction among participants themselves and with the research team, was the main tool to promote participant engagement and minimize dropout rates.

Sample Size

In the most recent review consulted by the authors, the sample sizes reached with web-based questionnaires in people who use illicit drugs ranged from 80 to 9867 [36]. The expected losses while filling these types of questionnaires are about 50% of the sample, but the authors have not found other online longitudinal studies including questionnaires like this one. According to the aforementioned review, the authors expected 80 candidates as the best possible estimate to achieve 40 final participants. Assuming that each participant takes one NPS every month during the duration of the study, the expected number of registered self-administration trials of NPS would be 480. As the study has been designed as exploratory, the sample size could not be determined based on the needs to perform specific statistical tests.

Study Procedures and Timeline

The study's internal timeline and workflow are graphically represented in Multimedia Appendix 4. The first recruitment effort consisted of online discussions with forum moderators and posting the institutional review board (IRB)–approved announcement for candidates (displayed in its entirety in Multimedia Appendix 3) in those forums. In the announcement, potential candidates were instructed to send an email from a secure and nonidentifiable address to the research team (admin@grasp.pw). Candidates were then informed more broadly about the study. Candidates were informed homogeneously by sending the IRB-approved *information for candidates' sheet* to their email (the sheet used in this study can be found in Multimedia Appendix 1). The principal investigator then offered the candidates to answer any questions that might have arisen after reading the participant information sheet. When the participants had read and discussed the given information about the study with the principal investigator, they were asked to register on the GRASP platform and send the IRB-approved

IC form, completed with the registered username to the study email. In Multimedia Appendix 2, the IC form is available for consultation. Finally, the candidates were asked to complete the screening questionnaire (Q0) and introduce themselves on the platform without providing information that might reveal their real-world identities. When all these processes were complete, the principal investigator checked the IC form, the screening questionnaire, and the platform introduction to assess if the participant met the inclusion or exclusion criteria. Candidates were then informed by email about the results of the assessment, thus either being rejected or accepted as participants.

Once participants were accepted, they could interact with other participants on the online platform and received detailed instructions on how to conduct the study. However, NPS sourcing and the effects of the substances included in the study were not allowed. In case of a severe protocol violation such as this one, participants were immediately removed from the study and their information was deleted. In case of minor protocol violations, participants were notified and given the opportunity, if applicable, to amend their noncompliant behavior.

The first mandatory step was to fill a sociodemographic and drug use history questionnaire (Q1). This questionnaire was available to each participant through a participant-specific link, which was sent by email once they were accepted. After that, participants were asked to fill the sample submission questionnaire (Q2), where information about the sample they intended to consume was asked. This questionnaire was then reviewed by the principal investigator and approved if the substance met the study criteria of being a new psychoactive substance. The samples that did not meet the inclusion criteria were not accepted, and the participant was notified by email. The sample submission questionnaire (Q2) was available to all accepted participants as a link on the platform. All the questionnaire answers were reviewed weekly by a member of the research team to communicate to the participant the acceptance of the sample and to mark them as valid or invalid data for later analysis.

If the sample was approved, the participant received a specifically generated sample code with the instructions to send a small amount of the sample (approximately 30 mg, usually below the psychoactive threshold) via traditional mail to the laboratory at the IMIM. The sample was analyzed there, and the result was sent back to the user, along with harm reduction advice when appropriate.

Meanwhile, the users could consume the substance whenever they decided, as the study was intended to be observational. However, most of the participants waited until they had the result of the laboratory analysis to proceed with the self-administration trial. The self-administration trial started with the users filling the drug effect baseline questionnaire (Q3a), and then, they consumed the reported substance and filled the drug effect questionnaire (Q3b) 24 hours after filling the baseline questionnaire (Q3a). The links to these questionnaires were available for all participants in the forum, and the veracity of the information was ensured by asking information only available to each participant, such as the sample code of the reported sample.

Study recruitment began in August 2019 and is still ongoing. In August 2020, the first participant concluded the 1-year follow-up.

IRB-Approved Protocol Changes During the Study

The protocol has been subjected to amendments twice, both approved by the IRB of the institution (Clinical Research Ethics Committee-IMIM).

The first amendment, submitted in January 2019, reported the following changes in the protocol:

1. Minor changes in the study advertisement sheet, participant information sheet, and IC form
2. The assessment of inclusion criteria was no longer done by the community moderators and was entirely assessed by self-reporting on online questionnaires
3. An increase in the required sample quantity to be sent to the laboratory from 30 to 50 mg by default, accepting exceptions depending on the substance potency
4. Addition of a key measurement timepoint at baseline before ingesting the substance.

The second amendment, submitted in November 2019, reported the following changes in the protocol:

1. Unblinding of the research team to the participant behavior and participation
2. Addition of an optional timepoint for data collection in the reporting of the subjective effects of the reported substances
3. Extension of the duration of the study from 6 months to 1 year for each participant
4. Reduction of the required age for inclusion from 21 to 18 years.

Outcomes

The domains and measurements used in the study are based on previous laboratory studies, to maximize consistency in methodology and to eventually develop a validation study for this methodology. Multiple studies have shown that web-based data collection and traditional methods (eg, paper and pencil) result in equivalent conclusions, demonstrating the validity and reliability of online data collection for research [37,38].

Certain studies have been used as model references to select the measured outcomes [39-52]. However, new outcomes regarding the subjective effects of psychoactive substances have been added to balance the amount of positive and negative effects reported. The order of the questions was kept the same to facilitate reports to those participants who completed the same questionnaire multiple times. However, 3 questions to assess validity were present in both the Q3a and Q3b. More information about study outcomes, including assessed domains, chosen measurements, metrics, and time points, can be found in Multimedia Appendix 5.

Data Collection

Questionnaires

The study data were collected using a Columbia University *Qualtrics* license, a well-known questionnaire platform compliant with the guidelines to store sensible information about the research participants. The screening questionnaire (Q0) and the sociodemographic questionnaire (Q1) collected self-reported information about the participants' medical and drug history, psychosocial situation, and beliefs and behaviors related to drugs.

The subjective effects of drugs were assessed via visual analog scales, using the same parameters used in most laboratory studies to determine the subjective effects of drugs. The main outcome was the difference in mm from the drug effect questionnaire (Q3b) at 24 hours (referring to the peak experience) and the baseline questionnaire (Q3a).

Each questionnaire also had at least one validity entry to be filled by the researcher directly using the *Qualtrics* database. There were no automated consistency or completeness checks before the questionnaire was submitted, other than the validation criteria for certain questions. For example, the question *sample code reported* could not be submitted if the answer was not a 5-digit number.

The participants could go back through the questionnaire, but once submitted, they could not change their answers. A summary of the answers was not displayed either before or after submission. Two options were available to change the participants' answers if they were incorrect according to the participant or not valid according to the researcher. If the change was small, the researcher could just edit the participant response in the *Qualtrics* database according to the correct response provided by the participant using email or the platform's private messaging system. If the changes were relevant, the researcher could mark the questionnaire as invalid and provide another link to the participant.

Public links to copies of the used questionnaires can be found in the references cited below:

1. Q0, screening questionnaire [53]: contained a total of 37 questions
2. Q1, sociodemographic questionnaire [54]: contained a maximum of 351 questions, with an expected average per participant of 50, due to adaptive questioning and questionnaire logic
3. Q2, sample submission questionnaire [55]: contained a total of 21 questions
4. Q3a, baseline drug effect questionnaire [56]: contained a total of 12 questions
5. Q3b, drug effect questionnaire given 24 hours after drug administration [57]: contained a total of 39 questions
6. Q4, 1-year follow-up questionnaire [58]: contained a maximum of 351 questions, with an expected average per participant of 50, due to adaptive questioning and questionnaire logic.

The number of pages and items on each page were optimized automatically by *Qualtrics* software and varied according to the screen size used to answer. The possibility to answer the questionnaires comfortably from the smartphone was assessed as an essential by the research team.

Laboratory Analysis

Preliminary sample identification was performed by GC coupled to MS using an Agilent 7890B gas chromatograph coupled to a 5977A quadrupole mass spectrometer detector (Agilent). The gas chromatograph was fitted with a G4513A auto-sampler injector. Insert liners packed with salinized glasswool were used, and the injector and interface were operated at 280 °C. Samples were injected in split mode into a 0.25 mm film thickness (5% phenylmethylsilicone) column (HP-5MS, Agilent Technologies). Helium was used as the carrier gas at a flow rate of 1 mL/min. The oven temperature was initially maintained at 90 °C for 2 minutes and programmed to reach 320 °C at 20 °C/min. It was finally maintained at 320 °C for 9.5 minutes (total run time was 21.5 min). The mass spectrometer was operated in the electron impact ionization mode at 70 eV. To confirm the mass spectra, 4 libraries were used: the NIST/EPA/NIH Mass Spectral Library, Data Version: NIST 14; Searchable Mass Spectral Library Version 2.3 [59]; Searchable Mass Spectral Library Cayman Spectral Library [60]; and EC's internal mass spectral library. Confirmation (when needed) was performed by liquid chromatography (LC) coupled to tandem MS (LC/MS/MS) using an Agilent 1100 series HPLC (high performance liquid chromatography) chromatograph (Agilent Technologies) and an Esquire 3000 plus mass spectrometer MRM (Bruker Daltonic GmbH). Chromatography was performed using a Poroshell 120 EC-C18 column (100 mm length×2.1 mm internal diameter; 2.7 mm particle size) at 30 °C. The mobile phases consisted of 1% formic acid and 1% formic acid in methanol. The following gradient elution was used: at time 0 minute, 15% B was changed to 90% B in 7 minutes, held for 1 minute, and changed back to the initial conditions in 1 minute. Before injection of the next sample, the column was re-equilibrated for 7 minutes. The flow rate was 0.35 mL/min. The electrospray source was operated in the positive ionization mode. Product ions that were obtained by collision-induced dissociation allowed the MS/MS to be operated in the multiple reaction monitoring mode. The dwell time was set at 0.25 seconds. The desolvation gas was nitrogen set at 365 °C and delivered at a flow rate of 9 L/min. The capillary voltage was 3.90 kV, and the collision gas was helium. The Bruker Compass Hystar system software Version 3.2-SR2 was used for instrument control and identification.

GRASP Forum

Secondary data about the participants' discussions on the study platform were supported by a licensed *discourse* (Civilized Discourse Construction Kit, Inc) account and the software used to build the platform. *Qualtrics* (SAP Global Corporate Affairs) data were downloaded for analysis, which was conducted using the institutionally licensed Microsoft Excel from the IMIM and R (R Core Team), which is a free software environment for statistical computing and graphics that does not require a license.

Data Management and Statistical Analysis

Data will be stored in *Qualtrics* software and will only be used according to the goals of the study described in the protocol. Most of the data will be entered directly by the participants, and a researcher will screen every questionnaire filled for consistency and ask the participants for clarifications in case of suspected errors in data entry or reporting. The principal investigator (MG) and 3 more researchers (GMF, XCM, and JGC) will have access to the complete data sets. Data on participant performance will be entered manually by one researcher in an internal Excel database. No personal information will be stored other than the *safe* email address asked in the study advertisement and the nickname the participant choses to use in the forum. This ensures the maintenance of pseudo-anonymity, as information about the online persona will be stored, but the link between the online identity and the real identity will not be impossible to establish with the collected information.

Data will be managed and processed using *Qualtrics* software and initially analyzed using Excel by the research team. At the same time, an independent statistician will use the same data from *Qualtrics* to perform a partially blind analysis using R. Only fully completed and valid questionnaires will be analyzed. The validity of the questionnaires will be assessed by a research team member based only on the consistency and completeness of the participants' answers.

As it is an exploratory study, the data analysis procedures will be mainly descriptive statistics, to maximize an adequate visualization of the data collected within the minimum space. In addition, as there is no control group, statistical tests will be limited to potential comparisons to assess bias on the results, such as comparing data from participants who complete the study with participants who drop out or are excluded. However, no statistical corrections will be applied to adjust the representativeness of the sample, as this validation will be done by comparing the sociodemographics of the study sample with the characteristics of the population of psychonauts widely reported in the literature. Statistical tests might also be used to compare information from the initial questionnaire Q1 and the data from the follow-up questionnaire Q4. The nonparametric Wilcoxon signed-rank analysis will be used to perform a mean comparison of the quantitative data and the chi-square test for qualitative data. In addition, factor analysis will be attempted to study the relationship between all the visual analog scales used to assess the subjective drug effects.

The data analysis will focus on the outcomes of the participants who completed the study. Data entries containing evident errors or inconsistent information will be discarded, and the extent to which this might have impacted the results will be reported.

Ethical Considerations

This study was approved by the IRB of IMIM on December 11, 2018, after the first submission in October 2018, when clarifications were asked and delivered in November 2018.

The study has been designed and is being executed according to the basic principles of rights and dignity of the human being, as stated in the Helsinki declaration, and this study complies with all the current regulations that apply, including institutional, local, national, and international regulations.

All information is being handled confidentially according to the organic Spanish law 15/1999 and the European regulation 2016/679. The IRB has always granted access to any study information required.

All participants will receive the participant information sheet and will be required to read and fill the IC form, which will be sent to admin@grasp.pw. The principal investigator will be responsible for reviewing all candidates' IC forms and screening questionnaires for inclusion and exclusion criteria. All candidates and participants will have the opportunity to ask as many questions as needed before proceeding to any part of the study, both through the forum and through contacting the leading researcher email (admin@grasp.pw).

Participants will not be required to sign IC forms to protect their anonymity and avoid sharing data that could be used to track their physical identity. The identity that will be protected by the researchers will be the online one, as no other information relatable to the real identities will be given. This procedure is consistent with the methodology of previous studies [61].

The researchers will try their best to limit the influence of their interactions on the participants' behavior, especially the ones targeted in the study. However, as recommended by previous research, the participants will be involved in discussing the study design and incentivized to share their opinions on how the study could be improved [8,21].

Protocol changes will be communicated to the participants through the online platform once they are approved.

A more extensive ethical analysis by principles can be found in Multimedia Appendix 6 [26,27,39-52,62-64].

Dissemination Policy

All individual and collective data, as well as all the results derived from the study, will be strictly protected and will only be published with the authorization of the principal investigator and the affected participants. All relevant findings will be sent for publication in suitable journals and submitted for presentation at relevant scientific meetings. The funding organizations will have no role in the publication process. In addition, data without identifiable information will be shared with study participants after assessment and approval by the research team. Finally, all results published in the scientific literature will also be made available in lay language to the communities of origin of the participants. Authorships in the publications will be determined by the amount of scientific and academic contributions of the members of the research team, including external collaborators. There are no plans to make the data sets publicly available.

Results

The research protocol was approved by the IRB of the *IMIM* on December 11, 2018. Data collection started in August 2019 and was still ongoing when the protocol was submitted (September 2020), finalizing in October 2020.

Data analysis began in November 2020, and it is still ongoing. The authors expect to submit the first manuscript with preliminary results by the end of 2021.

From a total of 182 screened candidates, only 17 (9.3%) completed at least one self-administration trial, resulting in a total number of 64 self-administration trials. From these, 40 different substances were analyzed.

Discussion

It is possible to conduct an IRB-approved study using this new methodology and collect the expected data. However, the meaning and usefulness of these data are still unknown.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Participant information sheet.
[DOC File , 50 KB - resprot_v10i7e24433_app1.doc]

Multimedia Appendix 2
Informed consent form.
[DOC File , 33 KB - resprot_v10i7e24433_app2.doc]

Multimedia Appendix 3
Announcement for candidates.
[DOC File , 33 KB - resprot_v10i7e24433_app3.doc]

Multimedia Appendix 4
Summary of study procedures.
[DOC File , 192 KB - resprot_v10i7e24433_app4.doc]

Multimedia Appendix 5
Main study outcomes.
[DOC File , 78 KB - resprot_v10i7e24433_app5.doc]

Multimedia Appendix 6
Ethical analysis by principles.
[DOC File , 34 KB - resprot_v10i7e24433_app6.doc]

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Abbreviations

EC: Energy Control
EC–ABD: Energy Control–Associació Benestar i Desenvolupament
GC: gas chromatography
GRASP: Global Research and Analysis of New Substances Project
HPLC: high performance liquid chromatography
IMIM: Hospital del Mar Research Institute
IC: informed consent
IRB: institutional review board
LC: liquid chromatography
MS: mass spectrometry
NPS: new psychoactive substances
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Protocol

Predictive Monitoring–Impact in Acute Care Cardiology Trial (PM-IMPACCT): Protocol for a Randomized Controlled Trial

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Abstract

Background: Patients in acute care wards who deteriorate and are emergently transferred to intensive care units (ICUs) have poor outcomes. Early identification of patients who are decompensating might allow for earlier clinical intervention and reduced morbidity and mortality. Advances in bedside continuous predictive analytics monitoring (ie, artificial intelligence [AI]–based risk prediction) have made complex data easily available to health care providers and have provided early warning of potentially catastrophic clinical events. We present a dynamic, visual, predictive analytics monitoring tool that integrates real-time bedside telemetric physiologic data into robust clinical models to estimate and communicate risk of imminent events. This tool, Continuous Monitoring of Event Trajectories (CoMET), has been shown in retrospective observational studies to predict clinical decompensation on the acute care ward. There is a need to more definitively study this advanced predictive analytics or AI monitoring system in a prospective, randomized controlled, clinical trial.

Objective: The goal of this trial is to determine the impact of an AI-based visual risk analytic, CoMET, on improving patient outcomes related to clinical deterioration, response time to proactive clinical action, and costs to the health care system.

Methods: We propose a cluster randomized controlled trial to test the impact of using the CoMET display in an acute care cardiology and cardiothoracic surgery hospital floor. The number of admissions to a room undergoing cluster randomization was estimated to be 10,424 over the 20-month study period. Cluster randomization based on bed number will occur every 2 months. The intervention cluster will have the CoMET score displayed (along with standard of care), while the usual care group will receive standard of care only.

Results: The primary outcome will be hours free from events of clinical deterioration. Hours of acute clinical events are defined as time when one or more of the following occur: emergent ICU transfer, emergent surgery prior to ICU transfer, cardiac arrest prior to ICU transfer, emergent intubation, or death. The clinical trial began randomization in January 2021.

Conclusions: Very few AI-based health analytics have been translated from algorithm to real-world use. This study will use robust, prospective, randomized controlled, clinical trial methodology to assess the effectiveness of an advanced AI predictive analytics monitoring system in incorporating real-time telemetric data for identifying clinical deterioration on acute care wards. This analysis will strengthen the ability of health care organizations to evolve as learning health systems, in which bioinformatics data are applied to improve patient outcomes by incorporating AI into knowledge tools that are successfully integrated into clinical practice by health care providers.

Trial Registration: ClinicalTrials.gov NCT04359641; https://clinicaltrials.gov/ct2/show/NCT04359641

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KEYWORDS

predictive analytics monitoring; AI; randomized controlled trial; risk estimation; clinical deterioration; visual analytics; artificial intelligence; monitoring; risk; prediction; impact; cardiology; acute care

Introduction

Patients in acute care wards who deteriorate and are emergently transferred to the intensive care unit (ICU) have poor outcomes [1-6]. Subacute illnesses, such as sepsis, hemorrhage, and respiratory decompensation, occur in 5% or more patients and result in significant increases in length of stay and mortality [7]. Although potentially catastrophic, these subacute illnesses can be mitigated or indeed avoided depending on timely decisions made by the care team. Simply paying greater attention to patients who may be deteriorating from imminent changes in physiological status can allow for earlier clinical action and care to be appropriately escalated [8,9]. Informing clinicians of those patients at greater risk for otherwise unexpected clinical deterioration rather than waiting until after the common vital signs become noticeably abnormal and usual care alarms are triggered may provide a window for treatment that is more effective. Nurses' worry or concern often precedes obvious deterioration in vital signs, suggesting that quantification of "concern" might lead to detection at an early stage when intervention may be more effective [10].

Advances in continuous bedside monitoring technology make a wealth of data available to assist evaluation by health care providers [11]. These data form the foundation for computational algorithms (artificial intelligence [AI]) that integrate real-time telemetric physiologic data to provide early warning of potentially catastrophic clinical events, including sepsis, emergent intubation, hemorrhage, and other events of clinical deterioration [12,13]. We have found subtle physiologic signatures of illness that are detectable through advanced mathematical analysis of cardiorespiratory dynamics trends up to 24 hours in advance of overt clinical deterioration [12,14-17]. Continuous predictive analytics monitoring involves advanced mathematical analysis of data from a variety of inputs (including parameters derived from telemetric monitoring) into an estimate of fold increase of risk that clinicians can observe in real time in a streaming environment [18,19].

In the neonatal setting, Griffin and Moorman [20] detected abnormal heart rate characteristics in the hours preceding a clinical diagnosis of sepsis and developed methods to process, characterize, and synthesize unprocessed cardiorespiratory monitoring data into a computational model that produced an estimation of risk. When these risk scores were visually displayed in the intervention arm of a multicenter randomized clinical trial of over 3000 very low birth weight neonates, there was a 20% decrease in mortality [21,22]. Thus, we know that early detection of deterioration improves outcomes, cardiorespiratory monitoring data are readily available, and trend-based models adding continuous monitoring outperform static vital sign models. We do not know, however, if displaying these visual AI risk scores can impact outcomes in adult patients of a variety of ages and historical comorbidities, who are susceptible to an array of adverse outcomes, as it does the outcomes in premature infants susceptible to sepsis.

Here, a cluster randomized controlled trial (NCT04359641) will test the use of Continuous Monitoring of Event Trajectories (CoMET; Figure 1), an AI-based visual analytic that dynamically displays risk estimates every 15 minutes for multiple adverse outcomes. CoMET uses continuous cardiorespiratory monitoring data and waveforms sampled every 2 seconds to perform mathematical measurements, such as measures of entropy and heart rate variability. R-R intervals and electrocardiogram-derived breathing rate were obtained from 200-Hz electrocardiogram waveforms; laboratory data and nurse-entered vital signs were obtained from the electronic medical records. These are used to derive an estimate of the fold increase in the risk of clinical deterioration. The models that have informed CoMET development have been described previously [7,12,18,23]. We expect that having access to a visual risk analytic for impending catastrophic outcomes will draw the clinicians' attention to those patients who warrant early or extra consideration. For example, those patients with a higher risk score for short-term crises may be prioritized for assessment during daily rounds. This study will test the use of the CoMET display on patient outcomes, the time to proactive clinical action, and the associated costs to the health care system.

Figure 1. CoMET artificial intelligence–based visual risk analytic. CoMET: Continuous Monitoring of Event Trajectories.

Methods

Overall Design

We will be conducting a parallel, cluster randomized controlled trial (RCT). All patients who are admitted to an 85-bed acute care cardiology medical-surgical floor will be enrolled in the study. In June 2020, institutional review board approval was granted for the Predictive Monitoring-Impact in Acute Care Cardiology Trial (PM-IMPACCT) along with waiver of informed consent, given the minimal risk nature of the study protocol. Clusters will be defined by room number, and upon enrollment, patients will be assigned to either intervention (CoMET display) or usual care (standard of care). The intervention will consist of CoMET display and charting in electronic medical records, mention of CoMET score on rounds, and standard of care cardiorespiratory monitoring when ordered. Meanwhile, usual care will consist of standard of care cardiorespiratory monitoring when ordered and no CoMET score displayed, charted, or mentioned on rounds. The study period will be 20 months. This report follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guideline [24].

Intervention Details

Data will be automatically collected electronically in real time for all patients (intervention and usual care) admitted to the randomized beds on the cardiology floor. The CoMET server is hosted within the hospital information technology environment and interfaces with the hospital interface engine to automatically gather clinical information, including numerical values in flow sheets, laboratory results, and continuous cardiorespiratory monitoring data [25]. For the intervention group only, the scores will then be displayed on monitors in real time and will be updated every 15 minutes.

Clinical research coordinators will routinely be present on inpatient rounding to bring up the web-based version of the CoMET display for the intervention arm and discuss relevant trends and answer questions about CoMET interpretation. Nurses will be asked to assess CoMET scores as part of routine vital sign collection. Every hour, the CoMET scores flow through directly to the electronic medical record vital sign flowsheet. Assessment protocol guidelines in response to CoMET scores on the intervention arm will suggest that if the CoMET score rises by 2 or more within a period of 3 hours, a nurse should assess the patient and consider alerting the nurse practitioner or resident physician caring for that patient. There is no direct clinical action or response mandated as a part of this RCT.

Inclusion and Exclusion Criteria

All patients admitted to one of the 85 beds in 56 rooms on the acute care cardiology medical-surgical and cardiothoracic surgery floor (which encompasses a floor of the University of Virginia Medical Center and is further divided into 3 wards) will be enrolled in this study.

Randomization Process

The room and bed in which a patient is placed is based on standard of care. The rooms are being cluster randomized to either intervention or usual care. The assignment of patients to rooms will not be influenced by the randomization status of the room.

There will be 14 clusters containing an average of 4 rooms (6 beds) each, with the aim of maintaining balance across wards and units (intermediate care unit, transplant, or neither). Clusters will be rerandomized every 2 months following a replicated Latin square design within each stratum to ensure balanced treatment assignment within each time period and over the length of the study. Randomization will be performed using the

randomization inference package in R (The R Foundation for Statistical Computing). The randomization will be masked until it is implemented every 2 months. Postimplementation, the randomization will not masked or blinded because it will be clear to anyone in the hall or central station which beds have a CoMET score displayed and which do not. Future randomization assignments will only be known by the study statistician (SR) and those technical personnel implementing CoMET at the time that randomization changes (MC).

Implementation and Education Considerations for Clinicians

All clinicians will be educated about CoMET to follow assessment guidelines in response to CoMET score. With consideration to alert fatigue, an increase of 2 or more within a period of 3 hours was selected as a guideline for assessment. In our retrospective cohort, a rise >2 units occurs 2 to 3 times per ward per day. On average then, a single nurse may experience 1 CoMET rise alert every 3 shifts. The clinicians will be provided education about what a score rising on either (or both) axes represents and the differential diagnoses to consider. This approach leaves the clinical context to that of the clinician and does not specify the specific diagnostics to order. The purpose of CoMET is to alert clinicians to prodromes or subtle physiological changes that precede overt clinical signs and draw attention to patients who may be in need of further attention, further clinical diagnostics, or escalation in care delivery. Clinicians may choose to draw a blood culture, initiate a rapid response team call, initiate oxygen therapy, or to do nothing but closely monitor or reassess the patient in an hour. Because CoMET models are trained on multiple events of clinical deterioration, clinicians understand the context of the CoMET score within the larger patient trajectory. There will be continual engagement and re-education throughout the entire study period across all clinician groups.

Study Outcomes and Statistical Analysis

Primary Hypothesis

The primary hypothesis is that display of predictive analytics monitoring on acute care cardiology wards increases the number of hours free from clinical deterioration.

The primary outcome is the number of hours free from clinical deterioration (acute clinical events) within 21 days of admission. Hours of acute clinical events are defined as the time when one or more of the variables found in Textbox 1 occur. A maximum score will be 21 event-free days (504 hours). Patients who are discharged from the hospital prior to 21 days without an event will be counted as having 21 event-free days (504 hours). Patients who die during the admission will be counted as having 0 event-free days (0 hours). As an example, a patient who has an emergent ICU transfer on hour 26 of their admission will have 25 event-free hours. Patients will be censored (with no event observed) at the time of nonemergent ICU transfer (ie, for planned bronchoscopy), nonemergent surgery transfer, or other transfer (change in bed assignment) because a change in bed assignment can result in a change in randomization allocation (as carry over could occur in patients who have a display and then become “undisplayed”). We will conduct a randomized (formerly called “intent-to-treat”) analysis, in which all available data on all randomized participants are included for the primary end point comparison between intervention and usual care.

For the primary outcome (hours free of an acute clinical event), the primary analysis will employ a generalized estimating equation (GEE) with Poisson link. This model will be able to handle the multiple levels of correlation in the study design—patients within a cluster and potentially different intervention arms within a patient who has an event and then returns to the ward—as well as differences in the amount of time at risk for each patient that is censored.

Textbox 1. Study outcomes by hypotheses.

Hypothesis 1 (primary study outcome)

1. Hours free from the following:

- An emergent intensive care unit (ICU) transfer (emergent defined as urgent, unplanned) and ICU stay
- Emergent intubation (emergent is defined by clinician's notes as a nonplanned procedure)
- Cardiac arrest, if prior to ICU transfer
- Death
- Emergent surgery prior to an ICU transfer (emergent is defined by clinician's notes as a nonplanned procedure)

Hypotheses 2 and 4

1. Proportions of the following individual events at any point in the hospital stay after admission to the fourth floor:

- Emergent ICU transfer (emergent defined as urgent, unplanned)
- Emergent intubation (emergent is defined by clinician's notes as a nonplanned procedure)
- 3 units or more of blood ordered in 24 hours
- inotropes or vasopressor use
- Shock requiring inotropes or vasopressors
- Sepsis (sepsis-2 definition)
- Septic shock requiring inotropes or pressors (defined by a combination of the 2 above criteria)
- Cardiac arrest
- Death
- Diuretic drip indicating congestive heart failure escalation
- Inotropes or pressors for heart failure
- Emergent surgery prior to ICU transfer (emergent is defined by clinician's notes as a nonplanned procedure)

2. Hospital length of stay

3. In patients who are never transferred to the ICU, the length of stay on the acute care floor

4. ICU length of stay

5. Proportion with readmission to hospital within 72 hours postdischarge

6. In patients who meet the sepsis-2 criteria, the proportion of shock (ie, hypotension requiring inotropes or pressors), and death

7. Number of days on intravenous antibiotics

8. Number of days on intravenous anti-infectives

9. Total duration of mechanical intubation (emergent and nonemergent)

10. Impact of sex on outcome

Hypothesis 2

1. Time of emergent intubation post-ICU transfer (emergent is defined by clinician's notes as a nonplanned procedure)

2. Time of the first order post-ICU transfer for transfusion of 3 units or more of blood ordered within 24 hours

3. Time of first order post-ICU transfer of intravenous inotropes or pressors administered for shock (including septic shock)

4. Time of cardiac arrest post-ICU transfer

5. Time of congestive heart failure escalation, defined by the time of first order for diuretic drip, time of first order for continuous venovenous hemodialysis, or time of dialysis initiation

6. Time of death post-ICU transfer

7. "Infinite" event-free survival, defined as discharge from the ICU without an event

Hypotheses 3 and 4

1. Time to the first order for transfusion of 3 units or more of blood ordered within 24 hours

2. Time to first order for blood or urine culture obtained for suspicion of infection

3. Time to first order for lactate drawn
4. Time to first order for anti-infectives given for suspicion of infection
5. Time to first order for fluid resuscitation given for suspicion of shock
6. Time to rapid response team medical emergency team call initiation
7. Time to first order for intravenous inotropes or vasopressors administered

Secondary Hypothesis

The secondary hypothesis is that display of predictive analytics monitoring on acute care cardiology wards increases the number of hours free of clinical deterioration among those emergently transferred to the ICU.

We will use the Kaplan-Meier method or Cox proportional hazards regression curve to show post-ICU transfer event-free survival and hours free of the events listed in Textbox 1. The analysis comparison will employ a 1-sided clustered log-rank test (survival analysis) assuming proportional hazard rates.

For secondary outcomes measured as proportions (ie, yes-or-no outcomes) we will use GEEs with logit link and binomial distribution, and use negative binomial distribution for rare events. GEEs will allow the correct modeling of the clustering design and estimation of the intracluster correlation.

Tertiary Hypothesis

The tertiary hypothesis is that the display of predictive analytics monitoring shortens time to proactive clinical response. We will quantify hours to proactive clinical response using variables found in Textbox 1.

We will use a Cox proportional hazards regression curve to determine differences in response time between intervention and usual care. We will also collect and analyze end points to evaluate clinician response and elements of situational awareness, including the number of alerts observed (per patient days) and clinical actions chosen (both individual actions or team/communication actions). By characterizing the clinical actions, we will be able to more fully understand the outcomes of dynamic decision making in the context of a predictive analytic and future state of disease. We will also be able to assess fidelity to the clinical guidelines that were provided to clinicians as a component of the optimized alert strategy.

Quaternary Hypothesis

The quaternary hypothesis is that the display of predictive analytics monitoring reduces costs to the health system.

We will determine whether the display of predictive analytics is cost-effective to the health care system. Collection of end points to understand trade-offs and potential burdens, consequences, and advantages for this platform from the clinician perspective is critical and presents novel knowledge. Additionally, we can form an estimate for not only the cost of intervening but also the overall costs of implementing a predictive analytics or AI monitoring platform within a health system using multiple criteria (Table 1).

We will conduct an economic cost-effectiveness analysis comparing the clinical outcomes and associated cost of care between the intervention and usual care group. We will use a Markov decision tree and Monte Carlo simulation to examine the impact of CoMET compared with usual care from a health system perspective. We will measure incremental effect as the in-hospital mortality difference and the number of quality-adjusted life years gained discounted at a 3% annual rate as per the guidelines of the Public Health Service Panel on Cost-Effectiveness in Health and Medicine. We will measure differences in hospital costs based on internal data warehouse cost data weighted by the Centers for Medicare & Medicaid Services Cost Report cost-to-charge ratio [26].

Table 1. Elements included in health system decision analysis for artificial intelligence implementation.

Element	Example
ROI[a]	ROI = profit or cost, inclusive of costs related to clinical deterioration cases averted and costs related to unnecessary intervention (ie, false positives)
Capacity changes	C-score = (delta LOS[b] in days x patients per week) + (added bed days/LOS of unit in days)
Staff training times	Average time to complete virtual cases per user group
Implementation costs	Costs associated with staff training or use of case-based approach
Impact on workforce	Number of false alarms as a unit of registered nurse time

[a]ROI: return on investment.

[b]LOS: length of stay.

Outcome Ascertainment and Event Adjudication

Numerical and categorical data (lab values, timestamps, room transfers, etc) will be extracted in bulk from the University of Virginia clinical data warehouse and uploaded into a Research Electronic Data Capture (REDCap) database for outcome analyses. For nonautomated outcome elements, such as suspicion of infection, emergent status of intubations, surgeries or transfers, suspicion of shock, actual shock, indications for vasopressors, and others, protocol-trained clinical research coordinators (consisting of registered nurses or medical doctors)

will individually review the electronic medical records of case and control participants.

Sample Size, Power Analysis, and Attrition

We expect 11% of participants to drop out of the primary outcome because they will be in a room that switches the randomization arm at the time when rooms are rerandomized or because they will transfer rooms during their admission to a room of the opposite randomization or to a nonstudy room. We have accounted for this attrition in clinical trial planning and sample size considerations. The number of admissions to a room which will undergo cluster randomization is estimated to be 10,424. The study type 1 error rate will be set to 5% and the type II error rate to 20% (80% power). Additionally, an interim analysis will prespecified after half of the participants have completed their primary outcomes assessment. The interim analysis will use an O'Brien-Fleming spending function, giving nominal α values of .003 (interim) and .047 (final) for the 2 analyses. Should the primary outcome cross a stopping boundary at the interim analysis, the data safety monitoring board (DSMB) will have the option of stopping the study early.

Results

Trial Status

Prior to the study commencing, we were able to complete several key steps of the clinical trial planning, setting a solid foundation for the RCT. Specifically, we partnered with clinical and administrative leadership within the health system heart and vascular clinical service lines, we enlisted 12 nursing and physician partners who will serve as Super Users and CoMET champions, we conducted over 50 education sessions with nursing and physician clinical users (reaching over 120 clinicians to date) and have made 7 online educational activities available on the learning management system for staff at large, we obtained institutional review board and DSMB approval, we completed internal validation on CoMET (displays not turned on to clinical users), we refined clinical nursing and nurse practitioner or physician response guidelines through feedback from clinical stakeholders and nurses from the rapid response team, we completed the REDCap database and integration with clinical data warehouse (SQL queries written and validated), and DSMB members and chair were selected (9 members in total) and have met twice thus far. Randomization began January 4, 2021, and we anticipate the study taking 20 months of enrollment to complete.

Discussion

We are evoking methodological approaches that have immersive properties (ie, clinician stakeholder engagement, immersive education, economic perspectives) and that offer a framework for scalability and long-term adoption. Additionally, we are taking on the task of conducting simultaneous evaluations of various populations within the acute care cardiology wards (surgical and medical patients with a variety of diagnoses). Even within a single hospital, each clinical unit will have varying environmental contexts of care, varying needs of the patient populations, and differing priorities of point-of-care clinicians, and we are including 3 distinct wards. In seeking to understand how to optimize a predictive analytic and effectively implement it within the context of a learning health system, we can learn how similar processes can be applied to nearly any predictive analytic and setting. Thus, we propose to focus on the process of testing these strategies through a randomized control trial and seek to disseminate consensus guidelines and provide expertise that can be applied to other analytics and a variety of care settings (a scalable approach). We anticipate a multicenter study following this single-center RCT.

We have extensive prior experience in the use of predictive analytics in the neonatal ICU and surgical-trauma ICU [11,23,27] through immersive qualitative approaches. We have learned that the clinicians prefer an open response protocol that relies on their expertise with some suggested actions without being too restrictive or adding additional burden to the system. These principles are also central to implementation science and pragmatic design perspectives. Further, our prior experience with the neonatal HeRO score [28] and the use of CoMET in a pre-post study in the surgical-trauma ICU [23] suggests that patient trajectory is of great use to practicing clinicians when the CoMET score is placed in the context of the overall clinical status. We have previously studied the role of alert thresholds using data from these hospital units and have optimized the sensitivity-versus-positive-predictive-value trade-off of establishing an alert threshold [29].

Very few AI-based analytics have been translated from algorithm to real-world use in complex health care settings. We believe that AI systems need to be developed and tested with end users in mind. Further, we think testing them in an RCT framework will allow for the assessment of efficacy and trade-offs within the system. Early identification of subtly worsening patients might allow for earlier clinical action and lead to reduced morbidity and mortality. The future of acute hospital care includes monitoring systems that integrate data streams of rapidly changing clinical information to estimate and communicate risk of imminent events. Too much data are collected and then discarded or ignored by the vast majority of hospital systems, representing an often crucial missed opportunity to optimize the care of patients. The proposed approach will facilitate a paradigm shift in care from reactive to proactive by exploiting all the data that are freely available in the majority of patients, using this to predict risk of adverse events and allowing clinicians to act early to promote optimal patient trajectories.

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Conflicts of Interest

LPM is chief implementation officer, MC is chief scientific officer, and JRM is chief medical officer of AMP3D in Charlottesville, VA. LPM, MC, and JRM are also shareholders in AMP3D. The other authors have no conflicts of interest to declare.

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Abbreviations

AI: artificial intelligence
DSMB: data safety monitoring board
GEE: generalized estimating equation
ICU: intensive care unit
PM-IMPACCT: Predictive Monitoring-Impact in Acute Care Cardiology Trial
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

The Hip Instructional Prehabilitation Program for Enhanced Recovery (HIPPER) as an eHealth Approach to Presurgical Hip Replacement Education: Protocol for a Randomized Controlled Trial

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Abstract

Background: Osteoarthritis (OA), leading to hip replacement (THR), is a primary contributor to global mobility impairment. In 2018, more than 59,000 THR surgeries were performed in Canada. Health promotion education, such as prehabilitation, is vital to optimizing surgical outcomes.

Objective: This study aims to evaluate the feasibility of the Hip Instructional Prehabilitation Program for Enhanced Recovery (HIPPER), an eHealth approach to prehabilitation education.

Methods: A single-blind (assessor-blind), 2-arm, feasibility randomized controlled trial will be conducted. We will recruit 40 (HIPPER group, n=20; control group, n=20) older adults with hip OA and on a waitlist for a THR. The HIPPER intervention consists of 12 online, interactive modules. The control group will receive the current standard practice consisting of 2 online educational sessions lasting 2 hours each (webinars). Feasibility outcomes (eg, recruitment and retention rates) will be evaluated.

Results: Recruitment started in March 2021. As of April 20, 2021, 18 participants were recruited. All 18 completed T1 measures. Only 1 participant has been scheduled to have a surgery and therefore has been scheduled to complete T2 measures. The remainder of the participants are waiting to be notified of their surgery date. This project was funded by a Canadian Institutes of Health Research Project Grant. Our institute's research ethics board approved this study in November 2016.

Conclusions: Results will lead to refinement of the HIPPER protocol in order to evaluate a standardized and geographically accessible prehabilitation program.

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KEYWORDS

total hip replacement; osteoarthritis; eHealth; prehabiliatation; preoperative education; randomized controlled trial; evaluation; feasibility; rehabilitation; recovery; hip; bone; surgery; education

Introduction

Total hip replacements (THRs) reduce joint pain and improve function in individuals with advanced osteoarthritis (OA). The incidence of THRs has grown over the last 5 years (~17.4%), with 59,000 THRs in Canada between 2017 and 2018, resulting in substantial health care costs [1]. Health promotion education provided prior to surgery can reduce direct and indirect costs [2], improve patient care and recovery [3-5], reduce hospitalization costs [6], accelerate rehabilitation [7,8], and reduce preoperative pain and anxiety [3,4]. It is thus a valid indicator of quality rehabilitation [9].

Provision of preoperative education and access to rehabilitation prior to THR are inconsistent and sometimes nonexistent in parts of British Columbia (BC). Given the majority of THRs are performed in southern urban centers, individuals from remote areas often travel great distances to receive prehabilitation ("prehab") — presurgery education and exercise training — or receive it immediately prior to surgery, reducing many benefits (eg, prehab exercise to maintain function). Prehab is often limited to written materials or didactic group sessions [8,10]. While the literature suggests prehab may be beneficial, study results are inconsistent, and effect sizes for the most prominent outcome (anxiety) are modest at best [8,10]. We hypothesize that this is due to issues with educational content or delivery and study design error with measuring the correct outcomes at the right time. For example, the assertion that prehab reduces anxiety and maintains function should be measured immediately before surgery.

Health education using eHealth (eg, delivered online) approaches have been lauded for being interactive and enabling learners to re-engage over sustained periods [11-13]. eHealth has the potential to improve quality of care for older adults [14], enhance communication between patients and health care providers, reduce costs, and increase access to health care and information [15]. For eHealth to be effective, understanding patient technology preferences, including adoption facilitators and barriers, is required [14]. Though less likely to embrace eHealth compared to their younger counterparts, computer use among older adults in BC continues to grow, with 86% of those 45-64 years old and 55% of those >65 years old using the internet from home [16].

For these reasons, we developed HIPPER (Hip Instructional Prehabilitation Program for Enhanced Recovery), an interactive, user-centered, eHealth, preoperative, THR education program based on adult learning principles [17,18]. HIPPER is a potential model for use across diagnostic groups (eg, knee or shoulder replacement), providing standardized, user-friendly prehab, reducing the time clinicians must spend on providing prehab education, decreasing the time patients spend on traveling to access in-person education, and leading to reduction in direct health care costs and indirect costs (eg, dependence on family). Finally, HIPPER has the potential to allow participants to personalize prehab education based on their needs, access prehab education at any time, review prehab education multiple times, and test their knowledge.

We will conduct a 2-year, single-blinded, feasibility, randomized controlled trial (RCT) to address the design and HIPPER intervention fidelity. The primary feasibility objectives are to assess (1) process issues (eg, participant recruitment, retention, perceived benefit), (2) resource issues (eg, treatment adherence and burden), (3) management issues (eg, participant processing, protocol administration), and (4) treatment issues (eg, safety, treatment effect). See Table 1. Secondary objectives are to evaluate the effect of HIPPER on primary and secondary clinical outcomes and obtain an estimate of treatment effect size. Specifically, we hypothesized that, in patients undergoing hip replacement surgery, using HIPPER is as effective as usual care in reducing preoperative anxiety. In addition, we hypothesized that, in patients undergoing hip replacement surgery, using HIPPER is as effective as usual care in improving physical function, self-efficacy, and health-related quality of life 1 month and 3 months after surgery.

Table 1. Feasibility indicators.

Feasibility component	Indicator	Criteria
Process		
Recruitment rate	Number of participants recruited; number of women and men recruited	Mean of 4 participants/month: total of 44 over 11 months
Consent rate	% of participants consenting	<10% participant refusal
Retention rate	% of participants with T3[a] data	Complete data collection for >80%
Perceived benefit	Posttreatment participant questionnaire; qualitative interviews at T3	>85% of responses will be "strongly agree/agree"; qualitative analysis will inform clinical importance
Assessor masking	% unaware of group status	100% of participants do not unmask their treatment
Resources		
Treatment adherence	HIPPER[b] group spends 2.5 hours on all modules; control group attends both prehab education sessions	>85% of participants
Data collection (T): participant & assessor burden	T1 duration; T2 & T3 durations	>85% of participants complete in ≤2 hours; >85% of participants complete in ≤1.5 hours
Collection of EQ-5D[c] data	Administration; EQ-5D pre/post score	Mean EQ-5D administration is <10 minutes; statistically significant change between T1 & T2
Educator burden	Time (minutes) spent in answering participants' questions and following up with them	Mean time spent per participant is <2 hours for T1 and <1 hour for T2; <20% phone call back for clarification
Management		
Internet stability	Downtime due to technical or mechanical issues	>90% of participants are not without internet for >2 days
Participant processing time	Time from data collection to treatment	Mean time is <10 days at each site
Treatment administration issues	Post-treatment evaluation form (study educator)	Any issues identified modifiable without substantial changes to the protocol
Treatment		
Safety (data collection & training)	Adverse events during assessment or training	No major injuries nor adverse events (eg, dislocation) reported
Dose level response	Correlation between training time and change score	Minimum practice time guidelines sufficient for a treatment effect

[a]Third measurement timepoint.

[b]HIPPER: Hip Instructional Prehabilitation Program for Enhanced Recovery.

[c]EQ-5D: EuroQol 5 Dimension.

Methods

This protocol has been written based on SPIRIT (Standard Protocol Items: Recommendations for International Trials) [19].

Trial Design

An equivalence, single-blind (assessor-blind), 2-arm, feasibility RCT with a 1:1 allocation ratio will be conducted to compare an eHealth program to standard care for people undergoing elective THR.

Study Setting

Patients referred to the OsteoArthritis Service Integration System (OASIS) program (n>250/year), a central intake program administered by Vancouver Coastal Health in Canada, will be approached to participate.

Eligibility Criteria

Inclusion Criteria

To be included, participants will be ≥50 years old, have hip OA, be scheduled to have a single THR in >12 weeks, and have internet access.

Exclusion Criteria

Individuals who cannot communicate and complete questionnaires in English, anticipate a health condition or procedure that may result in cancelation of their THR surgery, are actively receiving physical therapy for their hip symptoms, have had a previous THR (on either side), or have already received prehab education will be excluded.

Interventions

Standard Care

To provide a comparable level of education, control participants will receive 2-hour educational live webinars, as per current practice in OASIS. The webinar focuses on prehab material (eg, exercise, nutrition) and presurgical content (eg, home equipment, hip precautions). The participants will be able to have their questions addressed throughout the live webinars. In addition, the participants will receive an educational booklet that provides information on various topics related to their hip surgery such as exercise, preparing their home, and an equipment checklist. Participants in this group are verbally encouraged to take part in the live webinars.

Intervention

As a team, we created HIPPER with a user-centered approach consisting of focus groups and a "think aloud" cognitive processing technique, both of which provided improved usability. HIPPER consists of 12 interactive online modules (~20 minutes each), which permit self-paced progression and access from the participant's home or location of choice. HIPPER participants will be contacted by email or phone to provide them with website portal access and simple instructions using personalized encrypted login information. Upon login, the participants can immediately begin the modules. Participants can stop a module at any point, and their progress will be saved. When ready, they can continue where they left off or choose to go backward and review previous content. Modules are not "marked" complete until the participant hits the finished icon at its end. The module format includes embedded videos, narrated slides, and quizzes. Participants will be encouraged to have a family member view HIPPER with them. An education consultant (with expertise in designing courses with Articulate Storyline 360) will monitor and troubleshoot any platform issues throughout the study. The education consists of a comprehensive library of material addressing topics such as exercise, equipment needs and setup, pain management, nutrition, and weight management. The research coordinator who can remotely monitor online analytics (eg, login frequency, module progression) will phone the participant within 2 weeks if no online activity is noted to promote adherence and troubleshoot potential technical problems. The participant will be given a phone number and email to contact the research coordinator should they experience difficulty using the modules.

Participants in the HIPPER group will be asked not to attend the OASIS live webinars on prehab education. The research coordinator will send the name of the participants in the HIPPER group to staff at OASIS who can monitor whether HIPPER participants attended the online webinars.

Participants in both groups can withdraw from the study at any time. Some participants in the HIPPER group may gain access to the educational booklet through the surgery office or other sources. Having access to the educational booklet will not make the participants ineligible from participating in the HIPPER group.

Outcome Measures

Primary Outcome

The primary outcome will be measured using the Hospital Anxiety and Depression Scale (HADS-A)**.** Duivenvoorden and colleagues [20] have shown that at least 30% of patients undergoing THR surgery experience clinically significant levels of anxiety (treated by a psychiatrist or a psychologist for their anxiety). However, studies in other patient populations suggest as much as 50% to 80% of patients experience moderate to high levels of anxiety prior to major elective surgeries. Systematic reviews [8,10] report consistent and clinically meaningful improvements in preoperative anxiety with prehab education [9]. Therefore, preoperative anxiety was selected as our primary outcome in this feasibility study.

Secondary Outcomes

Given the internationally generated and recommended core self-report [21] and performance-based [22] measures for OA, recently published rehabilitation quality indicators [9] and the existing literature demonstrating the relationship between pain, physical function or activity, and self-efficacy on THR outcomes, a number of secondary measures will be administered.

The first secondary outcome will be measured using the Oxford Hip Score (OHS). The OHS is a 12-item tool that assesses pain and function in patients undergoing THR surgery. It demonstrates good construct validity and test-retest reliability in THR [23,24]. Participants will complete this measure at all time points (T1-T3).

The second secondary outcome will be measured using the 30-second Chair Stand Test (30-sec CST). Functional lower limb strength and dynamic balance will be assessed by having participants perform repeated sit-to-stands using a standard 43-46 cm straight-back chair with no arm rests. Excellent test-retest reliability has been reported in patients awaiting THR [25]. This test has been proven to have acceptable validity and high correlations with other measures of physical functions in patients with joint replacement [26]. Participants will be asked to complete this test at T1 and T2.

The third secondary outcome will be measured with the Physical Activity Scale for the Elderly (PASE). The PASE is a 12-item tool developed for older adults to assess home, occupational, and recreational activities in the previous 7 days [27]. It has moderate test-retest reliability (intraclass correlation coefficient=.77) in hip OA and correlates well with other self-report activity measures [28]. The intraclass correlation coefficient for the entire scale has been found to be .78 [28]. Participants will complete this measure at T1-T3.

The fourth secondary outcome will be measured using the Self-Efficacy for Rehabilitation Outcome Scale (SER). The SER is a 12-item questionnaire developed for patients undergoing hip or knee surgery and asks patients to rate their confidence on an 11-point Likert scale. It generates 2 subscale scores: self-efficacy for rehabilitation therapy exercises and self-efficacy for overcoming barriers [29]. The Cronbach alpha for the SER was .94 [30]. Participants will complete this measure at T1-T3.

The fifth secondary outcome will be measured using an equipment checklist. Patients acquire equipment and mobility aids prior to THR to ensure their safety and enable them to carry out activities of daily living [9]. A comprehensive checklist of recommended equipment will be created based on current guidelines, clinical recommendations, and our patient partners' input. Patients will use the checklist at T2 and T3 to record the number and type of equipment items they have used and how often they have used each (eg, dressing equipment). Participants will complete this measure at T2-T3.

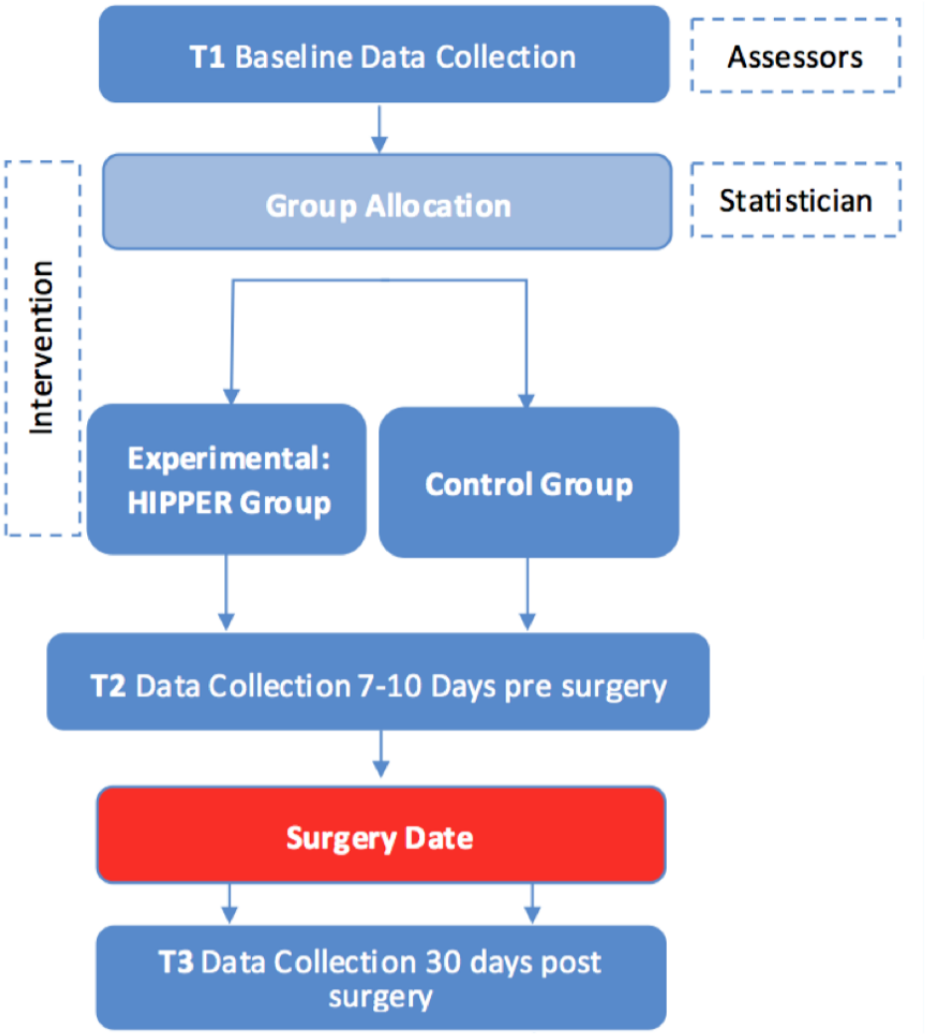
The sixth secondary outcome will be measured using the EuroQoL-5 Dimension, 5 Level (EQ-5D-5L). Health-related quality of life is a core outcome for hip OA [21], and its measurement is a recommended quality indicator [9]. The EQ-5D-5L is a brief and well-validated questionnaire that assesses 5 health status domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) [21,31]. Participants will complete this measure at T1-T3.

The final secondary outcome will be measured using the System Usability Scale. This scale consists of a 10-item questionnaire with 5 response options, ranging from "Strongly agree" to "Strongly disagree." Originally created by Brooke [32], it enables evaluation of a wide variety of products and services, including hardware, software, mobile devices, websites, and applications. Some examples are, "I think that I would like to use this system frequently." and "I needed to learn a lot of things before I could get going with this system." In this study, we replaced "the system" with "HIPPER" to capture the opinion of participants regarding the usability of our eHealth program. Participants will complete this measure at T2 and T3 (if randomized to the treatment group).

Participant Timeline

T1 data will be collected at approximately 12 weeks before the THR surgery. Follow-up data will be collected 7-10 days prior to surgery (T2), 30 days and (T3) postsurgery. Figure 1 shows the participant timeline.

Figure 1. Data collection procedure for the randomized controlled trial. HIPPER: Hip Instructional Prehabilitation Program for Enhanced Recovery.



Sample Size

The suggested sample size for feasibility RCTs ranges from 12 to 30 per arm [33,34]; therefore, we aim to recruit 40 participants and randomly assign them to the HIPPER group or control group (usual care). Following other feasibility RCTs (eg, [35,36]), descriptive information on feasibility outcomes and means, SDs, and Cohen d effect sizes will be provided to be used in the future multisite RCT.

The feasibility RCT is a vital step to estimate the parameters needed for designing a full-scale RCT [37] that selects the right outcome measures, fidelity of the protocol and randomization, feasibility of recruitment, adherence and response rate, and feasibility of quantitative measures.

Recruitment

The OASIS will send mail to or email patients who are on the waitlist for THR. Patients will be encouraged to contact the researchers to learn more about the study.

Data Collection Method and Data Management

Our collaborators at OASIS will send mail to or email the patients who are on a waiting list to attend prehab classes. Interested patients will be encouraged to contact our research center. They will be interviewed by the assessor to determine eligibility. Upon successful screening, participants will be sent a PDF version of the consent form to keep for their record and also a link to the online consent form on Qualtrics, a secure data collection tool. Participants will be asked to sign the online consent form. Participants will be given at least 24 hours to read the consent form before attending the T1 data collection online meeting. After signing the consent form, participants will be asked to attend the T1 data collection online meeting. During this initial meeting, the assessor will help them complete a set of questionnaires using Qualtrics. In addition to the self-reported measures, the assessor will ask participants to complete the 30-sec CST, which is a performance test. Participants will be asked to complete the test at home while communicating with the research coordinator as part of the online meeting. Participants will be video recorded during the 30-sec CST. Immediately after they complete the T1 measures and the 30-sec CST, the assessor will leave the meeting, and the research coordinator will join the participant and use secure online software [38] to randomize the participant. The assessor will remain blind to the randomization result.

To collect the data at T2 and T3, the assessor will send a link to the participants to complete the questionnaires in Qualtrics. In addition, at T2 the assessor will contact the participants to schedule a short online meeting during which the participants will be asked to do the 30-sec CST via videoconference. The assessor will ask the participants to not reveal their group allocation to them.

Allocation

After participants complete the T1 measures, the assessor will invite the research coordinator to join the Zoom meeting; then, the assessor will leave the meeting. During the meeting, the research coordinator will use the Simple Randomization Service provided by Sealed Envelope [38] to randomize the participant into the HIPPER or control group. The research coordinator will add the participant ID to the account that we created for this trial and then click on the randomize button. Then, the Simple Randomization Service provided by Sealed Envelope [38] will randomize participants into either group A (HIPPER) or B (Control). We will not stratify the sample. Block randomization will be used to ensure equal number of participants will be in each group. The assessor will remain blind to participants' group allocations. After randomization, the research coordinator will give participants instructions based on their group. In addition, the research coordinator will ask the participants to not reveal their group to the assessor.

Masking

Given the nature of the study, it is not possible to blind the participants and the research coordinator to the participant's group after baseline data collection. However, the assessor will remain blinded throughout the study. The assessor will be responsible for setting up the Qualtrics measures for the participants. In Qualtrics, the survey has been set up with only one arm; therefore, the assessor will not need the participant's group to schedule the invitations.

After baseline data collection, the assessor will only contact participants to remind them to fill out the questionnaires and perform the 30-sec CST. To address performance bias, participants will be instructed not to discuss their group allocation, and the assessor will reinforce this point before starting each data collection session. The assessors will be asked to track and report any unblinding. If unblinding occurs before the data collection for that session, the assessor will reschedule the session, and another assessor will complete the data collection. If unblinding happens after the data collection at T2 or T3, another assessor will be assigned for the remaining data collection session(s). Using patient-reported and standardized objective measures also decreases risk of performance bias. In addition, the assessor will video record the the 30-sec CST. This test will be scored by the assessor and another researcher (who has not been involved in performing the 30-sec CST). If there is a discrepancy between the assessor's and the other researcher's score on the 30-sec CST, a third researcher will be involved to score the 30-sec CST. This will prevent any bias in scoring the 30-sec CST that may arise from the assessor's assumptions about the participant's group allocation.

Statistical Methods

Analyses

Analyses will consider study feasibility as well as clinical (statistical) outcomes. Distribution of data will be evaluated by applying the one-sample Kolmogorov-Smirnov test. If data are found to be normally distributed, means and SDs (continuous variables) and frequencies and proportions (categorical variables) will be used to summarize demographic and outcome variables by groups. Descriptive statistics will be used to describe the sample and to assess online usage data (eg, time spent using modules) to evaluate dose response and adherence for the HIPPER group.

Missing Data

Similar to previous research on eHealth education (eg, [39]), missing data will be imputed using multiple imputation, and therefore, intention-to-treat analyses will be used. However, additional participants will be recruited to keep the sample size with complete data at 20 per arm.

Feasibility Indicators

The specific feasibility objectives (see Table 1) will be considered "successful," indicating a sufficiently robust protocol (small or no modification required), or "revise" if a substantive change is required prior to proceeding to a definitive RCT.

Clinical Outcomes

Primary and secondary outcomes at T2 will be compared between the HIPPER and control groups using analysis of covariance (ANCOVA), controlling for baseline score as a covariate [40]. Unequal cell sizes will be accommodated using Method 1 adjustment [41,42], and diagnostic assessments will be made for model assumptions. Statistical significance testing (*P*) and marginal means with 95% confidence intervals will be estimated with the alternative hypothesis favoring the HIPPER group. Effect size (partial 2) will be calculated as a ratio of the effect and total sums of squares, with a 95% confidence interval. To preserve prognostic balance, primary analysis will be intention-to-treat, but we will also consider per-protocol analyses as a secondary approach given one objective is to estimate the treatment effect [43]. The focus on a single primary variable indicates we will not control for multiple comparison, as the secondary outcomes are considered exploratory.

Data Monitoring

A Data and Safety Monitoring Board (statistician, occupational therapist/physical therapist, person with a THR) will review outcome data and advise the team on safety and any need to modify the study design [44]. The Data and Safety Monitoring Board is independent from the funding agency. More information about the board can be found by contacting the primary investigator.

Interim analyses will be conducted after the first 10 participants complete T2 and after the first 10 participants complete T3.

HIPPER incorporates extensive safety-related material including modified home setup (eg, elimination of scatter rugs) in the educational modules. However, adverse events (eg, falls during the 30-CST test) will be recorded and will be reported to the investigators. This process will be independent from the funding agency. In the very unlikely circumstance in which participants experience a decrease in function, substantial injury, or discomfort from their activities in this study, the investigators or study trainers will contact all participants by phone or email and inform them the study is being stopped and explain the reason.

Ethics and Dissemination

Ethics approval was obtained from our university Research Ethics Board (H16-02553) and the Vancouver Coastal Health Research Institute (V16-02553). Any changes in the ethics will be submitted as an amendment to our Research Ethics Board.

The assessor will be responsible for collecting consent forms from the participants. A PDF version of the consent form and a link to the online version of the consent form will be sent to the participants at least 24 hours before the T1 appointment. Participant will be given the option to either e-sign the PDF version or add their signature to the online consent form.

Email addresses will be captured because the measures should be sent to the same email address throughout the study; however, when conducting the analyses, all identifiable information will be removed from the data. The e-signed consent forms will be received through an email address provided by our research institute that will only be used for this project. Videos of participants will be labeled using a combination of their participant number and time point. Videos will be zipped, and we will add a password to the zipped file to ensure their security. The consent forms and videos will be password protected and will be saved in our lab drive, which is located on our research institute's servers in a separate folder than the data and the participants' contact list. The main participants' data will be collected with the University of British Columbia Qualtrics, and therefore, the servers are located in Canada.

The corresponding author will be responsible for the data for at least 5 years after the work is published or otherwise presented. At the end of this 5-year period, the paper copies will be shredded using a bonded company, and the computer files will be deleted. The videos will be zipped, and the zipped filed will be password protected. All videos will be saved in a separate folder on an encrypted and password-protected computer. Specifically, the videos will be only saved on our lab's drive, which is managed by our research institute's information technology department. All members of the study team will have access to the data. The list of the study team members can be found by contacting the corresponding author.

Our knowledge translation plan will target clinicians both nationally and internationally (clinicians' feedback will be used to further improve HIPPER), leveraging existing communication tools such as websites (eg, health authorities in BC), electronic and print newsletters (eg, Physiotherapy Association of BC), presentations at provincial practice forums, webinars for rural clinicians, and social media (eg, Twitter). Building on existing partnerships with Bone and Joint Canada and the Arthritis Health Professions Association, a summary will be prepared for their websites and electronic newsletters to reach a national audience. Abstracts will be submitted to conferences (eg, Canadian Orthopaedic Association Meeting). Manuscripts will be submitted for publication. If HIPPER is effective, we will collaborate with OASIS and will allow HIPPER to be hosted on the OASIS website [45]. OASIS and VCH will be responsible for updating and maintaining the content of HIPPER after the end of the research study.

There is no plan to use professional writers for disseminating the findings of this study. Participants who are interested in finding out about the results of this study will be sent a lay summary of the findings. The protocol of this study will be available to anyone interested.

Results

Recruitment started in March 2021. As of April 20, 2021, 18 participants were recruited. All 18 completed T1 measures. Only 1 participant has been scheduled to have surgery and therefore has been scheduled to complete T2 measures. The remainder of the participants are waiting to be notified of their surgery date. This project was funded by a Canadian Institutes of Health Research Project Grant. Our institute's research ethics board approved this study in November 2016.

Discussion

Potential Impact and Significance of the Study

eHealth is a promising way to address 2 substantial weaknesses in most prehab and presurgical programs, as it can (1) offer learning that is interactive (unlike printed materials) and (2) enable learners to engage over sustained periods (unlike single group sessions). Moreover, eHealth has the potential to improve quality of care for older adults [12,13,46], enhance communication between patients and health care providers [14], reduce costs, and increase access to evidence-based health information. Recent studies have shown that online interventions can substantially increase older adults' well-being [47] and physical activity levels [48]. In addition, available data show that internet use is growing rapidly among older Canadians. In BC alone, 86% of those aged 45-64 years make up the fastest growing cohort of individuals who need THR [49]. Considering the potential benefits of online education for older adults and the increase in the use of technology, it is reasonable and essential to develop eHealth tools for this population.

Clinical Contribution

HIPPER was developed with the aim to *improve access* to existing knowledge for patients and their families and *provide customized* (eg, through understanding patients' perspectives and having a digital interaction component), *interactive* (eg, quizzes), and *engaging eHealth education* (eg, using educational videos and audio) to better prepare patients for THR. In addition, HIPPER will *increase patient knowledge* and health literacy by facilitating access to prehab education. HIPPER will enable *self-paced learning*, with the support of family caregivers and from the comfort of the patient's home, thus *reducing the burden* on patients, families, and health care providers. It will also allow for *standardized information* to be delivered regardless of geographical boundaries. In contrast to written educational materials, HIPPER's content can be quickly updated with *minimal financial burden* on the health care system. Finally, it will reduce direct clinician contact and travel demands, leading to a reduction in both direct and indirect health care costs.

Strengths and Weaknesses of the Study

The results of this feasibility study cannot be generalized to all patients who are preparing for THR. However, considering that more than 85% of patients who undergo hip replacement are >50 years old [50] and more than 90% of BC's population speaks English [51], we are confident that this study will include a representative sample of THR patients. In our future full RCT, we aim to recruit patients from both urban and rural areas in BC to improve the generalizability of HIPPER. Despite developing the HIPPER modules with a user-centered approach, it is plausible that eHealth approaches may favor younger cohorts with greater computer experience and discourage older adults from participating [52]. While this assumption will be explored statistically, our patient partners' suggestions for "marketing" to older adults and adding basic computer training in the module introduction may address this issue. We will try to minimize barriers related to technology by sending each participant a guideline on how to use HIPPER, encouraging participants to contact the research assistant for further instruction, and inviting family caregivers to help participants use the online modules. In addition, in the current study, it is not possible to blind the participants to their group as it will be clear to participants what type of intervention they are receiving. Therefore, as other studies have suggested, the effect size might be substantially higher in trials in which participants are not blinded [53,54]. As recommended by previous research [55], to overcome the lack of participants' blinding, participants who previously attended OASIS webinars or in-person education will be excluded. In addition, participants in the control group will be prevented from accessing the HIPPER modules. Furthermore, the assessors in this study are blinded, and we will ask them to report any unblinding immediately. The assessors will be replaced if they report any potential or actual unblinding.

Finally, participants in the HIPPER group may be directed to the OASIS webinar educations by their surgeon, other health care providers, and other patients. Therefore, our educators at OASIS will be given the names of the participants and will be asked whether the participants attended any webinars. Participants in both HIPPER and control groups will also be asked at T2 whether they attended the OASIS webinars. Similar to previous studies [39], we anticipate a 20% dropout rate, meaning that participants will decline to participate in the study. If we encounter any dropout, we will recruit additional participants to keep the sample size for each group at 20.

Future Research

This project is a feasibility and preparatory study. The findings will be used to develop a definitive RCT, which will help us test the impact of HIPPER in a larger sample size before making it widely available for patients undergoing THR. If HIPPER is found to be effective in the future trial, we will collaborate with OASIS to host HIPPER on their website and encourage broad dissemination and implementation throughout BC.

Acknowledgments

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Authors' Contributions

WM, SM, WW, and MW designed the research. WM provided the equipment and facilities. WM and SM managed the project. WM, SM, and MW analyzed the data. MC, WW, and MW liaised with institutions. All authors were involved in data collection and writing the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Feasibility indicators.
[DOCX File , 16 KB - resprot_v10i7e29322_app1.docx]

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Abbreviations

ANCOVA: analysis of covariance
BC: British Columbia
CST: Chair Stand Test
EQ-5D-5L: EuroQoL-5 Dimension, 5 Level
HADS-A: Hospital Anxiety and Depression Scale
HIPPER: Hip Instructional Prehabilitation Program for Enhanced Recovery
OA: osteoarthritis
OASIS: OsteoArthritis Service Integration System
OHS: Oxford Hip Score
PASE: Physical Activity Scale for the Elderly
prehab: Prehabilitation
RCT: randomized controlled trial
SER: Self-Efficacy for Rehabilitation Outcome Scale
SPIRIT: Standard Protocol Items: Recommendations for International Trials)
THR: total hip replacement

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Protocol

An Electronic Registry for Improving the Quality of Antenatal Care in Rural Bangladesh (eRegMat): Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Digital health interventions (DHIs) can alleviate several barriers to achieving better maternal and child health. The World Health Organization's guideline recommendations for DHIs emphasize the need to integrate multiple DHIs for maximizing impact. The complex health system of Bangladesh provides a unique setting for evaluating and understanding the role of an electronic registry (eRegistry) for antenatal care, with multiple integrated DHIs for strengthening the health system as well as improving the quality and utilization of the public health care system.

Objective: The aim of this study is to assess the effect of an eRegistry with DHIs compared with a simple digital data entry tool without DHIs in the community and frontline health facilities.

Methods: The eRegMat is a cluster-randomized controlled trial conducted in the Matlab North and Matlab South subdistricts in the Chandpur district, Bangladesh, where health facilities are currently using the eRegistry for digital tracking of the health status of pregnant women longitudinally. The intervention arm received 3 superimposed data-driven DHIs: health worker clinical decision support, health worker feedback dashboards with action items, and targeted client communication to pregnant women. The primary outcomes are appropriate screening as well as management of hypertension during pregnancy and timely antenatal care attendance. The secondary outcomes include morbidity and mortality in the perinatal period as well as timely first antenatal care visit; successful referrals for anemia, diabetes, or hypertension during pregnancy; and facility delivery.

Results: The eRegistry and DHIs were co-designed with end users between 2016 and 2018. The eRegistry was implemented in the study area in July 2018. Recruitment for the trial started in October 2018 and ended in June 2020, followed by an 8-month follow-up period to capture outcome data until February 2021. Trial results will be available for publication in June 2021.

Conclusions: This trial allows the simultaneous assessment of multiple integrated DHIs for strengthening the health system and aims to provide evidence for its implementation. The study design and outcomes are geared toward informing the living review process of the guidelines for implementing DHIs.

Trial Registration: ISRCTN Registry ISRCTN69491836; https://www.isrctn.com/ISRCTN69491836

International Registered Report Identifier (IRRID): DERR1-10.2196/26918

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KEYWORDS

quality of care; antenatal care; maternal and newborn health; eHealth; digital health interventions; eRegistries; health information systems; Bangladesh

Introduction

Background

The evidence-based interventions that can prevent maternal, newborn, and fetal deaths are well known [1], but the lack of access to timely and actionable data is a significant obstacle toward achieving better maternal and child health [2]. Much of the existing data for monitoring maternal and child health in low- and middle-income countries (LMICs) come from national surveys, such as the Demographic and Health Surveys [3] and the Multiple Indicator Cluster Surveys [4]. Health information systems in LMICs, which can provide routine and critical data, are often underutilized. In many settings, health information systems do not collect and manage data in ways that provide personalized good quality health care [5]. Other known issues such as the lack of awareness of guidelines, inadequate feedback to providers, and a poor coordination between the levels of health care have been shown to hamper effective data use [6].

Digital health interventions (DHIs) have the potential to address many of these issues. In 2017, the World Health Organization (WHO) published the Classification of DHIs, describing how digital tools can support health and health systems [7], whereas in 2019, their first recommendations for a select set of DHIs for health system strengthening were released [8]. Even for the DHIs included in the WHO guidelines, there is insufficient evidence to fully inform their optimal implementation in health systems. Evidence for the use of DHIs at a large scale in the real-world settings is crucial for policy makers to make decisions about system-wide implementations [9]. Every recent review of DHIs has unequivocally stated the need for more evidence of what works, and if and how such DHIs can be made scalable and sustainable [10,11]. DHIs are frequently tested in isolation or with weak study designs [8], making it difficult to ascertain their efficacy. The combinations of DHIs may be most effective in delivering measurable impacts on strengthening the health system. Many countries have transitioned to the use of digital health information systems. The enormous amount of data collected in such systems can be harnessed to drive several DHIs to strengthen the health systems, an opportunity often missed. Although evaluations of digital health information systems have focused on assessing timeliness and completeness of routine data, more comprehensive assessments of the outcomes of implementations of DHIs driven by data collected in health facilities are relatively rare.

An electronic registry (eRegistry) is a digital health information system comprising the longitudinal tracking of clients' health status and services received, typically for maternal and child health [12]. In a health system with an eRegistry, health workers enter clinical data at the point of care into digital client health records. Data entry is typically set up as interactive checklists, which can minimize the documentation burden while enhancing data quality. The entered clinical data then drives several DHIs, for example, guideline-based clinical decision support for health workers [13] and targeted communication of personalized health information to clients [14]. An eRegistry can support additional DHIs such as feedback dashboards, stock notifications, routine health indicator data collection and management, and referral management. The specific set of DHIs included in an eRegistry, beyond the longitudinal tracking of clients' health status, depends on the exact needs of a given implementation context.

Since 2018, an eRegistry has been implemented for use in Bangladesh in the Matlab North and Matlab South Upazilas, Chandpur district. Bangladesh has made significant progress in terms of maternal and child health. From 1990 to 2013, the Millennium Development Goal 4 was achieved (reduction of under-five mortality from 133 to 52 per 1000 live births), whereas maternal mortality declined significantly (from 550 to 196 per 100,000 live births) [15]. The primary health care system, where a large portion of maternal and child health services are provided, is a complex landscape of governmental, private, and nongovernmental organization (NGO) providers. The digital health atlas, an open-source platform for DHI implementations maintained by WHO, lists at least 12 registered implementations of DHIs in Bangladesh as of September 2020 [16].

The first cluster-randomized controlled trial of the effectiveness of an eRegistry with clinical decision support compared with paper records on improving the quality of antenatal care was conducted in the West Bank, Palestine [13]. The effect of an eRegistry with multiple DHIs such as health worker clinical decision support, feedback dashboards with action items, and targeted client communication, compared with a simple digital data entry tool with no DHIs, is yet to be evaluated.

Objectives

The objective of this eRegistry trial (eRegMat) in Matlab, Bangladesh, is to assess the effect of an eRegistry with DHIs compared with a simple digital data entry tool without any DHIs in the community and frontline health facilities.

Methods

Trial Design

The eRegMat study is a two-arm cluster-randomized controlled trial. The unit of randomization is the primary care health facility, community clinics, and family welfare clinics. All pregnant women enrolled in the trial had their health information entered into the eRegistry. The intervention arm received 3 DHIs supported by the data in the eRegistry: (1) health worker clinical decision support, (2) feedback dashboards with action

items, and (3) targeted client communication. The control arm received only a digital data entry tool without any additional DHIs.

Study Setting

The public health system in two Upazilas (subdistricts)—Matlab South and Matlab North under Chandpur, Bangladesh—were included in the eRegMat trial. The public health system in Bangladesh is managed by the Ministry of Health and Family Welfare, where maternal and child health services are provided by two separate departments: the Directorate General of Family Planning and the Directorate General of Health Services. Under the Directorate General of Family Planning, family welfare visitors work at family welfare clinics located at the union level and family welfare assistants provide community outreach services. Under the Directorate General of Health Services, community health care providers offer maternal and child health as well as general health services from community clinics and health assistants who are tasked with visiting households and providing vaccination services to women and girls of reproductive age as well as young children through satellite clinics set up close to the community. A typical primary care health facility (community clinic or family welfare clinic) is permanently staffed by one clinical cadre (a community health care provider or a family welfare visitor). In addition, at the community clinics, the community health care provider is usually supported by a family welfare assistant or a health assistant. The community and facility workers cooperate to register pregnancies and encourage clients to seek reproductive, maternal, and child health services. In the existing paper-based health information system environment, there is no exchange of data or information between the different cadres of health workers or the different levels of the health system. The District Health Information Software 2 (DHIS2) [17] was used to generate aggregate reports of maternal and child health contacts in the study area.

In the study area, a substantial number of pregnant women access care at family welfare clinics and community clinics within the governmental health system. Antenatal care typically comprises the measurement of blood pressure, height, weight, fundal height; anemia assessment; the provision of vitamin and mineral supplementation; management of common illnesses; counseling; and referral, if needed. On the basis of these guidelines, pregnant women with complications are referred to a subdistrict (Upazila) hospital, where basic laboratory services as well as delivery services including cesarean sections are typically available. Some patients utilize tertiary care health facilities for delivery or when identified with complications during pregnancy. Women may also access private health care, where they are likely to receive ultrasound scans and laboratory tests. Most private hospitals perform cesarean sections. Several private and NGO-run facilities are also engaged in providing maternal and child health services in the study area.

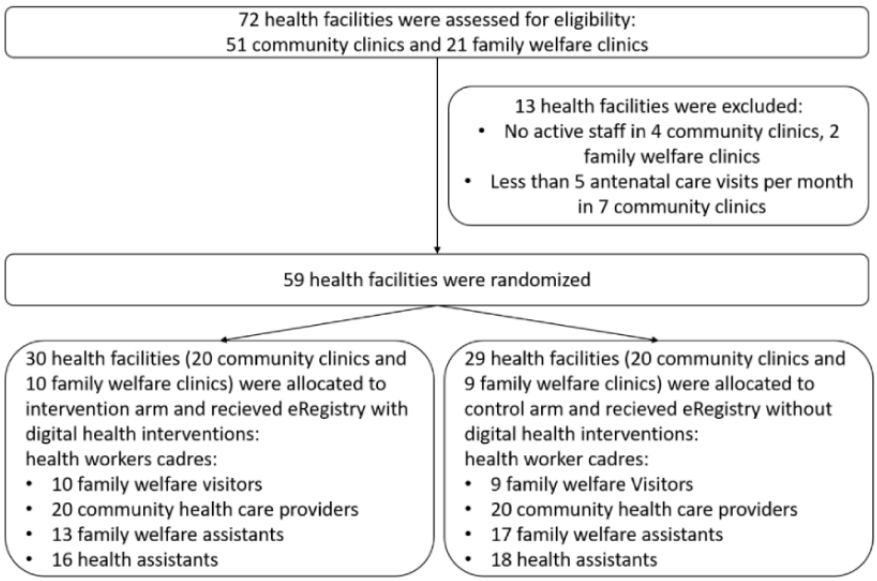
Eligibility Criteria

There were 2 levels of eligibility for this trial: (1) the cluster level, which refers to the randomized health facilities and their health workers and (2) the individual level, which refers to the women belonging to the clusters who provide informed consent.

Cluster Level

All government-run community clinics and family welfare clinics routinely providing antenatal care, delivery, or postnatal care services outside the referral health facility in the Matlab North and Matlab South Upazilas were eligible for the trial. Facilities were excluded if (1) there was no community health care provider or family welfare visitor to provide information on antenatal care visits in the previous month or (2) they reported fewer than five antenatal care visits in the previous month. Of the 72 health facilities in the study area, 59 (82%) were randomized (Figure 1). In total, 30 health facilities and 59 health workers were allocated to the intervention arm, whereas 29 health facilities and 64 health workers were allocated to the control arm (Figure 1).

Figure 1. Flow diagram. eRegistry: electronic registry.



Individual Level

Individual women with a confirmed pregnancy were registered, and their health data were entered into the eRegistry. Pregnancy identification and registration may be conducted by family welfare assistants or health assistants at the households or by community health care providers or family welfare visitors at the women's first health facility encounter. All pregnancies identified by a health worker using the eRegistry should be entered into the system. Only women who consent to have a household visit after birth were included in the trial because the outcome data were derived from the household survey.

Intervention

Overview

An eRegistry was implemented in the study area by the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr, b), in collaboration with the Norwegian Institute of Public Health, the University of Oslo, and the Ministry of Health and Family Welfare in Bangladesh. Health workers in both the intervention and control arms document clinical information in the eRegistry's digital client health records at the point of care. Health workers' cadres under both the Directorate General of Health Services and Directorate General of Family Planning (Table 1) use the eRegistry to create client health records across otherwise disjointed silos of the health information system. The eRegistry is configured in the free and open-source DHIS2 tracker. Health workers in the community (family welfare assistants and health assistants) use the eRegistry on a customized Android Tracker app installed on handheld tablets, whereas facility-based users (community health care providers and family welfare visitors) access the eRegistry through a browser on Chromebook (Figure 2). All devices were equipped with SIM cards for prepaid mobile data access. To improve client identification for optimal data continuity in an environment with a few unique identifiers, a palm-based biometric software provided by Element biometrics [18] was made available to the users of the eRegistry. The Element biometrics app was installed on the same device used by the health workers to access the eRegistry. A unique identifier was generated for each client in the biometrics app. Health workers were trained to copy this identifier to the client's records in the eRegistry. A unique identifier was also generated by the DHIS2 system during the registration of each pregnancy. A demo version of the eRegistry and DHIs is available upon request from the authors.

Paper-based documentation of pregnancies; register books with the number and dates of antenatal, postnatal, and delivery services; and public health reports were maintained along with the eRegistry in both intervention and control health facilities throughout the trial period. Table 1 provides a detailed comparison of the situation before eRegistry implementation in the governmental health system with the control and intervention arms of the trial.

Table 1. The paper-based health information system before the implementation of electronic registry, the electronic registry in the control arm, and the electronic registry with digital health interventions in the intervention arm.

Health information system feature	Cadres	Before the trial	Control arm	Intervention arm
Health worker: all				
Access to own records	FWA[a], HA[b], CHCP[c], FWV[d]	✓[e]	✓	✓
Access to all records in the system	CHCP, FWV			✓
Health worker: community				
Digital client health records	FWA, HA		✓	✓
Client identification (biometric and palm-based) and registration	FWA, HA		✓	✓
Feedback dashboards	FWA, HA			✓
Health worker: facility				
Client identification (biometric and palm-based) and registration	CHCP[f], FWV		✓	✓
Digital client health records	CHCP[f], FWV			✓
Clinical decision support	CHCP[f], FWV			✓
Feedback dashboards	CHCP[f], FWV			✓
Health worker: all				
Access to own records	FWA, HA, CHCP, FWV	✓	✓	✓
Access to all records in the system	CHCP, FWV			✓
Clients				
Targeted Client Communication via SMS	Pregnant women			✓

[a]FWA: family welfare assistant.

[b]HA: health assistant.

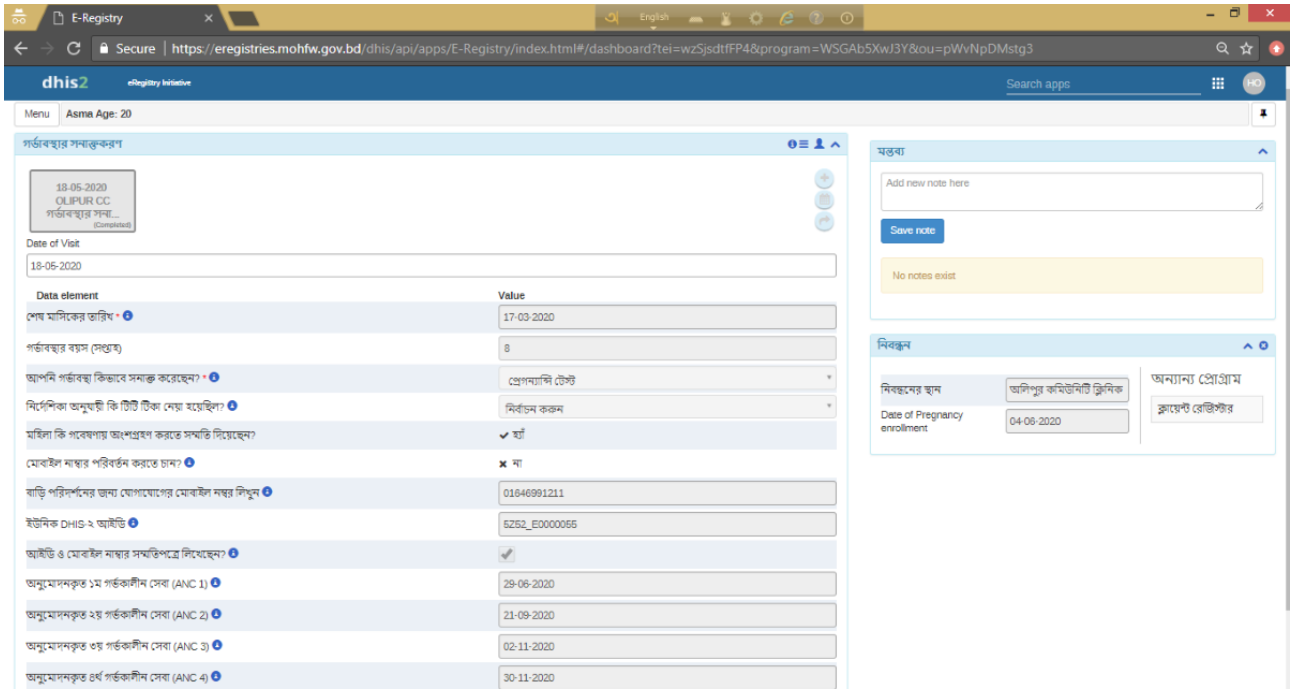
[c]CHCP: community health care provider.

[d]FWV: family welfare visitor.

[e]Features of the eRegistry with and without digital health intervention available in the intervention and control arms.

[f]Community health care providers use the District Health Information Software 2 system for separate aggregate reporting, not linked to the electronic registry.

Figure 2. Screenshot of electronic registry interface for data entry in the study area—intervention and control clusters.



Control Arm

In the control arm of the trial, the eRegistry comprised only digital client health records (Table 1). The data points included in the client records were almost identical to the paper-based client records, and drop-down lists were added to some data points to optimize the use of the digital data entry tool. The eRegistry in the control arm was set up such that control users had no access to client records entered by other users. Apart from basic data validation warnings, data-driven DHIs were not available in the control arm (Table 1).

Intervention Arm

In the intervention arm, the eRegistry supported 3 data-driven DHIs linked to the digital client health records (Table 1) as follows: (1) for facility-based staff, health worker clinical decision support based on national guidelines to promote the correct management of health conditions identified in antenatal care; (2) for both field- and facility-based staff, feedback dashboards tracking the health worker's progress toward pregnancy registration, antenatal care attendance and utilization, and clinical screening and management targets; and (3) for pregnant women, targeted client communication in the form of SMS text messages to address gaps in the timely attendance of antenatal care visits and facility delivery. Following the initial implementation of the eRegistry, the DHIs in the intervention arm were gradually introduced over the course of the trial; health worker clinical decision support was introduced in October 2018; targeted client communication via SMS and feedback dashboards were implemented in June 2019. Digital client health records were accessible across the cadres of health workers, facilities, and arms of the health system for a comprehensive longitudinal tracking of clients' health status and services received (Table 1).

Guideline-based clinical decision support and feedback dashboards were developed in close collaboration with health workers. The decision support comprised referral and counseling reminders, medication alerts, and scheduling based on the recommended guidelines in the public health system. Feedback dashboards were customized for each cadre of health workers, with indicators of antenatal care attendance and screening and management of gestational diabetes, hypertension, and anemia. Targeted client communication included SMS text message reminders of routine antenatal care, referral facilitation SMS text messages for those at risk, and facility delivery reminders for those who are advised to have an institutional delivery. All DHIs were triggered by data entry into the eRegistry at the point of care by the health workers.

Adherence

The Directorate General of Health Services in Bangladesh employs DHIS2 as their national health information system platform for aggregate data. A DHIS2 tracker app for individual-level data collection is available for one cadre of health workers, the community health care providers. The study team reinforced adherence to the use of the eRegistry in several ways. The study team members periodically attended monthly meetings with health workers. Technical support was provided for crosscutting issues around data entry, client identification, and verification to both the control and intervention arms throughout the trial. After the rollout of the eRegistry, all health workers were evaluated on key competencies in using the eRegistry and the Element biometrics app. Those identified with challenges in using digital tools were retrained. Field support staff from the study team also checked in periodically on such health workers to provide one-on-one support. The study team maintained a log of the most important issues that emerged with a possible direct impact on trial outcomes. Key indicators of adherence to the use of the eRegistry across intervention and control clusters will be presented along with the trial results.

Concomitant Care

At the start of the trial, no other health information system studies or implementations were ongoing in the study area. Both the control and intervention arms of the trial received similar support in the use of the eRegistry for data entry. Intervention and control clusters offer the same clinical antenatal care services, and the national treatment and management guidelines set by the Ministry of Health and Family Welfare for maternal and child health apply to both. All health facilities in the Matlab North Upazila are a part of separate demand-side incentive programs to encourage women to attend antenatal and postnatal care and to have a facility delivery [19]. During the postpartum home visit, we will capture data that allow the estimation of the proportion of women who utilized these programs and subsequently account for possible effects of this on the trial outcomes.

Outcomes

The outcomes were formulated based on their relevance to the health system context and were meant to capture the potential effects of the specific DHIs under assessment. Data for the primary (Table 2) and secondary outcomes (Table 3) will be derived from the eRegistry's client health records and through postpartum home visit interviews.

Table 2. Primary outcomes, data sources, and definitions.

Primary outcome	Sources of data	Measurement sequence	Definition	Intervention subcomponents with most direct effect
Timely attendance at eligible ANC[a] visits	Postpartum household survey	• Registrations continuously at point of care • Household visit after the completion of pregnancy	• Proportion with timely attendance	• Targeted Client Communication via SMS text message: ANC appointment reminders

Screening and management for hypertension in pregnancy	Case records from the eRegistry[b]	• Registrations continuously at point of care	• Proportion that has at least one ANC at a randomized health facility with:
			  • Blood pressure measurement at routine ANC visits, and
			  • Referred if blood pressure is high, or
			  • Referred if blood pressure is high outside of the routine ANC visit
				• Health worker clinical decision support
				• Feedback dashboards with action items

[a]ANC: antenatal care.

[b]eRegistry: electronic registry.

Table 3. Secondary outcomes, data sources and definitions.

Secondary outcome	Sources of data	Measurement sequence	Definition	Intervention subcomponents with assumed direct effect
Timely first ANC[a] visit	• Case records from the eRegistry[b] • Postpartum household survey	• Registrations continuously at point of care • Household visit after the completion of pregnancy	• Proportion of women that have an ANC visit at or before 16 weeks among those with a home pregnancy registration before 16 weeks	• Targeted Client Communication via SMS text message: ANC appointment reminders
High-risk women successfully referred to a skilled provider for additional care	• Case records from the eRegistry • Postpartum household survey	• Registrations continuously at point of care • Household visit after the completion of pregnancy	• Proportion of women that received additional care during pregnancy among those that are referred for severe anemia, or hypertension or diabetes during pregnancy	• Health worker clinical decision support • Targeted client communication via SMS: Referral reminders, high risk, facility delivery reminders
Facility delivery among those advised to deliver in a facility	• Case records in the eRegistry • Postpartum household survey	• Registrations continuously at point of care • Household visit after completion of pregnancy	• Proportion of women that deliver in a facility among those that should delivery in a facility based on certain risk factors identified during ANC	• Health worker clinical decision support • Targeted client communication via SMS text message: high risk, facility delivery reminders
Births with severe morbidity or mortality among all women and among those with any risk identified	• Case records in the eRegistry • Postpartum household survey	• Registrations continuously at point of care • Household visit after completion of pregnancy	• Proportion with a very preterm birth, very low birth weight, perinatal death, or hospitalization of the newborn for at least 7 days after birth among all women enrolled in the trial, and those with any identified risk during ANC	• Health worker clinical decision support • Targeted client communication via SMS text message: referral reminders
Severe postpartum anemia	• Postpartum household survey	• Household visit after the completion of pregnancy	• Proportion of women with severe anemia in postpartum	• Health worker clinical decision support • Targeted client communication via SMS text message: referral reminders

[a]ANC: antenatal care.

[b]eRegistry: electronic registry.

Sample Size

Sample size was calculated based on the 2 primary outcomes using the following assumptions: (1) a cluster size of 77 women and 140 antenatal contacts in the randomized health facilities for a 21-month enrollment period; (2) a 20% coverage of timely antenatal care visits and 12% of women screened and managed for hypertension in the control group, based on data from the 2014 Demographic and Health Survey; and (3) an a priori intracluster correlation coefficient of 0.1, commonly reported for such process outcomes [20]. The given sample size will have more than 80% power to detect a minimum clinically significant change from 20% to 33% for timely antenatal care visits and from 12% to 22% for hypertension screening and management. The sample size was calculated using Stata 16 (StataCorp).

Recruitment

Both the intervention and control health facilities received the same number of initial training sessions. The initial training duration was decided based on the underlying skill level of the health workers and the complexity of the tasks within the eRegistry. In total, 276 health workers (102 family welfare assistants, 71 health assistants, 44 community health care providers, 20 family welfare visitors, 20 family planning inspectors, and 10 assistant health inspectors) were trained over 21 sessions in using the eRegistry. Retraining was provided to health workers in both the intervention and control arms at

regular intervals of 3-6 months and over 36 sessions during the trial.

Allocation

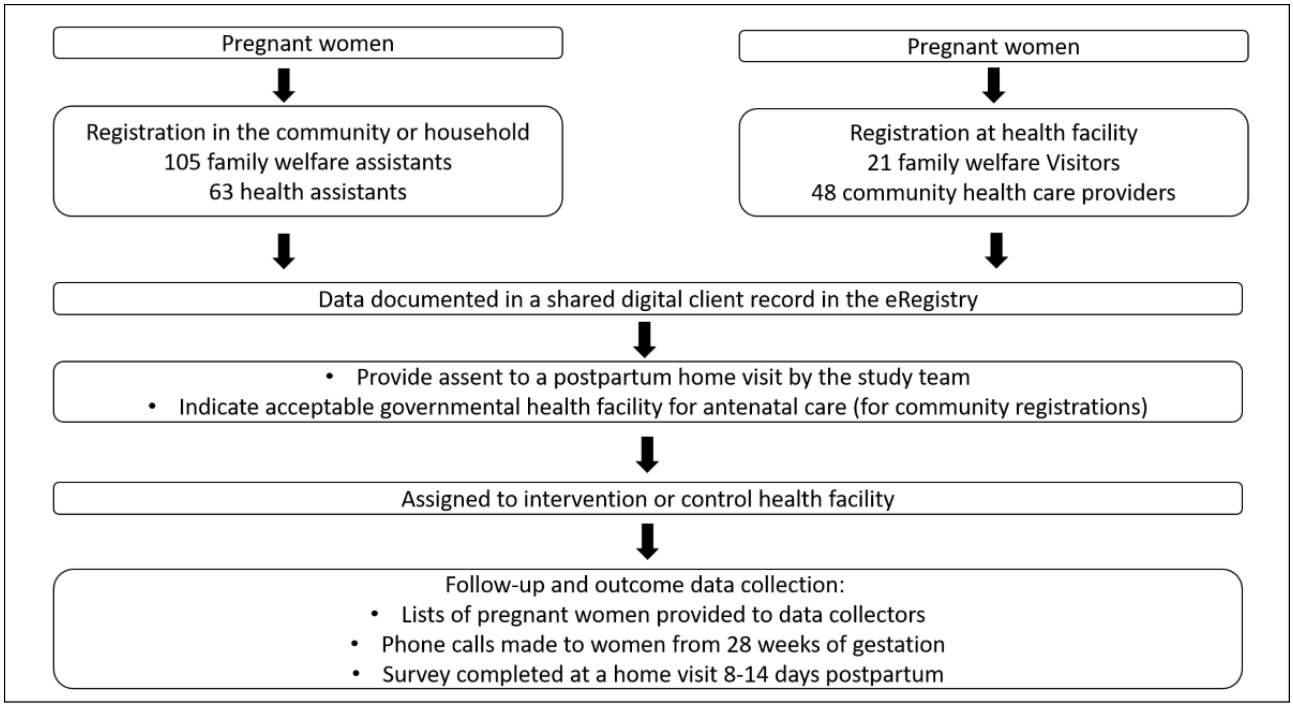
Randomization of Health Facilities

The unit of randomization was a health facility (community clinics or family welfare clinics) located in the study area, which provided antenatal, childbirth, and postpartum care. We performed stratified restricted randomization with a 1:1 ratio. The randomization was stratified based on the type of clinic (family welfare clinics and community clinics) and whether the facility was staffed with a care provider. The randomization within each stratum was then restricted based on (1) the clinic's allocation as intervention or control within a preceding project in the study area for strengthening maternal and child health services; (2) the technological skills of the staff; (3) the monthly number of clients attending the clinic; and (4) the monthly number of antenatal care visits. To measure the technological skills of the staff, we created an index using information from a provider and a clinic survey conducted by the study team in preparation for the trial. The index included items such as health workers' technological capabilities, such as the use of phones for SMS and internet, and their comfort using technology. Statisticians at the Centre for Intervention Science in Maternal and Child Health (CISMAC), University of Bergen, undertook randomization.

Individual Women Within the Trial

The family welfare assistant enrolled individual women in the trial at pregnancy identification and registration. At that time, women were required to provide informed consent to receive communication from the study team and a home visit 8-14 days after the birth of the child (Figure 2). Women were then asked about their preferred public health facility for antenatal care, which determined allocation to an intervention or control cluster (Figure 3). Women may also be first identified as pregnant at a health facility. At this contact, women were registered in the eRegistry and automatically assigned to an intervention or control cluster based on the allocation status of that health facility (Figure 3). After completion of the pregnancy, the data collection team conducted a postpartum home visit within 8-14 days of birth for collection of outcome data.

Figure 3. Identification and enrollment of individual pregnant women in the trial. eRegistry: electronic registry.



Blinding

Due to the nature of the intervention, it was not possible to blind facility-based health workers to the allocation. Community-based health workers registering and allocating pregnant women were blinded to the allocation status of their preferred health facility. The data collectors conducting the postpartum home interviews were blinded to the allocation of individual women. Researchers performing the final analyses will be blinded to group allocation.

Data Collection

Overview

The eRegistry used by health workers in the intervention and control arms will provide some of the data for outcome measurements. Independent trained project staff collected data regarding birth outcomes, antenatal care utilization, and referral care seeking from a subset of the population of registered pregnancies through a postpartum household survey. The postpartum household survey started in June 2019, 8 months after the commencement of recruitment. Data collectors were provided with a list of all pregnancies registered in the eRegistry that were beyond 28 weeks of gestation at a given point in time.

The data collectors made biweekly phone calls to clients from 28 to 35 weeks, and weekly thereafter to ascertain whether the pregnancy was ongoing. Postpartum household visits for data collection were conducted within 8-14 days of childbirth. A paper-based structured questionnaire was used for data collection (Multimedia Appendix 1), focusing on the experiences of pregnancy and childbirth, health care interventions received, and health outcomes of the mother and the newborn. The infant's weight was measured during the home visit; weight was measured in minimal clothing, and the weight of the clothes was subtracted from the total weight. Where possible, women's finger-prick blood was used to measure hemoglobin. The questionnaires were checked for completeness and consistency by the data collectors' supervisors, and women were interviewed again if needed. Data from the paper questionnaires are being made electronic, and consistency checks are performed by the study team after data entry.

Data Management

Data generated from this project are stored in the Government of Bangladesh's server located at the office of the Directorate General of Health Services. For analysis purposes, an authorized data manager from the study team will extract predefined data from the server in a secure manner. Data from the postpartum household survey will be stored in locked cabinets in the icddr, b premises, with the personal identifiers removed and stored separately. Once these data have been entered digitally, the data manager will relink the eRegistry data with the postpartum survey data using the study ID. No other personal identifiers were available or were retained. The data will be saved in a password-protected computer. The data manager will share anonymous data sets with researchers for outcome analysis.

Statistical Methods

The primary analyses will be conducted as an intention-to-treat analysis, based on the allocation question rather than the actual site of antenatal care services, comparing the intervention arm with the control arm for all outcomes. Health worker characteristics such as gender, age, and education and health facility characteristics such as distance to referral unit, volume of pregnant women seen per month, digital competency, and internet connectivity will be presented. Pregnant women's age, parity, socioeconomic status, and education will be presented as background characteristics. Primary analyses will be performed at the individual client level. Categorical variables will be analyzed using generalized linear models of the binomial family with a log link to estimate the relative risks and prevalence ratios. Random effects will be included to account for the inherent effect of clustering. Absolute and relative differences between the intervention and control groups with 95% CIs were calculated. Confounders will be adjusted for in the primary analysis only if there are important baseline imbalances (ie, when the effect measure changes by more than 5% when added to the model). Subgroup analyses will be performed based on categories defined as a priori, such as those related to demographic characteristics. We will present the equity analyses of the differential effectiveness across subgroups, including wealth quintiles, residence, educational levels, and employment status for each outcome. The imputation of missing data will be considered.

To understand the client base and their utilization of the health system, we will describe the client flow across providers, facilities, and arms of the trial. It is expected that some women will cross between the intervention and control clusters to receive health care services. Secondary analyses will be performed per protocol, where only the subset of women who remain in their assigned clinic type (ie, all visits are within the intervention group or control group) will be analyzed. We will perform a dose-response analysis (based on the proportion and number of visits to the intervention group) to assess whether there is a threshold or linear effect based on the increased utilization of intervention clusters. Finally, we will present population-level estimates of the impacts of the eRegistry if they were to be fully implemented in this community.

The study team will develop a code for analyses using dummy intervention or control allocation. A statistician not otherwise involved in the trial will conduct the final analyses using the actual allocations. All statistical analyses will be performed using statistical software such as Stata version 16 or later or RStudio version 1.2.1335 or later.

Data Monitoring

The eRegMat trial is considered to be a health systems research where the intervention aims only to support existing care processes for care providers and does not constitute a medical intervention for individual subjects. Hence, a formal data safety monitoring board was not established.

Harms

As such, we do not anticipate any harm from the introduction of the intervention. The introduction of new technology may have resulted in reduced efficiencies during the initial months of utilization; however, we expect this to have resolved before the data inclusion period of this trial.

Audit

The CISMAC was responsible for trial monitoring. An initial monitoring visit was conducted in June 2018 to assess readiness before the start of recruitment. Midway, monitoring was conducted in November 2019, when recruitment rates, fidelity to the intervention, and progress of data collection were assessed.

Ethics and Dissemination

Ethics and Consent to Participate

This study was reviewed and approved in Bangladesh by the Research Review Committee and Ethical Review Committee of icddr, b (Ref: PR-16054) and by the Regional Committee for Health Research Ethics–South East B Section (Ref: 2017/1028 C) in Norway. All health workers using the eRegistry and their supervisors at the Matlab North and Matlab South Upazilas were notified of their participation in the trial by the Ministry of Health and Family Welfare. No financial incentives were provided to the health facilities or care providers involved in this study; participation was considered mandatory by the central government. Financial support for participating in training

sessions and meetings was conducted according to the government guidelines.

Informed consent would typically not be warranted for health systems research studies using anonymous health data, but three features in the implementation of this trial required additional ethical considerations. First, national guidelines recommend that family welfare assistants perform a urine pregnancy test for women who are uncertain of their pregnancy status. Because test kits were often unavailable in the health system, they were provided to health workers for the purpose of this trial. Women's consent was required to obtain a urine sample for pregnancy testing. The sample never left the home, and the results were strictly confidential. If the woman declined to provide her sample, then the health worker privately counseled the woman of her options for testing. Second, the woman's consent was required to receive targeted client communication via SMS text message. Women were informed about the purpose of the service, the content of SMS text message reminders, measures to ensure data confidentiality, and their ability to opt out of the service at any time. Providing a mobile phone number was assumed to imply consent. The option to stop receiving SMS text messages was available at every encounter of clients with their health workers. Phone numbers were available only to health workers who had access to the client's health records. Third, all women enrolled in the eRegistry were asked to provide informed consent to undergo a postpartum home visit. This consent was for the purpose of being contacted by the study team during the latter part of their pregnancy and to allow the study team to conduct a visit 8-14 days postpartum. If women themselves notified the study team of the culmination of her pregnancy, a small incentive of 100 taka (approximately US $1) was given at the time of the home visit as a token of appreciation.

Confidentiality

The eRegistry data will be managed in accordance with the Ministry of Health and Family Welfare governance policies for health information systems. All data are stored securely on the national server under the custodianship of the Ministry.

Access to Data

The eRegistry data are owned by the Ministry of Health and Family Welfare in Bangladesh and subject to their regulations and legislation. Only one legally authorized person in the Bangladeshi Ministry of Health and Family Welfare will have access to individual-level data in the eRegistry. At no point will the researchers have access to identifiable data of any kind. The postpartum household questionnaire database will not be available outside the standard analysis protocols of the project, in accordance with the data access protocols of icddr, b.

Protocol Amendments

Changes in the secondary outcomes were written as amendments to the trial registration after being agreed upon in the study group. Amendments that amount to significant modifications to the study design have been reported to the CISMAC.

Collaborative Arrangements

The Norwegian Institute of Public Health owns the project and is ultimately responsible for the overall conduct; the institute has agreements with all the research partners detailing their roles and responsibilities. The icddr, b was responsible for the implementation and administration of the trial in Bangladesh, whereas the University of Oslo was responsible for the development of the eRegistry software in collaboration with other partners.

Dissemination Plan

The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines were followed for writing this protocol (Multimedia Appendix 2). The trial publication will follow the CISMAC rules for authorship and publication and the Bangladesh Ministry of Health and Family Welfare regulations. We will publish the results in peer-reviewed open access journals and report them in accordance with the CONSORT (Consolidating Standards of Reporting Trials) guidelines.

Funding

The Norwegian Research Council (project number 248073/H10; title: Strengthening the extension of Reproductive, Maternal, Newborn, and Child Health services in Bangladesh with an electronic health registry: A cluster randomized controlled trial) and the CISMAC, University of Bergen (project number 223269) funded this research. In addition to monetary inputs, CISMAC also provided intellectual input into the study design and monitoring of the trial.

Results

Implementation of the eRegistry started in April 2018, after preliminary field testing (Table 4). Data documentation in the eRegistry started after the health workers completed a second round of training between July and December 2018. Data on all women enrolled between October 2018 and June 2020 (21 months) will be included in the analysis. The follow-up ended in February 2021, when the last enrolled woman received a postpartum household visit. Approximately 8000 pregnancies were registered in the eRegistry during the trial. The results of the trial are expected to be available in July 2021.

Table 4. Timeline of the eRegMat cluster-randomized controlled trial.

Implementation of the study	2018		2019					2020				2021
	Apr-May	Jul-Oct	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec	Jan-Feb
Enrollment												
Trainings	✓[a]	✓			✓							
Enrollment			✓	✓	✓	✓	✓					
Intervention												
eRegistry[b] (intervention and control)			✓	✓	✓	✓	✓	✓	✓			
Assessment or follow-up												
Outcome data collection			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[a]Period during which the trial activity was conducted.

[b]eRegistry: electronic registry.

Discussion

Study Relevance

There is a global trend toward digital data collection in health systems in LMICs; however, the collected data are rarely used to support multiple DHIs. DHIs are shown to have relatively modest effects on their own, whereas a package of several simultaneously delivered DHIs is likely to be more effective and cost-effective. We designed a trial that compared two types of digital data collection systems: one where the longitudinally collected individual-level data in an eRegistry does not drive additional DHIs (control arm) and one where the data entered are used to generate three additional DHIs (intervention arm).

Antenatal care utilization in Bangladesh is suboptimal, with only 37% reported attendance of four or more visits [15]. In addition, gaps in antenatal care content and quality have been highlighted in studies conducted in other parts of Bangladesh [21]. The eRegistry's data-driven DHIs aim to address antenatal care utilization (through targeted client communication via SMS text messages) as well as the quality of care (through health worker clinical decision support based on national guidelines), thereby addressing the two essential components of the effective coverage of antenatal care [22].

The transition of clinical documentation from paper to electronic data entry in digital client records may affect clinical practices and health care service delivery, even without any additional DHIs such as clinical decision support. In our trial, we wanted to evaluate the effects of data-driven DHIs per se, while controlling for the possible effects of the transition from paper to digital systems. Consequently, the control arm of the trial uses the eRegistry, albeit only as a digital data entry tool, with no superimposed DHIs.

The different government health workers in Bangladesh largely operate in silos, which limits the use of routinely reported data. The eRegistry spans multiple cadres of health workers and departments of the health system. The use of an eRegistry purposefully implemented for use by all cadres of health workers who typically meet an individual client in the public health system can provide more reliable data and improve the quality of health services. Health workforce capacity is an important component of the enabling environment for digital health [23]. In our study setting, except for the community health care providers, the other cadres were not skilled in using digital tools. Furthermore, health care workers do not receive in-service training in the use of digital tools. Low technology skills and lack of in-service training in the use of digital tools are common issues in several LMICs [24]. In addition to the results of the trial, we will report on the delivery of different components of the intervention, training needs, and implementation support over the course of the study. Such reporting would not only be in line with the general recommendations of reporting of trial of health systems and of DHIs [25] but also serve as useful guides for others planning studies of DHIs for health system strengthening in comparable health system settings.

Strengths and Limitations

An important strength of the trial lies in the design and implementation of the intervention. We continuously engaged both health workers and clients to develop tailored DHIs. The eRegistry supports the creation of a single, individual-level health record across multiple cadres of health workers; few other initiatives have made efforts to implement such a system designed to provide continuity of data and care. The trial outcomes are meant to capture different aspects of the intervention, allowing for better interpretations of the effect while serving as another strength of the study.

This study had some limitations. Reduced fidelity to the use of the eRegistry as the primary documentation tool will adversely affect the DHIs driven by the entered data. The eRegistry is not set up to provide automated monthly public health reports. Public health reports are still largely paper-based, with one cadre of health workers using the DHIS2 system separately for aggregate reporting purposes. This continued use of paper-based documentation and aggregate reporting may lead to incomplete data entry into the eRegistry, thus affecting the optimal delivery of DHIs. The eRegistry is used only in public sector health clinics at the primary care level. As a result, the results of the trial are only indicative of care provision and utilization in the

public sector. The health system landscape in our study area also comprises private and NGO-run health care providers, and clients are known to seek antenatal care from multiple providers. We will report on clients' utilization of antenatal and delivery care from all health care providers, with the data collected during the postpartum household visit.

Acknowledgments

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Authors' Contributions

AR leads research, implementation, and data collection in Bangladesh and has contributed to the study design and outcomes. IKF contributed to the study design and formulation of outcomes and wrote the first draft of the protocol and this manuscript. IKF and AR contributed equally to this study. MV contributed to writing the manuscript and updating the study outcomes. JP and FK contributed to the study design, formulation of outcomes, and provided contextual knowledge. MR, BO, and AD were in charge of software customization, provided technical and implementation support, and ensured that the software matched the trial needs. BKS, UTN, and IF contributed to the design of eRegistry content and guideline-based clinical decision support. BKS, UTN, and AMQR have been instrumental in ascertaining the feasibility of trial aspects and ensuring that the final study design is appropriate for the context. IKF, JFF, and MV undertook registration of the trial. JFF conceptualized the study and contributed to the study design and formulation of outcomes. All authors read and approved this version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Postpartum household visit questionnaire.
[PDF File (Adobe PDF File), 505 KB - resprot_v10i7e26918_app1.pdf]

Multimedia Appendix 2
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 250 KB - resprot_v10i7e26918_app2.pdf]

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Abbreviations

CISMAC: Centre for Intervention Science in Maternal and Child Health
CONSORT: Consolidating Standards of Reporting Trials
DHI: digital health intervention
DHIS2: District Health Information Software 2
eRegistry: electronic registry
icddr, b: International Centre for Diarrhoeal Disease Research, Bangladesh
LMIC: low- and middle-income country
NGO: nongovernmental organization
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
WHO: World Health Organization

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Protocol

A Web-Based Cognitive Bias Modification Intervention (Re-train Your Brain) for Emerging Adults With Co-occurring Social Anxiety and Hazardous Alcohol Use: Protocol for a Multiarm Randomized Controlled Pilot Trial

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Abstract

Background: Alcohol use and anxiety disorders commonly co-occur, resulting in a more severe clinical presentation and poorer response to treatment. Research has shown that approach bias modification (ApBM) and interpretation bias modification (IBM) cognitive retraining interventions can be efficacious adjunctive treatments that improve outcomes for alcohol use and social anxiety, respectively. However, the acceptability, feasibility, and clinical utility of combining ApBM and IBM programs to optimize treatments among comorbid samples are unknown. It is also unclear whether integrating ApBM and IBM *within* each training session or alternating them *between* each session is more acceptable and efficacious.

Objective: This paper describes the protocol for a randomized controlled pilot trial investigating the feasibility, acceptability, and preliminary efficacy of the *Re-train Your Brain* intervention—an adjunct web-based ApBM+IBM program—among a clinical sample of emerging adults with hazardous alcohol use and social anxiety.

Methods: The study involves a three-arm randomized controlled pilot trial in which treatment-seeking emerging adults (18-30 years) with co-occurring hazardous alcohol use and social anxiety will be individually randomized to receive the *Re-train Your Brain integrated* program, delivered with 10 biweekly sessions focusing on *both* social anxiety and alcohol each week, plus treatment as usual (TAU; ie, the model of care provided in accordance with standard practice at their service; n=30); the *Re-train Your Brain alternating* program, delivered with 10 biweekly sessions focusing on social anxiety one week and alcohol the next week, plus TAU (n=30); or TAU only (n=30). Primary outcomes include feasibility (uptake, follow-up rates, treatment adherence, attrition, and adverse events) and acceptability (system usability, client satisfaction, user experience, and training format preference).

Secondary efficacy outcomes include changes in alcohol approach and interpretation biases, social anxiety, and alcohol use (eg, drinks per day, binge drinking, drinking motives, severity of dependence, and cravings). The primary end point will be posttreatment (6 weeks postbaseline), with a secondary end point at 3 months postbaseline. Descriptive statistics will be conducted for primary outcomes, whereas intention-to-treat, multilevel mixed effects analysis for repeated measures will be performed for secondary outcomes.

Results: This study is funded from 2019 to 2023 by Australian Rotary Health. Recruitment is expected to be completed by mid-2022 to late 2022, with follow-ups completed by early 2023.

Conclusions: This study will be the first to evaluate whether an ApBM+IBM program is acceptable to treatment-seeking, emerging adults and whether it can be feasibly delivered via the web, in settings where it will ultimately be used (eg, at home). The findings will broaden our understanding of the types of programs that emerging adults will engage with and whether the program may be an efficacious treatment option for this comorbidity.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12620001273976; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=364131

International Registered Report Identifier (IRRID): PRR1-10.2196/28667

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KEYWORDS

alcohol; anxiety; cognitive bias modification; interpretation bias; approach bias; emerging adults

Introduction

Background

Social anxiety and alcohol use disorders are highly prevalent [1] and frequently co-occur [2,3]. When they are comorbid with one another, the presenting symptoms tend to be more severe and associated with greater functional impairment than either disorder in isolation [4,5]. This is likely because of the existence of a bidirectional, self-perpetuating cycle, whereby ongoing interactions between the disorders serve to maintain or exacerbate symptoms of both conditions [4,6,7]. The co-occurrence of social anxiety and alcohol use disorders can also interfere with treatment and recovery, with evidence from clinical trials showing that standard single-disorder treatments are less effective for people with comorbid anxiety and alcohol use [4,8-11].

Given the frequent co-occurrence of these disorders and the additional complications that this comorbidity confers on the individual (eg, physical and psychological health, relationships, work, and education) and society (eg, social and economic costs) [4,5,12], it is essential to understand and modify factors that contribute to the maintenance of these conditions. One such factor is implicit or automatically activated cognitive biases. Although there are a variety of implicit cognitive biases associated with social anxiety and alcohol use disorders, two of the most common are alcohol *approach biases* (ie, the tendency for alcohol cues to induce an automatic and habitual approach action [13,14]) and *interpretation biases* (ie, the tendency to interpret ambiguous stimuli, scenarios, and events in a negative manner [15-17]). Alcohol approach biases have been shown to contribute to heavy drinking and predict future alcohol use among adults with an alcohol use disorder [14] and have also been associated with relapse to alcohol following treatment [18,19]. Interpretation biases have been linked to the development of anxiety symptoms and disorders, and the maintenance and severity of these conditions [20,21].

Over the past two decades, several computer-based cognitive training paradigms, known as cognitive bias modification (CBM), have been developed to reduce symptoms by modifying a range of maladaptive implicit biases, including alcohol approach and anxiety-related interpretation biases. *Approach bias modification* (ApBM) is one of the most common types of CBM programs trialed as an adjunctive treatment for alcohol use disorders. It seeks to train adaptive alcohol-avoidance tendencies by getting an individual to repeatedly push away images of alcohol shown on a computer screen. *Interpretation bias modification* (IBM) is one of the dominant CBM programs for ameliorating anxiety symptoms, particularly social anxiety. IBM directly targets negative interpretation biases by repeatedly presenting individuals with emotionally ambiguous social scenarios and training them to resolve the uncertainty in a positive or neutral (vs threatening) way [22]. Several large randomized controlled trials (RCTs) among clinical samples show particularly promising findings for ApBM and IBM interventions, especially in instances where they are added as an adjunct to standard evidence-based treatments, such as cognitive behavioral therapy (as described in detail later) [23-28]. It is argued that this is likely because clients in treatment are typically motivated to change their thoughts and behaviors, which may be a prerequisite for successful training effects [29]. By adding CBM on top of conventional treatment approaches, treatment not only is able to target conscious, deliberate, and explicit negative thinking styles and behavioral responses but can also target unhealthy habitual and implicit processes [30-32]. Thus, a combination of these complementary approaches further aids in the effectiveness of treatment on clinical outcomes. In contrast, there has been mixed empirical support for the efficacy of ApBM and IBM programs as stand-alone interventions among nonclinical samples (eg, heavy drinking university students) [29,33,34]. Meta-analyses that synthesize findings on efficacy from a mixture of clinical and nonclinical studies have produced similar inconclusive findings [34,35], perhaps as a result of the substantial heterogeneity in study samples, designs, and methodologies [29,36].

Several large RCTs [23-26] and reviews [29,37,38] have provided evidence in support of the beneficial effects of ApBM when delivered to clinical samples in conjunction with standard treatments. Notably, 3 studies in Germany showed that the provision of 4-12 sessions of ApBM alongside treatment as usual (TAU; eg, inpatient alcohol use treatment or abstinence-oriented cognitive behavioral therapy) to alcohol-dependent adults was associated with significantly lower alcohol consumption and 7%-13% reduced rates of relapse one year later compared with patients who received TAU plus a sham placebo training or TAU only [23,24,26]. One of these studies reported that the change in alcohol approach biases mediated the change in relapse rates and a stronger approach bias at baseline moderated ApBM effects [24], whereas another was unable to replicate these effects [26]. Furthermore, a recent multisite RCT conducted in Australia reported significant improvements in abstinence rates among those given four sessions of ApBM during inpatient detoxification (54%), relative to sham control training (42%) [39]. A significant reduction in approach bias was observed among those in ApBM but not in the sham-training condition after training. Overall, ApBM has shown fairly consistent promising effects in clinical contexts and has since been added to German and (forthcoming) Australian guidelines for treating alcohol-related disorders [40,41].

Clinical studies investigating the efficacy of IBM have shown that training can promote the development of a positive interpretive bias in socially anxious populations and that these modifications are associated with reductions in social anxiety symptoms [27,28]. Although there are fewer clinical RCTs in number relative to ApBM, one study in the United States found that adults diagnosed with generalized social anxiety disorder who received 12 sessions of IBM experienced significantly greater reductions in negative interpretations of ambiguous scenarios, self-reported and clinician-rated social anxiety symptoms, and rates of social anxiety disorder diagnosis (65% vs 13%) from pre- to postassessment, relative to a sham control-training condition. Moreover, the effects on social anxiety were sustained at the 3-month follow-up [27]. Similarly, a pilot study found that the provision of four IBM sessions combined with CBM for attentional biases to an outpatient sample diagnosed with social or generalized anxiety disorder was associated with significant reductions in both types of cognitive bias and state and trait anxiety [28]. Studies investigating the mechanism of change for these effects have reported that negative interpretation biases mediated the relationship between the training group and improvement in social anxiety symptoms [27]. These findings are also supported by a recent review of meta-analyses and a systematic review and meta-analysis of CBM programs for anxiety, which both concluded that single- or multisession IBM training among clinically diagnosed and subclinical samples can significantly reduce threat-related interpretation biases [42] and reduce anxiety levels compared with a sham training or waitlist control condition [43].

A limitation to the clinical utility of ApBM and IBM interventions to date is that they have predominantly been restricted to the confines of a laboratory or clinic [44]. Despite this, internet delivery is a promising option for increasing the scalability and sustainability of these interventions. A handful of published studies evaluating the effectiveness of web-based ApBM and IBM have indicated that there is promise in this mode of delivery; however, additional studies are required to make more definitive conclusions regarding their efficacy. For instance, two studies in Europe provided evidence that web-based IBM training can significantly shift interpretations from negative to positive [45,46], with one study showing clinically significant improvement in social anxiety symptoms (eg, 48% of participants no longer met criteria for social anxiety disorder after eight IBM sessions) [46]. Another study found that four sessions of web-based ApBM among nontreatment-seeking problem drinkers were associated with improved drinking outcomes across three active intervention groups; however, this effect was also evident in the sham control-training group [47]. The authors highlight that despite their null findings, integrating web-based ApBM with more traditional cognitive and motivational interventions may be key to improving results and call for further research that combines these supplementary treatments. It is apparent that there is a need for more studies of web-based CBM programs (particularly ApBM) with clinical populations where there is a motivation to change their thoughts and/or behaviors.

Overall, although the evidence base for the efficacy of laboratory- and web-based ApBM and IBM is accumulating for adults with singular disorders, their efficacy when delivered to people with co-occurring social anxiety and alcohol use problems remains largely unknown. To the authors' knowledge, only one RCT exists that examines the efficacy of an attention bias–focused CBM program among a socially anxious, alcohol-dependent adult sample (N=86) [48]. The findings indicated that there were significant reductions in attentional biases, alcohol use disorder, and social anxiety symptoms in both the intervention and control groups; however, no significant between-group differences were identified for any symptom measures. Given the interconnections between anxiety and alcohol use problems and the likely coexistence of approach and interpretation biases, a promising avenue that has not been explored is the potential of combining existing effective ApBM and IBM cognitive retraining protocols to optimize standard treatments among comorbid anxiety-alcohol samples. Moreover, given the peak onset and disability associated with anxiety and alcohol use disorders occurs between adolescence and early adulthood [49,50], the provision of a comorbidity-focused ApBM+IBM training program at an earlier age (and earlier in the course of their disorder) represents a promising opportunity to intervene before problems become chronic and entrenched in adulthood.

Addressing these gaps in the literature, the research team codeveloped a hybrid, web-based ApBM+IBM for emerging adults with co-occurring hazardous alcohol use and social anxiety (*Re-train Your Brain*), as a supplement to TAU for anxiety and/or alcohol use. As trial repetition, boredom, and disengagement are serious concerns for CBM training [28], it deemed was important to assess attitudes toward this treatment and adapt the program where necessary. In line with this, a study was conducted to evaluate the acceptability of a beta version of

the *Re-train Your Brain* program according to the perspectives of clinicians and emerging adults with hazardous drinking and heightened social anxiety [51]. The results indicated that the ApBM+IBM intervention was an acceptable adjunct to traditional evidence-based treatments with potential clinical utility, a finding that mirrors previous CBM acceptability studies [52,53]. To enhance engagement, clinical utility, and intrinsic motivation to complete the training, clinicians and emerging adults suggested that the program should include a psychoeducational and motivation enhancement-type module before the first training session. In light of the aforementioned issues surrounding boredom and disengagement from CBM programs, it was considered possible that the format in which the ApBM+IBM program is delivered might influence engagement and outcomes. For instance, one delivery option could be to integrate the ApBM and IBM components into each training session (50:50 ratio) to provide variation in tasks *within* each training session and reduce boredom. This may, in turn, result in better retention, engagement, and outcomes because of a shorter time being spent completing each repetitious task. An integrated variation might also be especially beneficial because it gives people practice shifting multiple cognitive processes close in time, which likely better mimics the cognitive flexibility needed in daily life (where a cue may require both healthy alcohol-avoidance reactions and healthy interpretation bias in a short space of time) as compared with more temporally distant application of modified cognitive processes. It is equally possible, however, that doing shorter bursts of the two types of training within each session may water down any potential clinical effects. Another option could be to alternate the ApBM and IBM training *between* sessions, thereby providing full-length sessions of each type of training, although fewer in number to achieve the same treatment dose. Clinicians and emerging adults were asked to rate the format they perceived would be most preferable to end users of the program: (1) an *integrated* program that combines shortened versions of both ApBM and IBM within each training session or (2) an *alternating* program that provides ApBM in one training session and IBM in the next, in an alternating pattern. The results indicated that there was no consistent preference for the program format (8/15, 53% vs 7/15, 47% for integrated and alternating, respectively), and further research is required to better understand the impact of training format on acceptability and efficacy outcomes. Overall, the beta *Re-train Your Brain* ApBM+IBM program was well received, and obtaining feedback from service providers and emerging adults was critical to ensuring that the program was age-appropriate, engaging, and potentially useful for end users. However, to date, no research has been conducted to evaluate the feasibility of delivering this program, whether it is deemed acceptable by people who complete the training, and how efficacious it is in reducing the targeted cognitive biases, hazardous drinking, and social anxiety symptoms.

Aims

This paper describes the study protocol for a randomized controlled pilot trial investigating the feasibility, acceptability, and preliminary efficacy of the *Re-train Your Brain* intervention—a web-based hybrid ApBM+IBM program—as an adjunct to TAU for anxiety and/or alcohol use, compared with TAU only, among emerging adults with co-occurring hazardous alcohol use and social anxiety disorder symptoms. The *Re-train Your Brain* program will be delivered in two formats (integrated or alternating) to ascertain which is preferred by emerging adults and whether one shows more promising signs of efficacy.

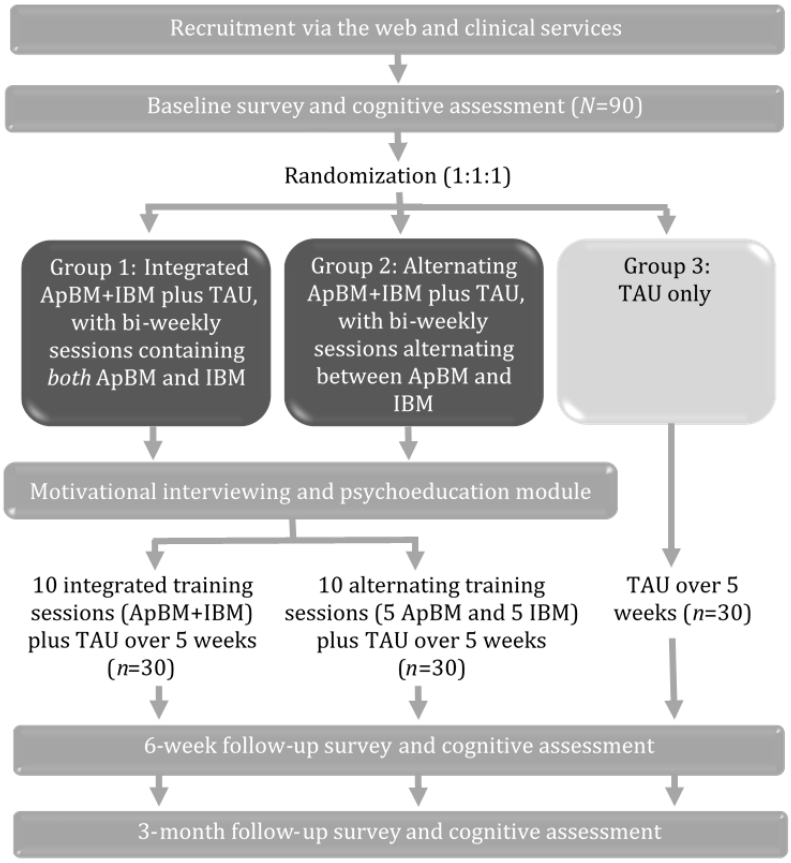
It is hypothesized that the integrated and alternating *Re-train Your Brain* ApBM+IBM programs will both be feasible to implement and deemed acceptable by emerging adults. It is hypothesized that the integrated format will be rated as more acceptable and engaging than the alternating format because of the variation of tasks *within* each session (ie, less time will be spent on each task within each session, which may reduce boredom and disengagement often experienced because of the repetitive nature of each task). Although this is a pilot trial that is not powered to detect clinically significant group-by-time interaction effects, based on previous research, it is likely that both the integrated and alternating *Re-train Your Brain* programs will result in trend improvements in cognitive biases, anxiety, and alcohol-related outcomes, relative to the control condition. It is further hypothesized that greater effect sizes will be observed in the integrated *Re-train Your Brain* intervention group than in the alternating intervention group because of greater levels of engagement with the program. The results will be used to inform the design and power analysis of a future definitive trial.

Methods

Setting and Trial Design

The study will be conducted nationally across Australia and will involve a three-arm randomized controlled pilot trial in which eligible participants will be individually randomized to receive (1) the *integrated Re-train Your Brain* program, delivered with 10 biweekly sessions focusing on *both* social anxiety and alcohol each training (50:50 ratio) plus TAU for anxiety and/or alcohol use (ie, the model of care provided in accordance with standard practice at their service); (2) the *alternating Re-train Your Brain* program, delivered with 10 biweekly sessions focusing on social anxiety in one training and alcohol in the next training in an alternating pattern plus TAU; or (3) TAU only. The treatment *dose* in terms of total intervention time will be the same for the two intervention groups (groups 1 and 2). The primary end point will be the posttreatment assessment, conducted at 6 weeks following baseline, with a secondary end point at 3 months postbaseline. The study design is shown in Figure 1.

Figure 1. Study design for the *Re-train Your Brain* pilot trial. ApBM: Approach Bias Modification; IBM: Interpretation Bias Modification; TAU: treatment as usual.



Ethics Approval and Registration

The *Re-train Your Brain* pilot trial was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12620001273976) and received ethical approval from the University of Sydney Human Research Ethics Committee (#2020/135).

Participants

Participant Recruitment

Young Australians (n=90) aged 18 to 30 years with harmful alcohol use and heightened social anxiety symptoms who are currently receiving psychological treatment will be recruited into the study via an array of advertising methods, including clinician referral, poster, and flyer advertisements (eg, in clinical services and universities), and online advertising via platforms, such as Facebook, Twitter, and Google AdWords.

Inclusion and Exclusion Criteria

To be eligible, participants must (1) be Australians aged 18-30 years; (2) be currently reporting hazardous or harmful alcohol use, that is, a score of ≥8 on the Alcohol Use Disorder Identification Test [54]; (3) be currently experiencing at least mild symptoms of social anxiety, that is, a score of ≥7 on the Social Interaction Anxiety Scale-Short Form or ≥2 on the Social Phobia Scale-Short Form [55]; (4) have access to the internet via a laptop or PC and have a mouse-operable computer; (5) be currently receiving psychological treatment from a health professional for anxiety and/or alcohol use problems, for example, psychologist, psychiatrist, mental health, or alcohol or other drug counselor; and (6) be willing to complete all 10 ApBM+IBM sessions, if allocated to one of the active intervention groups.

Individuals will be excluded because of the following reasons: inability or unwillingness to provide contact information (ie, phone and email); insufficient English literacy; active symptoms of psychosis, that is, a score of ≥3 on the Psychosis Screening Questionnaire [56]; self-reported history of neurological disease or head injury with a loss of consciousness exceeding 30 minutes; self-reported intellectual disability or cognitive impairment; and eyesight not normal or corrected to normal.

Measures

Overview

Table 1 summarizes the schedule of assessments (including measures used for primary and secondary outcomes and potential moderators or covariates) and procedures over the study period.

Table 1. Schedule of assessments and procedures over the study period.

Assessments	Study period								
	Enrollment	Preallocation; t_1 (baseline)	Intervention week					Postallocation	
			1	2	3	4	5	t_2 (6 weeks postbaseline)	t_2 (3 months postbaseline)
Enrollment									
Informed consent	✓[a]								
Eligibility survey	✓								
Baseline survey		✓							
Cognitive assessments		✓						✓	✓
Randomization		✓							
Interventions									
Group 1: Integrated ApBM[b]+IBM[c] plus TAU[d]			✓	✓	✓	✓	✓		
Group 2: Alternating ApBM+IBM plus TAU			✓	✓	✓	✓	✓		
Group 3: TAU (routine anxiety or alcohol treatment)			✓	✓	✓	✓	✓		
Assessments or measures									
Primary outcomes									
Treatment feasibility questions								✓	
Acceptability questions								✓	
System Usability Scale								✓	
Client Satisfaction Questionnaire								✓	
Treatment feedback questions								✓	
Postuser experience questions (intervention groups)			✓	✓	✓	✓	✓		
Secondary outcomes and covariates or moderator variables									
Approach Avoidance Task		✓						✓	✓
Interpretation Recognition Task		✓						✓	✓
Comorbid Interpretation and Expectancy Biases		✓						✓	✓
Social Phobia Scale and Social Interaction Anxiety Scale-Short Forms	✓							✓	✓
Patient Health Questionnaire-4		✓						✓	✓
Alcohol Use Disorder Identification Test	✓							✓	✓
Timeline Follow Back		✓						✓	✓
Alcohol Craving Questionnaire–Short Form–Revised		✓						✓	✓
Severity of Alcohol Dependence Questionnaire		✓						✓	✓
Drinking Motives Questionnaire-Revised		✓						✓	✓
Weekly Social Anxiety and Alcohol Symptom questions			✓	✓	✓	✓	✓		

Assessments	Study period								
	Enrollment	Preallocation; t_1 (baseline)	Intervention week					Postallocation	
			1	2	3	4	5	t_2 (6 weeks postbaseline)	t_2 (3 months postbaseline)
Readiness to Change Ruler		✓						✓	✓
University of Rhode Island Change Assessment		✓							
Psychological and pharmacological treatment		✓						✓	✓

[a]Denotes which assessments and/or measures were conducted at each time point.

[b]ApBM: approach bias modification.

[c]IBM: interpretation bias modification.

[d]TAU: treatment as usual.

Primary Outcome Measures

Feasibility

The feasibility of the program will be assessed according to the percentage of successfully recruited participants who agree to participate (ie, uptake), commence training, and decline participation. At postintervention, feasibility will be measured by the number of sessions completed; reporting of adverse events via spontaneous reports in open-feedback questions or to the study team or deterioration of social anxiety or alcohol use symptoms (see Multimedia Appendix 1 [54,55,57-66] for full details) [57,58]; and the proportion of participants who (1) complete the 10-session protocol (as a proportion of those who commence at least one session of training, ie, treatment adherence or compliance), (2) complete the mean optimum number of six sessions, based on ApBM research [67], and (3) drop out before training is completed. Survey or cognitive assessment follow-up rates will also be recorded as a measure of the feasibility of the RCT methodology at the 6-week and 3-month time points.

Acceptability

Measures of acceptability and usability of the program will be assessed at postintervention (6-week postbaseline). *The usability of the program* will be assessed using the 10-item System Usability Scale [68]. Items are rated on a 5-point Likert scale ranging from 1 (*strongly disagree*) to 5 (*strongly agree*). The scores for each item are converted to a new number, ranging from 0 to 4. A total score is then computed by summing the converted item scores and multiplying this by 2.5, giving a range of 0 to 100. Higher values denote greater usability and higher satisfaction with the program. Cut-off scores using a *school grade analogue* have recently been suggested for interpreting the scores (F=0-51.7; D=51.8-62.6; C=62.7-72.5; B=72.6-78.8; and A=78.9-100), with a score over 68 being considered above average [69]. *Satisfaction* with the program will be measured by Client Satisfaction Questionnaire-8 [70]. Items are rated on a 4-point Likert scale from 1 to 4, with total scores ranging from 8 to 32. Higher scores indicate greater client satisfaction. Acceptability will also be assessed by 13 acceptability items (eg, how user-friendly, simple to use, logical, and engaging the tasks were), rated using a 5-point Likert scale from 0 (*not at all*) to 4 (*very*). The survey will also contain several open-ended questions about the most or least helpful and enjoyable features of the program. To determine *which intervention delivery model is preferred*, participants in the active intervention groups will complete four user experience questions after completing each of the *Re-train Your Brain* sessions. The four items will assess their motivation while training, how much they enjoyed the training, how much they liked the delivery format, and whether they found the training simple and user-friendly, using a 5-point Likert scale (from 0 *not at all* to 4 *extremely*).

Secondary Outcome Measures

Overview

The following measures will be assessed at baseline, postintervention, and 3 months postbaseline (a more detailed description and interpretation of scores are given in Multimedia Appendix 1).

Cognitive Biases

Alcohol approach biases will be assessed using the Alcohol Approach Task [13]. Participants are instructed to pull or push a computer mouse (in place of a joystick, which is typically used in laboratory-based studies) in response to an irrelevant feature of images (ie, the orientation as portrait or landscape) shown on a computer screen while ignoring the content of the pictures. Two categories of pictures are used: 20 alcoholic beverages and 20 color- and shape-matched nonalcoholic beverages. Each picture appears one by one in both landscape and portrait formats in a quasi-random order (maximum 3 consecutive pictures of the same category or format). Contingent upon a pull or push movement, the picture zooms in (becomes larger on the screen to generate the subjective experience of an approach behavior) or zooms out (becomes smaller on the screen to give a sense of avoidance behavior). A correct response is followed by feedback, as indicated by a green ✓on the screen, whereas an incorrect response is followed with error feedback, as indicated by a red X. The task begins with 5 practice trials showing empty rectangular frames in a landscape or portrait format. Format movement assignments are counterbalanced (half of the participants pull pictures that came in landscape format and push portrait pictures, and half of the participants received the opposite instruction). The images have been

selected to represent the beverage type and brands most commonly consumed by this population, as documented in a recent acceptability study [51]. Each image is repeated twice, for a total of 80 trials.

Social anxiety interpretation biases will be measured using the Interpretation Recognition Task [22,71]. The Interpretation Recognition Task contains two parts: an encoding phase and a recognition test phase. During the encoding phase, participants are asked to read a set of 10 ambiguous social scenarios presented on a computer screen. Each scenario consists of a title and three short sentences that are ambiguous in terms of valence. In the final sentence, a word fragment is presented. After reading a scenario, participants are asked to complete the word fragment as quickly as possible by pressing the spacebar when they know what the word is. They then press the key corresponding to the first missing letter. Next, the participant is asked to answer yes or no to a question that measures comprehension of the story, also followed by feedback (ie, *correct* or *wrong*). An example of the encoding phase is provided as follows:

(Title): *The evening class.*

(Scenario): You've just started going to an evening class. The instructor asks a question and no one in the group volunteers an answer, so he looks directly at you. You answer the question, aware of how your voice must sound to the...

(Word fragment): oth-rs

(Correct word): others

(Comprehension question): Have you been going to the evening class for a long time?

(Response): No

(Feedback): ✓ Correct answer

In the recognition test phase, participants are presented with the identifying titles of each ambiguous scenario, together with four interpretations of each of the scenarios, presented one at a time. Participants are asked to rate each summary statement independently for their similarity in meaning to the original scenario on a 4-point Likert scale from 1 (*very different in meaning*) to 4 (*very similar in meaning*). The four summary statements always contain one valid, positively valanced interpretation (positive target); one valid, negatively valanced interpretation (negative target); one positively valanced statement that was not a possible interpretation of the original scenario in that it did not correspond to the previously presented ambiguity (positive foil); and one negatively valanced statement that was not a possible interpretation of the original scenario (negative foil). Foils are included to assess any wider priming effects, indicating a potential response bias for endorsing any information of a certain emotional valence. Examples of the summary statements that would be provided for the aforementioned scenario are shown as follows:

1. Positive target: You answer the question, aware of others listening attentively.
2. Negative target: You answer the question, aware of how unsteady your voice sounds.
3. Positive foil: You answer the question and then realize what a good answer it is.
4. Negative foil: You answer the question but realize that you have made a mistake.

Interpretation and expectancy biases for co-occurring social anxiety and alcohol use will be assessed by the self-report Comorbid Social Anxiety and Alcohol Interpretation Bias task [59]. Participants are presented with a set of eight ambiguous social scenarios, followed by three possible explanations for the situation. Participants will rate the degree to which each of the explanations would likely be true if they were in that situation (0 *not at all likely* to 8 *extremely*).

Alcohol Use

Alcohol consumption (average drinks per day) and frequency of binge drinking days (>5 standard drinks per drinking day) in the past month will be assessed through a computerized version of the Timeline Followback Procedure [60-62]. *Hazardous alcohol use* will be assessed using the 10-item Alcohol Use Disorder Identification Test [54]. *Severity of alcohol dependence* will be assessed using the 20-item Severity of Alcohol Dependence Questionnaire [63]. *Alcohol cravings* will be assessed using the 12-item Severity of Alcohol Craving Questionnaire–Short Form–Revised. *Motives for alcohol use* in the past month will be assessed through the 28-item Drinking Motives Questionnaire-Revised [64]. To assess *alcohol use* throughout the intervention period, all groups will be asked to complete the Timeline Followback twice per week [60-62].

Anxiety

Symptoms of social anxiety will be assessed using the short forms of the Social Interaction Anxiety Scale and the Social Phobia Scale [55]. *Symptoms of depression and anxiety* will be assessed using the 4-item Patient Health Questionnaire-4 [65]. To assess changes in *social anxiety symptoms* throughout the intervention period, all groups will be asked to complete the Social Phobia Weekly Summary Scale [66] biweekly.

Covariates and Additional Variables

Sociodemographic characteristics will include age, sex, gender, education, employment, country of birth, and primary mental health or substance use concerns. Participants will also be asked about any *psychological and pharmacological treatment* received in the past 3 months (full details given in Multimedia Appendix 1). *Readiness and motivation to change* will be assessed via a readiness ruler (eg, on a scale of 1-10, how ready are you to change your anxiety or drinking) and the University of Rhode Island Change Assessment [72]. The *frequency of other drug use* (cannabis, nonprescribed benzodiazepines, and psychostimulants) will be assessed by the National Institute on Drug Abuse quick screen [73], and *sleep disturbance* over the past month will be assessed using the Pittsburgh Sleep Quality Index [74].

Intervention and Control Groups

Re-train Your Brain ApBM+IBM Intervention Groups

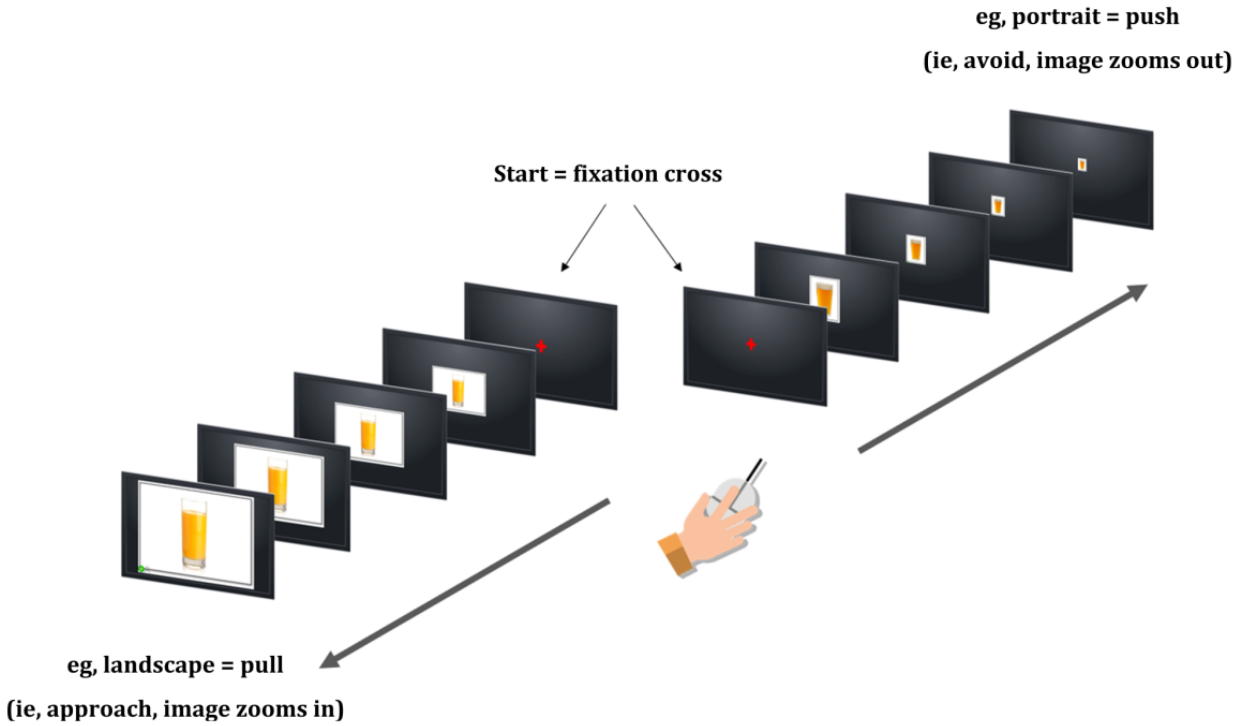
Overview

Both the integrated and alternating Re-*t*rain Your Brain interventions contain ApBM and IBM components, delivered in addition to TAU. Participants in both groups will be asked to complete 10 training sessions over a 5-week period. Two sessions will be available to complete each week, and participants will be given 1-week flexibility to complete all the 10 training sessions. Each training session will be of approximately 20 minutes. In addition, as per previous trials [52], before the commencement of the first training session, participants in both intervention groups will receive an online psychoeducational and motivational interviewing–based module, which was adapted from a previous efficacious online program for anxiety and alcohol use [75]. The module provides psychoeducation about anxiety and alcohol use, the interrelationship between these problems, the existence of automatically activated cognitive biases, and the importance of changing these biases. It also explores participants' reasons for change, and aims to increase intrinsic motivation for (and decrease ambivalence about) change, promotes autonomy and *change talk*, helps participants set goals for what they hope to achieve by completing the training, enhances motivation to train, and harnesses the individual's capacity for change. The ApBM and IBM components of the integrated and alternating training programs are described later.

Alcohol ApBM Component

ApBM is a modified training version of the assessment Alcohol Approach Task, in which participants pull or push a computer mouse in response to the orientation of images (containing alcoholic or nonalcoholic beverages), which zooms the image in or out (Figure 2). For ApBM (unlike the Alcohol Approach Task), 95% of the orientations used to implicitly train avoidance behaviors will contain images of alcoholic beverages, whereas the remaining 5% of frames will contain images of nonalcoholic beverages (and vice versa for orientations used to train approach behaviors). The required push-pull movements are counterbalanced so that half of the participants pull pictures that come in landscape format and push pictures in portrait format, whereas the other half receive the opposite instruction. Participants receive feedback in the form of a green tick or red cross presented on-screen, with a corresponding smiley or sad face emoji. The presentation is repeated if the response is incorrect. To increase motivation, points are awarded for each correct push-pull movement (+1). To familiarize participants with the task requirements, a brief practice round involving five empty rectangular frames in landscape or portrait format will be provided. The alcoholic and nonalcoholic images used in this study were selected to represent the beverage types and brands most commonly consumed by this population, as documented in a recent acceptability study [51].

Figure 2. Example of Approach Bias Modification scenario to illustrate the training procedures.

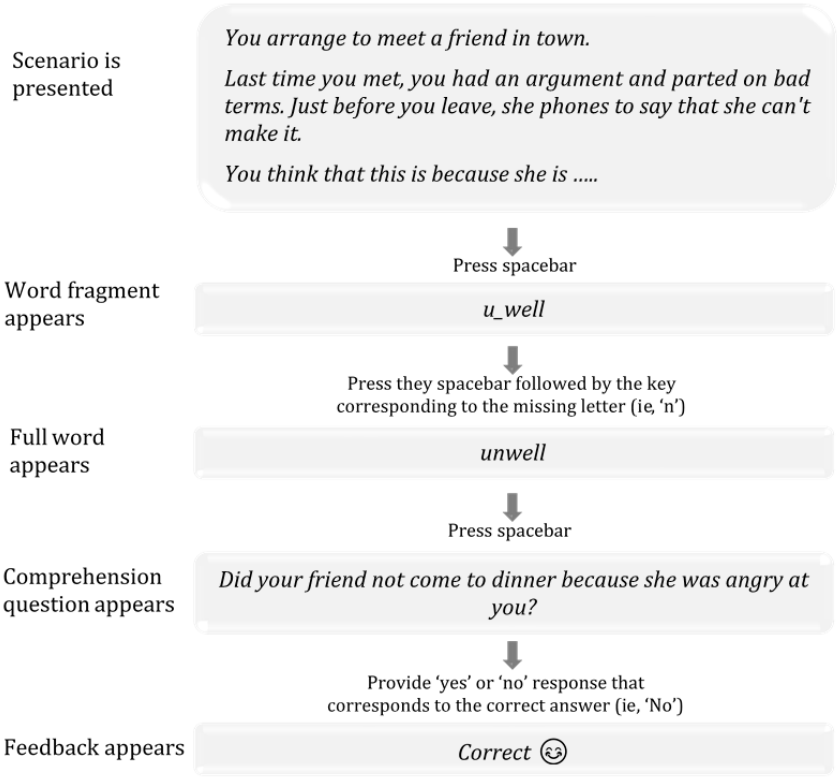


Anxiety IBM Program Component

In IBM training, participants are trained to resolve ambiguous social scenarios with either positive or benign outcomes through the completion of a word fragment (Figure 3) [22]. Each scenario consists of three lines that are ambiguous in terms of valence or emotional interpretation. The participants are instructed to imagine or visualize themselves in each situation described. One word of the story is presented as a word fragment, which disambiguates the story in a positive or benign way. Participants are asked to complete the fragment as quickly as possible by pressing the spacebar when they know what the

word is and then to press the key corresponding to the missing letter. The reaction times are recorded. The program continues only when a correct response is provided. After this, a comprehension question appears that reinforces the assigned meaning when the word fragment is completed. Participants answer the question with a *Yes* or *No* response. They subsequently receive feedback (a *correct* or *wrong* answer, with a corresponding smiley or sad face emoji) to reinforce the interpretation imposed by the word fragment. Points are awarded for each correct letter (+1) and correct answer to the comprehension question (+1). The social scenarios are translated versions of those used in previous research [22,45,76], adapted for this study's target age range of 18-30 years and the Australian context [51]. Three practice trials are given at the outset of the IBM training component.

Figure 3. Example of Interpretation Bias Modification scenario to illustrate the training.



Delivery Formats of the Re-train Your Brain ApBM+IBM Intervention

Group 1: Integrated ApBM+IBM Intervention, With Biweekly Sessions Combining IBM and ApBM

Group 1 will receive 10 biweekly training sessions containing shortened versions of *both* IBM and ApBM within each session (50:50 ratio) plus TAU. For the ApBM component, participants will be presented with frames containing 10 images of alcoholic beverages and 10 images of nonalcoholic beverages, in a random order. Each alcoholic and nonalcoholic beverage is presented three times, for a total of 60 image presentations. For the IBM component, participants will be presented with three blocks of 10 social scenarios (ie, 30 scenarios per session; 300 across the 10 sessions). Each block will contain eight positive modification (*induction*) scenarios and two probe or irrelevant scenarios that have either a positive or benign outcome, to make the induction less obvious. Blocks are in a fixed order, but the order of the scenarios within blocks is random for each participant.

Group 2: Alternating ApBM+IBM Intervention, With Biweekly Sessions Alternating Between IBM and ApBM

Participants in group 2 will receive the same treatment dose as group 1; however, on alternating weeks, participants will receive either ApBM *or* IBM (ie, each session will switch between retraining alcohol or anxiety biases in an alternating pattern; five ApBM and five IBM sessions) plus TAU. For each of the five ApBM training sessions, participants will be presented with 120 (rather than 60) alcoholic and nonalcoholic beverage images (20 alcoholic and 20 nonalcoholic, shown three times in random order), and each of the five IBM sessions will provide 60 scenarios (rather than 30).

Control Group (Group 3: TAU Only)

The control group will receive TAU, which will be the model of care provided in accordance with standard practices at their service. The focus of the psychological treatment will not be limited to the provision of treatment for anxiety and/or alcohol use (ie, clients may be receiving treatment for other conditions in addition to anxiety and/or alcohol use). No restrictions will be placed on the type of psychological treatment or how long the client has been receiving the treatment. Details regarding the type, length, and focus of treatment will be ascertained during the baseline and follow-up surveys and reported upon in the trial outcomes (more information given in Multimedia Appendix 1). The decision to have few restrictions tied to the treatment offered as part of TAU follows a desire to test the CBM program in the context of real-world care and to evaluate

the adjunctive intervention with a deployment focus. This group will be offered the opportunity to receive the *Re-train Your Brain* program (in whichever format is deemed preferable by participants) after all follow-up surveys and measurements are taken at the 3-month assessment point.

Procedure

Study Procedure

All participants will be directed to the *Re-train Your Brain* website, which contains detailed information about the study and provides a direct link to the online participant information statement and consent form. After providing consent, prospective participants will complete a brief, 10-minute online screening survey to determine eligibility. Eligible participants will gain access to an online baseline survey, which will take approximately 30 minutes to complete. Participants will be asked to provide their name, email, and postal address so that the research team may post them a computer mouse to complete a cognitive assessment (*note*: as these assessments are reaction time based, this will ensure consistency in mouse settings between participants, such as pointer speed, etc) and send them a link to the alcohol approach and interpretation bias cognitive assessment. Immediately following the cognitive assessment, participants will be individually randomized by the study website to receive the following: (1) the *integrated Re-train Your Brain* intervention plus TAU (n=30), (2) the *alternating Re-train Your Brain* intervention TAU (n=30), or (3) TAU only (n=30). Participants in the *Re-train Your Brain* intervention groups will be asked to complete a 30-minute motivational interviewing or psychoeducation-based module, followed by 10 cognitive training sessions, delivered online twice per week for 5 weeks (approximately 2-4 days apart). Participants will be reminded of these training sessions via multiple reminder calls, emails, and SMS text messages. As difficulty and boredom are intrinsically part of these kinds of implicit interventions, participants will also receive 3-4 brief motivational enhancement texts or emails over the 5-week program to normalize any difficulties encountered in the training execution and reaffirm their commitment to change. In addition, to maximize engagement with the research trial, participants in all groups will be asked to complete two weekly 5-minute assessments of their anxiety and alcohol use symptoms, for which they will receive a Aus $5 (US $3.80) e-gift voucher per occasion (10 total), with an accumulated voucher (max Aus $50; US $37.70) paid at the end of the treatment period.

All participants will be emailed a link to complete an online survey and a (separate) cognitive assessment at postintervention (ie, 6 weeks postbaseline, to provide 1 week of flexibility in the rate of training completion) and 3 months postbaseline. The survey and cognitive assessments are expected to take approximately 45-60 minutes (combined) to complete at each time point. Consistent with previous online trials [77,78], participants who complete both the online survey and cognitive assessment will receive an Aus $30 (US $22.60) e-gift voucher at each time point as reimbursement for their time participating in the research. To minimize data attrition, the following evidence-based strategies will be used [79,80]: (1) monetary incentives for each assessment completed, (2) collection of multiple sources of contact information (eg, email, mobile number, and postal address), (3) user-friendly electronic survey design that can be completed via multiple devices (eg, via mobile phone), (4) personalized reminder messages (SMS text messaging and email) to complete surveys or cognitive assessments, and (5) a follow-up letter and telephone call to those participants who do not respond. The intervention and cognitive assessments will be accessed via the study website and run using JavaScript, whereas all online surveys will be delivered via Qualtrics. The trial will be conducted in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 Statement and CONSORT (Consolidated Standards of Reporting Trials) guidelines.

Randomization

To avoid bias, participants will be individually randomized to the *Re-train Your Brain* integrated group, the *Re-train Your Brain* alternating group, or the control group (on a 1:1:1: basis) via the trial website using a computer-generated randomization sequence, which is concealed from the investigators. This process removes the potential for researcher involvement. Randomization will occur directly after the completion of the online baseline cognitive assessment (Figure 1).

Statistical Analysis and Power Calculations

As this is a pilot trial, a formal power calculation is not required [81,82]. The pilot trial is essential to determine the expected size of effect, which will be used to inform the sample size of a future definitive RCT aiming to assess the efficacy of the *Re-train Your Brain* program. Rates of attrition will be used to indicate estimated follow-up rates in future trials. On the basis of several rules of thumb used to determine an appropriate sample size for a pilot study [83-85], a sample size of 90 young people (30 per arm) was selected to provide sufficient data on the feasibility, acceptability, and preliminary efficacy of the program, although we recognize that the scope of this pilot trial does not allow for a fully powered test of efficacy. Data will be collated and analyzed using StataCorp data analysis software [86].

Descriptive statistics for primary and secondary outcomes will be conducted based on frequencies and cross-tabulations. Analyses for secondary (preliminary) efficacy outcomes will use multilevel mixed effects analysis for repeated measures, which is a flexible analytic approach for modeling change over time using RCT data [87,88]. All models will use baseline measurements as the reference point to estimate participant-specific starting points and change over time. The intervention condition will be represented by a dummy-coded variable, and the condition by time interaction will be examined to assess between-group differences in outcomes over time. Analyses will be consistent with an intention-to-treat framework, with all randomized participants included in the analysis models, regardless of training completion or loss to follow-up. Missing data will be accommodated in these models using maximum likelihood estimation. Preliminary models will be estimated, with model fit statistics examined to determine the most appropriate model and covariance structure. Cohen *d* will be calculated from model-estimated marginal means and SEs to

determine the size of the effect between conditions at the relevant end point. In addition, effect sizes will be analyzed as a function of session completion (ie, completion of six or more training sessions, given that this has been identified as the mean optimum number of ApBM sessions in past research [67]).

Results

Recruitment is expected to be completed by mid-2022 to late 2022, with the 6-week and 3-month follow-ups to be completed by early 2023. The results are expected to be submitted for publication in 2023. The research team intends to present the findings of this trial at professional seminars and national and international conferences. Only aggregated group data will be reported, and no individuals will be identified.

Discussion

Principal Findings

This paper presents the design of the *Re-train Your Brain* study, a randomized controlled pilot trial seeking to evaluate the feasibility, acceptability, and preliminary efficacy of a 10-session, web-based ApBM+IBM brain training program for hazardous alcohol use and social anxiety among young Australians aged 18-30 years, when combined with TAU. To the best of our knowledge, this is the first study to evaluate a comorbidity-targeted intervention of this kind, using a cost-effective, web-based delivery method.

Strengths and Limitations

This study has several strengths. First, the intervention was co-designed with emerging adults who have direct lived experience of hazardous drinking and social anxiety and clinicians who have experience treating anxiety and/or alcohol use concerns. This bottom-up approach, whereby emerging adults and clinicians were involved in the development of the methodology and stimuli used within the intervention (eg, the alcoholic or nonalcoholic beverages used in ApBM and the scenarios included in IBM), was critical to ensuring that the program is relevant, engaging, and useful for end users. This codevelopment process also helps to ensure that the program can be feasibly implemented and is responsive to the needs of service providers.

An additional strength of this study is the web-based delivery of the interventions. The *Re-train Your Brain* intervention is simple, inexpensive, and can be self-administered via the internet without any specific skills or knowledge. This format allows for easy and convenient access anywhere and at any time (eg, in the privacy of one's home), thereby offering a larger outreach and greater availability. It is also being investigated in the setting in which it is most likely to be implemented, if proven effective in a future RCT. On theoretical and practical grounds, incorporation of a web-based psychoeducational or motivational enhancement-type module at the outset of training will aid its efficacy and will also likely boost engagement and user buy-in. It may also increase treatment adherence and reduce study attrition. Thus, the web-based delivery of this program has the potential to enhance clinical outcomes at a minimum cost in terms of time and effort for both patients and service providers.

Finally, despite their high co-occurrence, to date, most CBM programs have addressed anxiety and alcohol use in isolation of one another, with a few exceptions for attention bas modification [48]. The current intervention is unique in that it combines effective alcohol ApBM and anxiety IBM-focused protocols to optimize standard treatments among a young comorbid sample. Given the interconnections between anxiety and alcohol use problems, whereby each disorder fuels the other and impedes recovery from the other, it is possible that combining these programs will have incremental (or synergistic) effects on anxiety and alcohol use outcomes in a vulnerable group that responds poorly to standard treatments [10,89].

One of the main strengths of this study is also its main limitation: that is, its web-based delivery. First, internet interventions are conducted in a less-controlled home environment that may pose several online distractions (eg, email notifications) and offline distractions (eg, housemates or phone calls), which have the potential to impact the study results. Second, web-based interventions also have higher rates of attrition compared with standard face-to-face treatments (eg, 34.2% vs 24.6%, respectively) [90]. Further increasing the risk of attrition, CBM interventions are inherently repetitive and as such are sometimes considered boring because of the monotonous nature of the tasks [28,91]. To help overcome these limitations, at the start of each session, participants are reminded of the importance of conducting training in a quiet environment where they can concentrate for a 20-minute block. To leverage on participants' intrinsic motivation for change and maximize their initial buy-in, a compelling rationale and motivational enhancement module is provided at the outset of the program. These components will set expectations about the purpose and nature of the intervention (eg, computerized and repetitive training), which will likely enhance motivation to train and, thus, result in increased adherence and lower attrition. In addition, multiple evidence-based strategies to minimize treatment and study attrition will be used, such as monetary incentives, email and SMS text messaging reminders, and explanation of the importance of completing the sessions and follow-up surveys to participants [79,80]. Taken together, the possible threats presented by the web-based delivery of the intervention are outweighed by the possibilities and benefits it may offer.

Furthermore, this study uses a control group that receives TAU and zero training, rather than a control group that is matched for both stimulus exposure (ie, time spent completing the ApBM and IBM tasks) and response requirements. Sham control-training groups are considered the optimal comparator groups for these reasons and because participants remain blind to their group allocation [92]. However, some research has shown that there is no significant difference between experimental and sham control groups (as both groups improve [33,92]), suggesting that sham training may in fact have an active component rather than it being a *neutral* or *placebo* training it is intended to be. This is particularly the case for online trials and less so for laboratory-based trials [47]. This way, it is conceivable that both online-delivered sham and

experimental conditions represent placebo effects; however, this cannot be ruled out in a two-arm design (active vs control training). Given that this study is a pilot trial with primary outcomes focused on feasibility and acceptability (as opposed to efficacy) and secondary outcomes on preliminary efficacy, an active control group could mask any possible intervention effects, and thus, a no-training group was selected as the comparator. Indeed, in this study, priority was given to testing two experimental varieties on top of TAU, as compared with TAU. Future RCTs aiming to evaluate the clinical efficacy of this hybrid intervention may consider a different three-arm design, comparing the ApBM+IBM intervention against both an (active) sham-training control and a zero training control condition (ie, TAU), and examine potential mediation effects across the three conditions.

Conclusions and Implications

This world's first hybrid ApBM+IBM training program combines the best elements of efficacious ApBM training programs for alcohol use problems and IBM for social anxiety into a hybrid program for emerging adults who experience both of these problems. This innovative program can be delivered over the internet and can thereby maximize efficiency and scarce resources and sustainably increase the intervention options for vulnerable populations at a low cost. Given the costs of conducting an RCT, it is important to establish whether the *Re-train Your Brain* ApBM+IBM program is acceptable to emerging adults and whether it is feasible to deliver via the internet, in settings where it will ultimately be used and easily scaled to, including at home. The pilot trial findings will contribute to understanding the types of programs that emerging adults will engage with and whether there are signs of it being an efficacious treatment option for this comorbidity.

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Authors' Contributions

KP, ES, RWW, and LAS designed the study and obtained the funding support. KP and MP prepared the first draft of the manuscript. ES and VM shared study documents and materials related to ApBM and IBM. All authors assisted with the methodological aspects of the trial and reviewed and contributed to the final manuscript.

Conflicts of Interest

The authors are the developers of the *Re-train Your Brain* web-based program.

Multimedia Appendix 1
A detailed description and interpretation of scores for primary and secondary outcome measures.
[DOCX File , 20 KB - resprot_v10i7e28667_app1.docx]

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Abbreviations

ApBM: approach bias modification
CBM: cognitive bias modification
CONSORT: Consolidated Standards of Reporting Trials
IBM: interpretation bias modification

RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TAU: treatment as usual

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Protocol

Building on Lessons Learned in a Mobile Intervention to Reduce Pain and Improve Health (MORPH): Protocol for the MORPH-II Trial

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Abstract

Background: Engaging in sufficient levels of physical activity, guarding against sustained sitting, and maintaining a healthy body weight represent important lifestyle strategies for managing older adults' chronic pain. Our first Mobile Health Intervention to Reduce Pain and Improve Health (MORPH) randomized pilot study demonstrated that a partially remote group-mediated diet and daylong activity intervention (ie, a focus on moving often throughout the day) can lead to improved physical function, weight loss, less pain intensity, and fewer minutes of sedentary time. We also identified unique delivery challenges that limited the program's scalability and potential efficacy.

Objective: The purpose of the MORPH-II randomized pilot study is to refine the MORPH intervention package based on feedback from MORPH and evaluate the feasibility, acceptability, and preliminary efficacy of this revised package prior to conducting a larger clinical trial.

Methods: The MORPH-II study is an iteration on MORPH designed to pilot a refined framework, enhance scalability through fully remote delivery, and increase uptake of the daylong movement protocol through revised education content and additional personalized remote coaching. Older, obese, and low-active adults with chronic multisite pain (n=30) will be randomly assigned to receive a 12-week remote group-mediated physical activity and dietary weight loss intervention followed by a 12-week maintenance period or a control condition. Those in the intervention condition will partake in weekly social cognitive theory–based group meetings via teleconference software plus one-on-one support calls on a tapered schedule. They will also engage with a tablet application paired with a wearable activity monitor and smart scale designed to provide ongoing social and behavioral support throughout the week. Those in the control group will receive only the self-monitoring tools.

Results: Recruitment is ongoing as of January 2021.

Conclusions: Findings from MORPH-II will help guide other researchers working to intervene on sedentary behavior through frequent movement in older adults with chronic pain.

Trial Registration: ClinicalTrials.gov NCT04655001; https://clinicaltrials.gov/ct2/show/NCT04655001

International Registered Report Identifier (IRRID): PRR1-10.2196/29013

(JMIR Res Protoc 2021;10(7):e29013) doi:10.2196/29013

KEYWORDS

aging; physical activity; sedentary behavior; weight loss; chronic pain; mHealth

Introduction

Physical activity is a key behavioral medicine for supporting quality of life [1] and managing chronic pain [2]. A healthy activity profile for all individuals, including those with chronic pain, involves achieving a sufficient volume of physical activity, which can reduce pain sensitivity and pain intensity [3], while minimizing the presence of prolonged bouts of sitting, which can exaggerate pain symptoms [4,5]. Promoting these behaviors is especially challenging among older adults with chronic pain whose pain symptoms act as a potent daily barrier to movement [6,7]. In fact, Chastin and colleagues [8] reported that pain was the most potent driver of sedentary behavior in a sample of community-dwelling older adults. Often exercise and sedentary behaviors are treated independently: Participation in a single daily bout of sustained and intense exercise leaves much of the day for prolonged sitting [9] and may even lead to compensatory increases in sitting [10]. This is particularly problematic from the perspective of weight management in older adults with chronic pain. Obesity is powerfully associated with pain [11], and physical activity is considered a central component to weight management [12]. However, the tendency for older adults to engage in compensatory sitting following structured exercise can result in a counterproductive reduction in daily energy expenditure in the short term, which may in turn contribute to long-term weight gain [13-16].

Modifying both exercise and sedentary behavior requires unique behavior change strategies. Motivating exercise involves supporting the individual to engage and sustain a single challenging behavior each day in the face of barriers (eg, changing life events, fatigue, injury) [17,18]. Breaking up prolonged sitting requires an individual to develop an awareness of a habitual behavior (ie, one that occurs normally with little thought) [19] and maintain the motivation needed to self-regulate this behavior consistently across the day [20,21]. It is notable that many have difficulty recognizing how much they sit—as indicated by our tendency to dramatically underreport daily sitting time [22,23]—and so objective self-monitoring tools are especially important for altering sedentary behaviors [24].

A novel approach to addressing physical activity and sedentary time in tandem is to focus on the accumulation of physical activity with an emphasis on distributing this activity throughout the day, thereby indirectly breaking up sustained sitting bouts [20]. A distributed movement goal aligns with the second edition of the United States Federal Physical Activity Guidelines [1], which emphasize a “move more, more often” approach to physical activity and remove the need to separately target structured exercise and sitting behaviors. We illustrated this approach in the Mobile Intervention to Reduce Pain and Improve Health (MORPH) pilot trial wherein older adults with chronic pain attempted to lose weight and improve function through caloric restriction and increased physical activity via the accumulation of activity throughout the day [20]. Compared with a control condition, 12 weeks of MORPH resulted in weight loss, improved function, and reduced sedentary time and pain intensity [25]. We also identified key limitations in the technological tools and coaching model used in MORPH (detailed in the Design Consideration section). Thus, the purpose of MORPH-II is to refine the MORPH intervention toolset and coaching model based on feedback from the first implementation of MORPH prior to testing the package in a large and costly clinical trial [26]. The primary aim of this study is to determine the feasibility and acceptability of this refined MORPH intervention delivered entirely remotely. We will also explore the effect of MORPH-II for increasing time spent active while reducing sedentary time relative to a no-contact control.

Methods

Study Overview

A description of the full 24-week study period is detailed below. Protocols were reviewed and approved by a university institutional review board in January 2021. All eligible and interested individuals will complete an approved informed consent prior to participation.

Participants

MORPH-II is a randomized controlled pilot study in which participants (minimum n=30, allowing for at least 3 waves with refinements between) will enter the study in waves of 8 to 12 individuals (4 to 6 per condition). Eligible participants must use a study-provided iPad (Apple Corp) tablet, own a smartphone to facilitate preintervention in-home testing, have pain on most days during the previous 3 months, have no contraindication for participation in exercise, and be aged 55 to 85 years, obese (BMI: 30 to 45 kg/m^2 based on self-reported height and weight and corrected via the Shields equation) [27], weight-stable (ie, no weight loss or gain of more than 5% of body weight in the past 6 months), and low-active (ie, engaging in less than 2 days per week of structured physical activity for at least 20 minutes). Exclusion criteria will be inability to walk without assistive devices for short distances or cognitive impairment as indicated by a modified telephone interview for cognitive status [28] score below 31. Individuals will be recruited to participate in a 2-group randomized controlled trial wherein they will be assigned to either the 24-week mobile health (mHealth) and telecoaching intervention (12 weeks of active intervention, 12 weeks of follow-up) or a control group. The primary outcomes for this pilot study include feasibility and acceptability, and secondary outcomes include daily steps and sedentary time as assessed by the ActivPAL 4 (PAL Technologies Ltd).

Recruitment, Screening, and Randomization

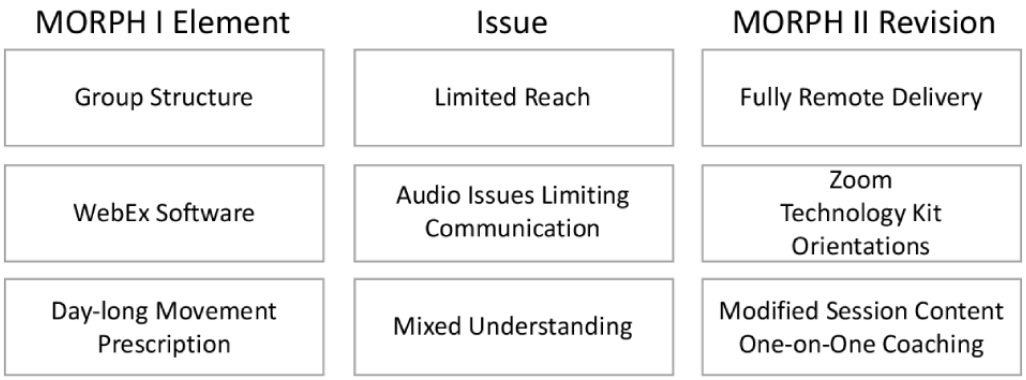
We will recruit participants using several methods. We will leverage targeted mass mailings via postcards to individuals across North Carolina fitting demographic characteristics of our target population. We will place phone calls or send emails to individuals identified in regional research databases comprising individuals who inquired about other research studies and opted to be contacted for future research opportunities. We will advertise the study using digital and print newspapers within the state of North Carolina and regional newsletters that advertise research opportunities and medical news for those who opt in. All individuals who respond to our recruitment strategies will be screened via telephone for eligibility. Those who pass phone screening will be scheduled for a phone visit

and mailed a packet containing an informed consent document and questionnaire forms, and the informed consent will be completed via telephone in accordance with our review board policy before any data collection occurs. The completed baseline questionnaires will be returned in postage-paid envelopes. After completing paper questionnaires and the phone-based cognitive assessment [28], participants will complete a remote Short Physical Performance Battery (SPPB) [29]. Eligible participants will then be randomized to the MORPH-II intervention or a control condition using a web-based randomization scheme.

Intervention Design Modifications

The first iteration of MORPH revealed key design issues we believe hampered uptake of the movement prescription and limited its potential for widespread delivery. These are noted in the following sections in detail and depicted in Figure 1.

Figure 1. Design modifications for MORPH-II. MORPH: Mobile Intervention to Reduce Pain and Improve Health.



Study Orientation and Tool Set

MORPH-II comprises a focused 12-week program followed by a 12-week no-contact maintenance period wherein intervention participants will be encouraged to sustain their weekly group contacts without researcher support. The first iteration of MORPH was limited in its ability to scale, as all testing was conducted in person, as were the first 3 group meetings. MORPH-II addresses these limitations by conducting the program remotely and employing remote testing and orientation appointments. This orientation appointment will occur over the telephone and video conference software and will allow the behavioral interventionist to introduce the study technology tools (Figure 2) and provide initial information on the study's approach to accumulating physical activity and dietary weight loss for those in the active arm. This will occur after the baseline physical activity data collection to avoid any contamination from the Fitbit activity monitor. Those randomized to the control condition will receive the scale and Fitbit activity monitor as well.

Figure 2. Intervention condition technology tools include iPad equipped with the MORPH companion app, Fitbit app, and teleconference software; BodyTrace cellular scale; and Fitbit Inspire activity monitor. Control participants receive the Fitbit monitor only.

MORPH-II Intervention

The model underlying the MORPH-II intervention package is depicted in Figure 3. MORPH-II is informed by our previous work in theory-based mHealth activity promotion in older adults [20,25,30,31], grounded in social cognitive [32] and self-determination [33] theories. The intervention involves an emphasis on regular group meetings as a motivational tool and for developing knowledge related to the importance of frequent physical activity and weight loss. The group meetings are supported by brief one-on-one meetings to reinforce the distributed movement goals and provide technology support. The MORPH-II intervention also involves the use of an mHealth toolset to instill an awareness of habitual sedentary behaviors, allow for unique goal setting and self-monitoring, and foster the development of self-efficacy via mastery badges [30], which act to cue successful experiences. The MORPH-II study timeline is depicted in Figure 4.

Figure 3. MORPH-II intervention model is based on social cognitive and self-determination theories.

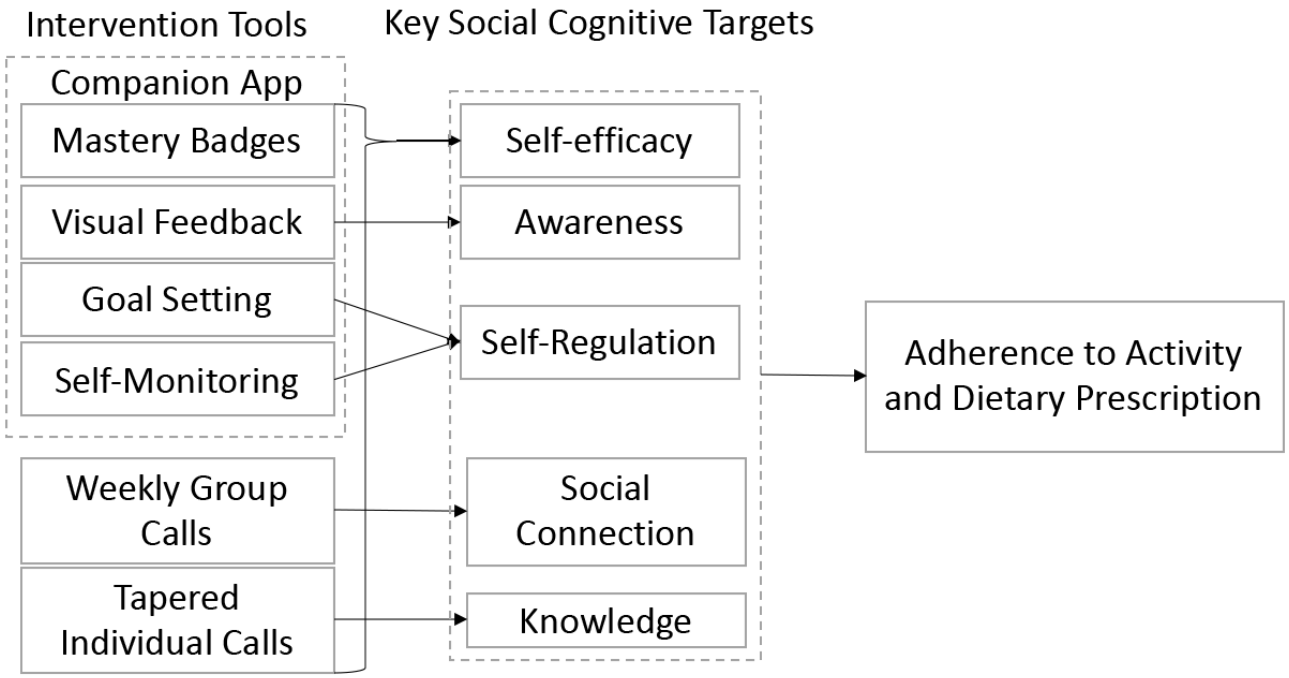
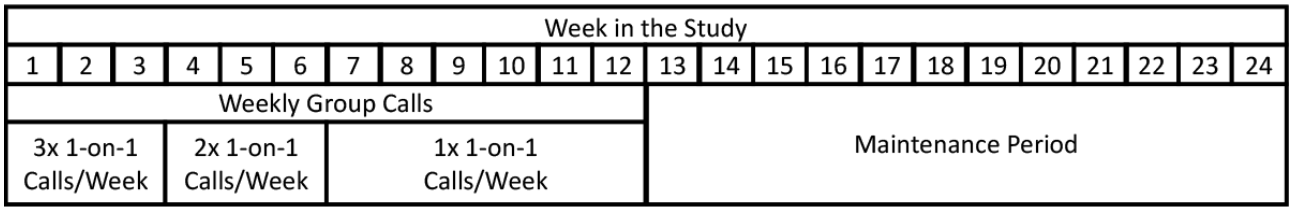


Figure 4. Study timeline.



Group-Mediated Teleconference Contacts

During the active intervention, participants will meet via Zoom teleconference software once weekly as a group. In a key design issue in the first iteration of MORPH, the Webex (Cisco) software often muted speakers when there was background noise, an important limitation in a group-mediated program. We have selected Zoom and will employ headphones with built-in microphones to foster more natural communication in group sessions. These sessions help to form social bonds to support long-term behavior change, foster self-efficacy through modeling, allow participants to share successes, and provide a venue for troubleshooting barriers as they arise. Within these group sessions, the behavioral interventionist will also work with participants to develop the basic skills needed for successful daily movement and weight loss (eg, regular self-monitoring, food tracking, use of the app each day). A more thorough description of the group-mediated model used in this study and a list of session topics is provided in Multimedia Appendix 1.

Movement and Weight Loss Goals

The movement component of MORPH involves increasing time spent in light and moderate-to-vigorous physical activity across the day through a focus on accumulating all forms of stepping activity while reducing the presence of sustained sitting bouts. This is supported in the study mHealth app via unique daily step goals that must be accumulated across 3 periods of the day, visualization of movement patterns, and goals related to the number of shifts (ie, breaks) between nonmoving and moving periods. The distal goals of the activity component are increasing daily steps in the range of 5000 to 10,000 steps based on individual abilities and distributing these steps throughout the day.

The content for the dietary weight loss intervention is based on our extensive experience in community-based trials [20,25,31,34]. The aim of the dietary intervention is to drive weight loss through caloric restriction while maintaining a nutritious and balanced diet. Individual goals for caloric intake will be prescribed to achieve an energy deficit of ~400 kcal/d from daily weight maintenance energy requirements (resting energy expenditure × activity factor of 1.3 for sedentary adults). During an initial orientation appointment, participants will be introduced to key concepts in nutrition (eg, self-monitoring, importance of protein consumption). Participants will work with the intervention team to set weekly calorie goals based on food logs collected during the week, behavioral challenges that arose during the prior week, and weight loss progress. The lowest caloric goal prescribed will be 1100 kcal/d for women and 1200 kcal/d for men. In the first MORPH study, the nutrition content was front-loaded, causing many participants to have difficulty conceptualizing the daily movement goals. Thus, we have reduced the focus on dietary topics such that nutrition content is introduced during an orientation and then covered in depth during weeks 7 to 12. Nutrition topics include eating to maintain satiety, managing a calorie balance on a weekly basis (eg, to account for celebratory eating events), and maintaining a healthy diet in the long term. This approach produced a significant weight reduction of nearly 3 kg compared with the control condition in the 12-week MORPH study [25]. Sessions also include nutritional education, teaching and reinforcement of self-regulatory skills, exposure to mindfulness-based stress reduction and pain management, and strategies that optimize social connection.

MORPH Companion App and Individual Coaching Calls

Participants in the intervention condition will be urged to engage with the MORPH companion app at least 3 times daily (morning, midday, and evening). This progressive web app will come preinstalled on the participant's iPad and will stream data in near real time from the Fitbit activity monitor and BodyTrace scale. The primary functions of the app are to provide immediate feedback on behavioral successes (thus supporting self-efficacy) via highly specific mastery badges, allow for ongoing social connection between weekly meetings via an in-app chat function, foster self-monitoring of weight via a connected smart scale, and instill an awareness of one's patterns of movement and sitting behaviors. This is primarily achieved through a timeline bar (Figure 2, lower image) wherein active minutes collected from the Fitbit are displayed in green and inactive minutes are displayed in blue. Participants aim for a "tree rings" profile on their timeline bar such that stripes of green movement are evenly dispersed throughout the day, interrupting any lengthy blue sitting bouts. Additionally, participants receive periodic step goals, which are modified step goals designed to disincentivize a single bout of exercise surrounded by sitting time. Here, participants are able to achieve up to 40% of their daily goal before 12:30 PM, again between 12:30 PM and 5:30 PM, and once more after 5:30 PM, necessitating at least 20% of their daily steps during any one period.

To reinforce these unique activity goals, MORPH-II participants will receive brief one-on-one coaching calls in a tapered fashion, as noted in Figure 1. These are designed based on feedback from the first iteration of MORPH and are intended to foster a stronger understanding of the daylong movement prescription—something that appeared unintuitive to some participants in our first iteration of MORPH. During these conversations, the coach and participant will view the participant's timeline bar from the previous day. They will discuss whether the participant felt they were successful in their daylong movement goal and troubleshoot periods of sustained sitting visible on the bar. The pair will work to develop actionable goals designed to enhance daylong movement over subsequent days, and these goals will be reviewed in the next one-on-one call. To facilitate rapid uptake of these goals, we have front-loaded these calls such that there will be 3 of these calls each week during weeks 1 to 3, 2 during weeks 4 to 6, and 1 during weeks 6 to 12 (Figure 4).

Maintenance Recommendations

One key advantage of fully remote telehealth delivery of group meetings is that participants may sustain their sessions without the need for a physical meeting space. During the final weeks of the focused intervention period, participants will receive instruction on continuing their weekly group calls without the assistance of the intervention team, emphasizing the importance of social connection for behavioral maintenance. No contact will be made with participants except for the purpose of scheduling and assessment during weeks 12 to 24. We will continue to collect app use and Fitbit data during this period.

Control Condition

Those in the control condition will be offered a print-based version of the intervention upon completion of the final testing time point. This will include a pamphlet detailing activity monitoring and how to use the Fitbit to monitor movement across the day. The pamphlet will also include a guide to food tracking and safe caloric restriction goals. These individuals will also receive the BodyTrace cellular scale and instruction on the value of daily weighing for weight management.

Measures

Baseline demographic data, medical information, and medication use will be recorded based on participant self-report. For the purposes of screening, BMI will be estimated using self-reported height and weight. The Shields adjustment [27] will be applied using the following formulas:

$$BMI_{Males} = -0.29227 + X_{Self\text{-}reported\ BMI} \times 1.03239$$

$$BMI_{Females} = 0.10927 + X_{Self\text{-}reported\ BMI} \times 1.02584$$

Adverse events will be assessed by questioning participants at each assessment visit and during weekly telecoaching calls.

To assess physical function, we will conduct the SPPB [29] via video conference and recorded video prior to the start of the intervention, after week 12, and after week 24. As described elsewhere, participants will receive a testing kit via mail including a camera, rope and tape to mark a walking course, and instructions. The participant will meet a blinded tester via video conference. The tester will review the testing setup with the participant, and then prior to each task will provide verbal and written instructions and ask whether the participant feels

safe completing the task. We will also require a second individual such as a family member or friend to be present and in the same room during any SPPB appointment to assist in case of a fall. We will provide this safety partner with an information sheet listing their responsibilities—to be in the same room and actively observing the participant during the appointment—as well as the requirement to have a phone on hand in order to call 911 if necessary. The kits will be returned by mail, and the camera footage will be used for test scoring. We will also gather self-reported disability using the Pepper Assessment Tool for Disability [35].

We will assess pain symptomology using the Patient-Reported Outcomes Measurement Information System [36] pain intensity (3 item) and pain interference (8 item) scales. We will monitor body weight throughout the study in the home using the BodyTrace cellular-enabled scale. We will use the ActivPAL 4 monitor to assess treatment effects on daily sedentary behaviors (time spent sedentary, sedentary breaks, average bout length) and physical activity (steps, minutes of total activity, minutes of moderate-to-vigorous activity). Participants will be asked to wear the devices continuously for 7 consecutive days at each time point. Data will be downloaded at the end of each 7-day period and cleaned and summarized for statistical analyses. We will also obtain daily Fitbit data throughout the study, which will provide ongoing assessments of physical activity and sitting behavior.

We will assess self-efficacy expectations related to physical activity [37,38] and outcome expectations for physical function and appearance [39]. Perceived stress will be evaluated with a short-form of the perceived stress scale [40], and control in resisting food using the power of food scale [41]. Depression will be assessed using the Center for Epidemiological Studies Depression scale [42], and health-related quality of life using the 36-item Short Form quality of life scale [43]. Next, we will capture the extent to which participants' self-determinative needs are being met using the Needs Satisfaction Scale specific to this study [44]. We will assess an individual's life space using a modified life space questionnaire [45]. The Pittsburgh Sleep Quality Index [46] will be used to assess sleep at each assessment visit. Fatigue will be measured using the Functional Assessment of Chronic Illness Therapy fatigue scale [47]. Cognitive function will be assessed during screening using the modified telephone interview for cognitive status [48]. Those scoring below 32 will be exclude from the study. We will use the Hopkins verbal learning test to assess word recognition and delayed recall as it has been validated for use over the phone.

Recognizing the dynamic relationship between pain and health behaviors, we will collect ecological momentary assessments [49] of pain, sleep quality, and affect throughout the program. To minimize participant burden, we selected well-used single-item assessments of each of these domains. Sleep quality will be assessed once daily via items from the Pittsburgh Sleep Quality Index [46] that we have used previously to investigate the relationship between sleep quality and activity behavior [50]. Specifically, participants will respond to "My sleep quality last night was..." on a 5-point scale ranging from very poor to very good. They also self-report the number of hours they slept the previous night. Affect, pain, and pain medication use will be assessed 6 times daily (1 unprompted waking survey and 5 prompted surveys delivered between late morning and midevening). Affect will be assessed using the single-item Feelings Scale that was developed and validated by Hardy and Rejeski [51]. This is a widely used assessment of affect, including in ecological momentary assessment studies [52]. Responses are provided on an 11-point scale ranging from feeling very bad to very good. Participants will be asked to rate their level of pain right now on an 11-point numeric rating scale [53] with responses ranging from none to severe. Finally, participants note whether they have taken a medication to manage their pain since the previous survey. We will collect these for 1 week at the beginning of each month of the intensive intervention phase (ie, weeks 1, 5, and 9), with surveys prompted via push notification and completed within a study web application.

Following weeks 12 and 24, those in the intervention condition will be asked to reply to several Likert-type and short-response items pertaining to their perceived use and usability of the app and acceptability of the intervention. Additionally, we will conduct a telephone guided interview with participants who received the active intervention after week 12 to collect qualitative data pertaining to study usability and acceptability. Finally we will collect the system usability scale [54] from intervention participants after week 12.

Statistical Analyses

The primary aim of this study is to describe the feasibility (ie, recruitment yield, percentage attendance at one-on-one and group coaching sessions) and acceptability (ie, participant feedback, system usability) of the MORPH-II intervention. We will present descriptive statistics for each of these outcomes. We will also look for group differences in physical activity and sedentary time to explore whether effects are in the appropriate direction. We will apply the following generalized linear modeling approach:

$$Y_{FU} = \beta_0 + \beta_1 Y_{BL} + \beta_2 Int + \text{covariates} + \varepsilon$$

where Y represents the focal outcomes (sedentary time, time spent in physical activity); subscripts FU and BL denote follow-up and baseline measurements, respectively, at week 12; Int represents intervention status; β represents regression coefficient; and ε represents random error. We also plan to conduct similar analyses of additional outcomes of the randomized controlled trial (eg, weight loss and function and disability scores) using the aforementioned model. Finally, we will replicate these analyses on scores at week 24 to investigate the extent to which those in the intervention condition maintain their behavior. We will also present descriptive statistics related to app use over the full 24-week study period.

Results

The study has received institutional review board approval and recruitment is ongoing as of January 2021. The study was registered at ClinicalTrials.gov [NCT04655001].

Discussion

Summary

Accumulating sufficient levels of physical activity and minimizing long bouts of sitting are widely recognized as important behavioral treatments for many health conditions, including chronic pain [3-5]. The development of effective and scalable interventions for promoting movement throughout the day is in its infancy, and as such it is vital that a careful iterative approach is used to identify effective intervention components while rectifying those that are ineffective. MORPH-II builds on an initial intervention framework [20,25] that demonstrated early success while bearing several important limitations. MORPH-II accomplishes the important step of further refining our initial intervention approach prior to testing it in a large and costly clinical trial. Our findings will serve as helpful guidance for other researchers working to intervene on sedentary behavior through frequent movement.

Limitations

While we believe the remotely delivered MORPH-II study will represent an important step toward socially rich and scalable activity programming, we also recognize several limitations that will be addressed in future research. This pilot study is intended to refine a complex remote intervention framework and as such will not be powered as an efficacy study. Additionally, the program sessions are designed to be led by a trained behavioral coach. Therefore, future work would benefit by recruiting a sufficiently large sample to determine efficacy and by working with community partners to deliver the program more broadly.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Information on the group-mediated behavior change model used in MORPH-II.
[DOCX File , 16 KB - resprot_v10i7e29013_app1.docx]

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Abbreviations

mHealth: mobile health
MORPH: Mobile Intervention to Reduce Pain and Improve Health
SPPB: Short Physical Performance Battery

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Protocol

Web-Based Multifaceted Approach for Community-Based HIV Self-Testing Among Female Sex Workers in Indonesia: Protocol for a Randomized Community Trial

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Abstract

Background: New HIV infections in Indonesia continue to be concentrated among key populations, including female sex workers (FSWs). However, increasing HIV testing among this subpopulation remains a challenge, necessitating exploration into alternative testing modalities.

Objective: This study aims to assess whether the addition of an oral fluid testing option in community settings would increase the rate of HIV case identification among FSWs. Because the study was implemented early in the outbreak of COVID-19 in Indonesia, a secondary objective is to assess approaches and tools for implementing both community outreach and community HIV screening for FSWs during pandemic conditions.

Methods: We undertook a community-based randomized trial in 23 national priority districts in which community outreach services were being provided. Community-based screening using an oral fluid-based rapid test was added to the community outreach standard of care in intervention districts with clients having the option of performing the test themselves or being assisted by outreach workers. A web-based system was created to screen for eligibility and collect participant data and test results, facilitating the process for both unassisted and assisted participants. Participants with reactive screening results were encouraged to undergo HIV testing at a health facility to confirm their diagnosis and initiate antiretroviral treatment as needed. Multiple means of recruitment were deployed including through outreach workers and social media campaigns.

Results: Of the 1907 FSWs who registered, met the eligibility criteria, and gave consent to participate, 1545 undertook community oral fluid test (OFT) screening. Most (1516/1545, 98.1%) opted for assisted screening. Recruitment via social media fell far short of expectations as many who registered independently for the OFT because of the social media campaign did not identify as FSWs. They were eventually not eligible to participate, but their interest points to the possibility of implementing HIV self-testing in the general population. The successful recruitment through outreach workers, facilitated by social media, indicates that their roles remain crucial in accessing FSW networks and improving HIV testing uptake.

Conclusions: The addition of HIV self-testing to the standard of care supported by a web-based data collection system was able to increase HIV case identification among FSWs in intervention districts. The high satisfaction of OFT users and the interest of the general population toward this alternative testing modality are promising for scaling up community HIV screening nationally.

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International Registered Report Identifier (IRRID): RR1-10.2196/27168

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KEYWORDS

HIV; self-testing; oral fluid test; community-based screening; female sex worker; Indonesia

Introduction

HIV Epidemic in Indonesia

Indonesia is one of the countries with high HIV burden in World Health Organization's (WHO) South-East Asian Region, having 20% of the region's people living with HIV and being the only high burden country estimated to experience continued increases in people living with HIV [1] and AIDS-related death [2]. Although overall HIV prevalence among most population subgroups is projected to decline between 2019 and 2024, the number of AIDS-related deaths among these populations is projected to increase [3]. It has been estimated that only 51% of people living with HIV in Indonesia know their status [2], and only 23% of adult people living with HIV have been estimated to be on antiretroviral therapy (ART) [3], making Indonesia one of the countries falling behind in reaching the 90-90-90 goal. However, with commitments to increase ART coverage in the latest National Strategic Plan, ART coverage is targeted to reach at least 75% by 2024 [4] to reverse the trend of AIDS-related deaths [3].

New HIV infections in Indonesia are concentrated among key population groups, including female sex workers (FSWs). Sex work was previously categorized as "direct" (ie, based in brothels, *lokalisasi*, streets, etc) and "indirect" (ie, based in entertainment facilities, such as bars and karaoke clubs, massage parlors, etc), and it is believed that many FSWs have shifted their work to indirect due to policies mandating the closing of brothels [3,5]. The term *lokalisasi* is an Indonesian word meaning "localization," which describes areas designated for sex work establishments. FSWs have also become harder to reach, as previous prevention efforts were based on established locations of sex work activities and as digital platforms have gained popularity to facilitate transactions [5].

In 2019, it was estimated that there were 277,624 FSWs throughout Indonesia with around 4,688,216 clients annually [3]. This mode of transmission continues to the clients' other sexual partners and their children. Lowering HIV transmission between FSWs and their clients will lower onward transmission. To increase ART coverage, more undiagnosed people living with HIV need to know their status. Given the increasingly challenging landscape in sex work in Indonesia, alternative strategies for increasing HIV testing uptake among FSWs are needed [6].

HIV Testing Among FSWs

The FSW population is at greater risk for not only HIV infection, but also stigma, discrimination, and violence due to the nature of sex work, which can affect their access to HIV testing [7]. Achieving high HIV testing coverage among FSWs is a global challenge [8]. While there is sizeable literature on the efficacy of community-based HIV prevention interventions for FSWs [9-12], there is limited global evidence on how to best increase rates of HIV testing among FSWs. Although the WHO [13] strongly recommended community-based testing approaches to supplement facility-based HIV testing, available evidence on the efficacy of this approach among FSWs is quite limited. A recent systematic review [8] reported 10 studies that examined recent testing in response to HIV promotion interventions for FSWs. Reported HIV testing uptake was found to vary, for example, in Canada, it was reported that 76% FSWs had HIV tests within the last 1 year [14], while in China, only 22% FSWs reported taking HIV tests within the last 1 year [15]. Reported barriers for service access included financial factors, time, stigma, discrimination, low-risk perception, fear, lack of accessibility, reluctance from health service providers to offer HIV testing, and limited human resources. A review by Tokar et al also found that social support from peers and managers could increase HIV testing uptake among FSWs [8].

Community-Based HIV Screening

At present, the only HIV testing performed outside of health facilities in Indonesia is via mobile clinics deployed from government community health centers. Although this eliminates the need to go to health facilities for testing, the linkage of testing with treatment has proven problematic for the mobile clinic strategy. The cost-effectiveness of this approach, at least in Jakarta, has also been questioned [6]. The cost of mobile voluntary counselling and testing to identify one HIV positive case among FSWs was almost six times higher than that to identify one HIV positive case among transgender individuals and men who have sex with men (MSM) and 17 times higher than that to identify one HIV positive case among people who inject drugs.

The latest WHO HIV testing guidelines [16] highlight community-based and HIV self-testing (HIVST) as a tool to identify more people with undiagnosed HIV who are at high risk of HIV infection. Privacy, confidentiality, and elimination of stigma are some of the advantages offered by this method in removing barriers to service access. UNAIDS [7] also suggested that HIVST has the potential to increase access to HIV testing especially among people living with HIV and key population

groups who do not yet know their status. Although the acceptability of HIVST, which includes both oral fluid test (OFT) and blood-based kits, has been studied among key populations, the studies are overwhelmingly performed among MSM in high-income countries and with varied types of supervisions [17-22]. However, the studies performed among FSWs demonstrated HIVST as a highly accepted strategy [21,23-26], which is a promising alternative to facility-based HIV testing.

In Indonesia, there have been few studies on the use of the OFT among key populations. One pilot study conducted among MSM used the OFT in exploring alternatives to facility-based HIV testing [27]. Although more MSM were able to know their status, this study found that only 38% of MSM with reactive OFT results went to health facilities for a confirmatory test, which is a requirement to receive government-subsidized HIV treatment. Another study, the HIV Awal (Early) Testing & Treatment Indonesia (HATI) Study [28], explored the impact of different approaches to HIV care, including use of the OFT among MSM, FSWs, *waria* (transgender women), and people who inject drugs. However, participants recruited were mostly MSM, and there was considerable difficulty recruiting FSWs at two of the three implementation sites [29].

An approach that has been increasingly employed to improve HIV testing uptake is internet-based outreach, which utilizes social networking sites [30], mobile apps [31], and websites [32]. The benefit of internet recruitment as opposed to traditional in-person recruitment is its ability to reach participants beyond the local area [33]. Furthermore, trials utilizing the web-based approach can also be combined with self-testing using the OFT, allowing the entire counselling and testing process to be conducted remotely [34,35]. This approach not only allows users to test at their convenience, but also allows testing and data collection to be performed in private, supporting HIV testing uptake [36]. However, a recent systematic review on technology-supported HIV testing revealed that most of these trials were performed among MSM, with only one trial performed among FSWs utilizing text messaging instead of an internet-based approach [36]. In light of this, it is essential to examine how implementing community-based HIVST supported with the internet will impact HIV testing uptake among FSWs in Indonesia.

The HIVST strategy using the OFT is yet to be employed to increase testing among FSWs in Indonesia, a key population group that has become increasingly hidden due to persistent police harassment [37] and brothel closures. Accordingly, a randomized community trial was designed to examine whether shifting screening from health facilities to community settings using noninvasive HIVST with the OFT can increase the number of FSWs who know their HIV status and subsequently increase treatment uptake for those who test positive. The acceptability and potential differences between assisted and unassisted testing can also be evaluated, as was observed in the study by Nguyen et al [25], where the cases were lower among participants undergoing lay-provider testing as opposed to self-testing.

Aim

This trial aims to answer the primary and secondary objectives outlined below. The initial trial protocol was designed prior to the COVID-19 pandemic. Although data collection websites were part of the initial plan, support activities, such as training, liaising, data monitoring, and participant recruitment, were designed to be carried out in person. This paper aims to describe the study protocol that was configured such that it could be implemented during COVID-19 pandemic conditions through internet and telecommunication technologies.

The primary objective of the study is to answer the following questions: (1) Does the introduction of community-based HIV screening (CBS) increase the proportion of HIV cases confirmed through facility-based testing and subsequent linkage to care among FSWs? (2) Are there differences in the proportion of cases confirmed through facility-based testing and subsequent linkage to care among FSWs undergoing assisted and unassisted CBS?

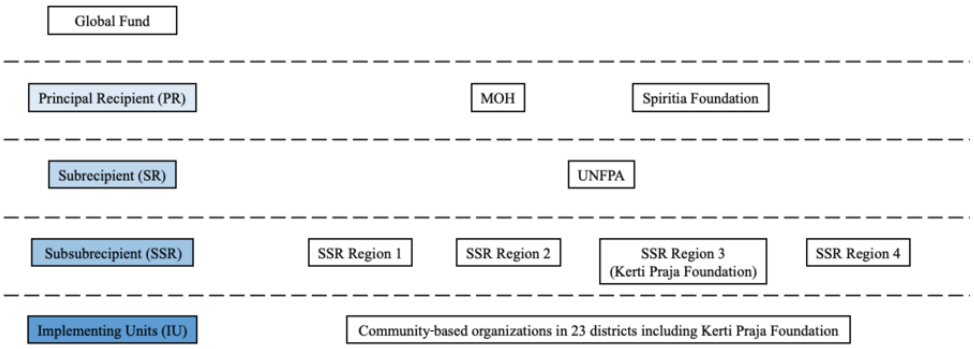
The secondary research questions are as follows: (1) How is CBS perceived among FSWs? (2) What are the differences in the characteristics of FSWs receiving assisted and unassisted CBS?

Methods

Study Setting

This trial is integrated into the structure of HIV prevention programs in Indonesia, which consists of different levels of implementors and networks (Figure 1). HIV prevention and treatment have long involved FSW peer leaders and non-FSW outreach workers (OWs), and Kerti Praja Foundation is an implementing unit for HIV programs and an implementing partner for this study. All peer leaders and non-FSW OWs will be collectively referred as OWs. Following brothel closures in 2016, United Nations Population Fund (UNFPA) Indonesia, the funding agency for this study, initiated a unique programmatic change that aims to have a minimum of 80% of OWs who are current or former sex workers. This was done to strengthen outreach as previous structures of sex work became fragmented [5] and have not previously been implemented by other large-scale programs where OWs are familiar with the FSW network, but might not be FSWs themselves. Furthermore, a national network of sex workers, *Organisasi Perubahan Sosial Indonesia* (OPSI) or Organisation of Social Change in Indonesia, had an advisory role from the early stages of this study during proposal development and remained closely engaged throughout study implementation. As such, the instruments and manual of the operating procedure of the study were developed and revised in consultation with FSWs and OWs.

Figure 1. HIV program network in Indonesia. MoH: Ministry of Health; UNFPA: United Nations Population Fund.



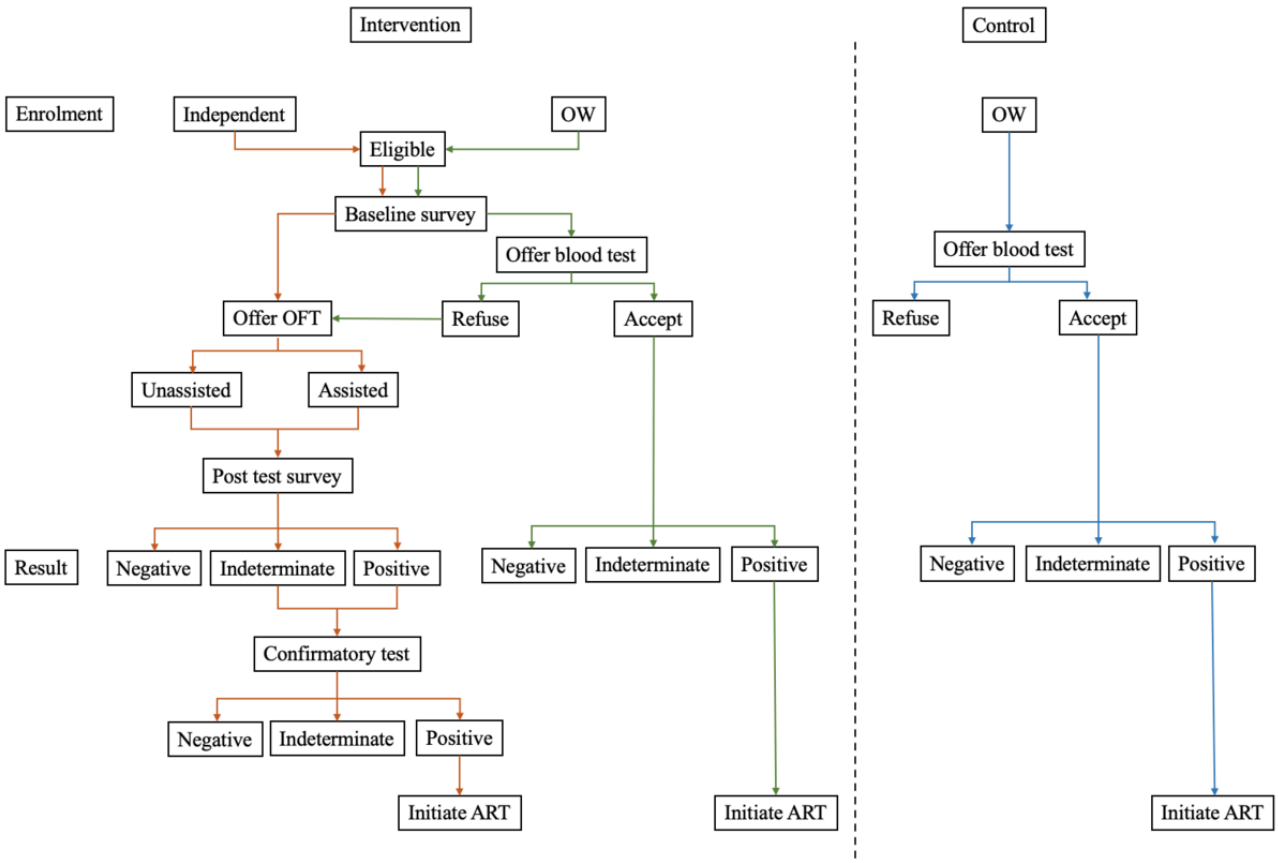
Outreach activities by OWs were performed through both face-to-face and virtual methods, with the latter being an alternative when physical contact was too risky for OWs and FSWs. An infection control protocol was developed by the United Nations Population Fund (as per unpublished 2020 report "Panduan Bagi Peer Leader dalam Situasi COVID-19" by the United Nations Population Fund, Jakarta, Indonesia) for OWs when face-to-face outreach was necessary.

Sustained engagement with key stakeholders gave rise to an evaluative qualitative study, which was developed and led by researchers from OPSI. FSWs were purposively selected from the CBS trial to reflect insights from a diversity of participants. Details of the evaluative study will not be covered in this article, as it aims to describe the protocol of the main trial.

Study Design

The design of this study is a randomized community trial whereby priority districts are randomized into intervention and control arms [38]. Control districts implemented the community outreach standard of care. The current standard HIV prevention program involves implementing units, which are community-based organizations that coordinate outreach to FSWs. Outreach activities include distribution of educational media on HIV and AIDS, distribution of condoms and lubricants, and advocacy for FSWs to receive periodic HIV tests at health care facilities or through mobile clinics deployed by the Ministry of Health. Each implementing unit was given a target number of HIV tests that renews every 6 months. FSWs with positive test results are referred to initiate ART (Figure 2).

Figure 2. Study flowchart outlining processes in the intervention and control arms. ART: antiretroviral therapy; OFT: oral fluid test; OW: outreach worker.



In the intervention districts, in addition to standard of care, FSWs were reached through multiple methods. Those recruited through OWs were given the option of choosing the OFT if they refused facility-based HIV blood tests. Conversely, FSWs recruited independently through social media could only select the OFT. All participants choosing the OFT could select either the assisted or unassisted method. Study kits were delivered through OWs for the assisted method and through courier services for the unassisted method. Participants with indeterminate or reactive OFT results were encouraged to access health services for confirmatory blood testing and proceed to initiate ART if confirmed to be HIV positive. All participants in the intervention arm completed baseline surveys, while only OFT participants completed posttest surveys. After uploaded data were verified, both participants and OWs were compensated in Indonesian Rupiah (IDR) as indicated in Table 1.

Table 1. Incentives for outreach workers and female sex workers.

Arm	Incentive (IDR)[a]	
	Outreach workers	Female sex workers
Control (standard of care)		
Facility-based testing	70,000	N/A[b]
Mobile VCT[c]	25,000	N/A
Intervention		N/A
Facility-based testing	70,000	N/A
Mobile VCT	25,000	N/A
Unassisted OFT[d]	100,000	N/A
Assisted OFT	150,000	N/A
Baseline survey	N/A	50,000
HIV test (blood test, OFT, confirmatory test)	N/A	100,000
Posttest survey	N/A	50,000

[a]The average Indonesian Rupiah (IDR)/USD exchange rate during the study period was USD 1 = IDR 14,600.

[b]N/A: not applicable.

[c]VCT: voluntary counselling and testing.

[d]OFT: oral fluid test.

District Allocation

The districts in the study consisted of the 23 cities and regencies designated by the Indonesian Ministry of Health as being the highest priority for HIV and AIDS programming. Allocation to study arms was performed using stratified randomization by firstly creating sampling strata through sorting from largest to smallest the mean average of achieved HIV testing per semester from 2018 to 2019 in each district. The 23 districts were then sorted into seven groups of three districts and one group of two districts. Randomization for the intervention and comparison groups was performed with a ratio of 2:1 to increase the likelihood of reaching the target number of FSWs receiving the OFT. The districts serving as intervention sites included Medan City, Deli Serdang Regency, Palembang City, Tangerang Selatan City, Tangerang Regency, East Jakarta City, Central Jakarta City, West Jakarta City, Bogor Regency, Depok City, Surakarta City, Malang City, Surabaya City, Denpasar City, and Sorong City. The districts serving as control sites included Bandar Lampung City, South Jakarta City, North Jakarta City, Bandung City, Depok City, Semarang City, Makassar City, and Jayapura City.

Study Population

This trial aims to recruit FSWs from the 15 intervention districts with the following eligibility criteria: female sex, age 18 years or above, history of having sex (vaginal, anal, or oral) at least once within the last month with reward (gifts, money, items, etc), duration of at least 6 months since the last HIV test, not currently planning or receiving HIV-related care at a health service, negative HIV report or unknown HIV status, not currently participating in another HIV-related study, and agreement to participate in the study.

FSWs in the control arm were reached through routine community-based outreach and health promotion package as those in the intervention districts, with the exception of OFT, which was only available in the intervention districts.

Due the web-based component of this study, participants are those who have access to the internet either through their own mobile devices or computers, or through OWs' devices.

Study Kits and Media

In order to better promote the intervention on digital platforms, the name *Tes Mandiri Komunitas*, which means community self-testing, was abbreviated to *Teman Kita*, which means "our friend." A logo bearing the name (Multimedia Appendix 1) was attached to digital and printed material used for the intervention arm.

This trial used OraQuick ADVANCE Rapid HIV1/2 Antibody Test kits to screen oral fluid samples, which has been shown to

have high sensitivity and specificity [39,40]. The study kits included an OFT kit; an instruction booklet in Indonesian adapted from the product insert; another booklet on further instructions for positive test results; a card containing the contact information of the principal investigator, study coordinator, and office; a referral form for confirmatory testing at a health facility; and an ART initiation form (Multimedia Appendix 2). All study kits were labelled with an ID indicating the district and kit serial number on the OFT packaging and on the external packaging (Multimedia Appendix 3). The study process for each participant can be seen in Figure 3. Participants were able to complete the study process at their convenience. Those recruited by OWs were followed up as desired by OWs, and those enrolled independently were followed up by researchers until they completed all steps or until they ceased responding.

Two videos were created to facilitate participants' and OWs' use of the study kits. One video provided information for the informed consent, outlining the purpose, process, and reward of the study. This video was only made available to those who were deemed eligible on the website's eligibility checklist (see Data Collection). The other video was a tutorial outlining the contents of the study kits, instructions for the OFT kits, and instructions for using the web-based data collection system (Multimedia Appendix 4). Institutional affiliations were indicated on the informed consent form and on the study website.

Figure 3. Timeline of the intervention arm showing processes for different types of HIV tests chosen. ART: antiretroviral therapy; OFT: oral fluid test; OW: outreach worker.

Test type	Timeline / Recruitment Method	Study initiation → Study completion							
OFT		Outreach	Registration	Eligibility Survey	Baseline Survey	OFT Result	Post-test Survey	Confirmatory test	ART Initiation
	By OW								
	Independent								
Blood test		Outreach	Registration	Eligibility Survey	Baseline Survey	Blood test Result			ART Initiation
	By OW								

Sample Size Calculation

In order to detect a 10 percentage point difference in the rate of HIV testing between FSWs choosing assisted and unassisted OFT methods in intervention districts and have (1) 95% certainty that a difference of this magnitude would not have occurred by chance and (2) 90% certainty of detecting a difference of this magnitude if the difference was "real," the sample of FSWs needed for the intervention districts was calculated using the formula in Multimedia Appendix 5 [41].

The required sample size was $n \geq 635$ per OFT method and was increased to $n \geq 761$ to allow for 20% loss to follow up. To assess whether "assisted" or "unassisted" OFT results in a larger increase in the rate of facility-based HIV testing, a sample size of $n \geq 761$ receiving an assisted or unassisted OFT was necessary; thus, a sample size of $n \geq 1522$ participants in the intervention districts was required. All the FSWs reached during the study period using standard of care in the intervention and control districts will be accounted for the analysis.

Sample size requirements also considered the number of participants who tested positive through facility-based testing and were therefore eligible to initiate treatment. This depended on (1) the number of FSWs presenting at health facilities for testing and (2) the positivity rate among those tested. Based on an assumption of a 3% positivity rate, the expected number of participants eligible to initiate treatment will be small and lack sufficient statistical power to make meaningful comparisons with the control arm. For this reason, the impact of the OFT was measured using data from *Sistem Informasi HIV AIDS* (SIHA) in intervention and control districts, which is a database for reporting HIV and AIDS cases in Indonesia.

Recruitment

Outreach Workers

OWs in 15 districts were trained by research staff on the study protocol and use of the web-based data collection system. Trainings were conducted between April 15, 2020, and May 19, 2020. Trainings were initially designed to be conducted in person, but due to the COVID-19 pandemic, trainings were carried out virtually through Zoom for 14 districts and in-person for one district, as the organization conducting the study is also located in the same city. Prior to training, each OW and implementing unit coordinator was given a manual for the website, a practice OFT kit for each implementing unit, spare print material for the study kits, and packaged study kits. Two additional tutorial videos were developed to assist the implementing unit coordinators and OWs in operating the data collection system. These videos were distributed through WhatsApp to each district's chat group so that individuals could easily store the video in their phones. The link to the developer version of the website was also given prior to training so that implementing unit staff could practice beforehand. Each virtual training session lasted two working days. Interactions with supervision of OWs and implementing unit coordinators' use of the website were made possible using the screenshare feature on Zoom. Each research staff was responsible to oversee three implementation districts along with one to two control districts, and conduct additional communications and meetings periodically as needed.

Social Media Campaign

Teman Kita utilized social media platforms to engage with its audience and reach FSWs who were unreached by conventional

outreach methods. This approach arose from the understanding that closures of *lokalisasi* in recent years have prompted FSWs to shift their service advertisements online [42]. The COVID-19 pandemic further drove FSWs to seek clients online, as establishments, such as karaoke bars and spas, were forced to operate for limited hours or close down completely [43]. Furthermore, social media has previously been used as a method of recruiting participants from key populations in Indonesia for survey-based studies [44]. Given the covert nature of sex work even on digital platforms [45], it was essential to employ a method that allows FSWs to access study materials and services privately.

A refined digital marketing job posting was formulated in June 2020, and a digital marketing team was recruited to create content, perform analysis on content performance, and generate targeted advertisements. Paid promotions were created to increase awareness toward HIV, testing, and the study, and divert traffic to the study website. Similar strategies of participant recruitment have also been utilized among key populations [46,47], resulting in improved engagement. In addition to creating routine image or text posts, interviews with HIV-positive FSWs and professionals, such as doctors and sexologists, and testimonies on the OFT were obtained and then adapted into posts. OWs were also encouraged to incorporate social media content into their virtual outreach efforts through personal social media accounts or forward information to known FSW networks through WhatsApp messaging chain and dating applications commonly used for sex work. All material published on social media can still be accessed on Facebook, Instagram, and Twitter through the media handle @studitemankita.

Satelit Pengambilan Kit OFT/Satellite OFT Pickup Point

The satellite OFT pickup point (SPOT) was a location identified by implementing unit coordinators in the corresponding districts as venues frequented by local FSWs. Although conceived early in the protocol development, this enrolment strategy was only implemented halfway during the data collection in an attempt to recruit more FSWs to access and perform the OFT independently. One SPOT was established in East Jakarta, overseen by a person in charge who stored the study kits and was responsible to refer FSWs to the study website.

Data Collection

There were two sources of data for this study. The first was the web-based data collection system (Multimedia Appendix 6 and Multimedia Appendix 7), and the second was the outreach data from each implementing unit. The use of the web-based data collection system was informed by the concept of telehealth, which has previously been used to combine home-based testing and video-based consultation to enhance linkage to care among MSM [34] and gender-diverse youth [35]. This approach was able to overcome barriers to facility-based services, suitable for those who fear stigma and live far from services. For our purposes, an external web developer was recruited to develop a web-based data collection system with consultation from key stakeholders. Prior to the development of this system, a survey was conducted among 15 intervention districts to assess regional telecommunication quality and availability, as well as the capabilities of OWs in operating smartphones. Initial plans to develop a smartphone app similar to one described in the study by Biello et al [48], which would allow offline data input, was eliminated due to time constraints.

All instruments used in the intervention of this study were placed on the web-based system, which included the informed consent, baseline survey, posttest survey, and features to upload images of OFT and blood or confirmatory test results (Multimedia Appendix 8). Participants could provide consent digitally by selecting the “agree” button on the informed consent page after correctly answering a series of questions to indicate their understanding of the study. Districts experiencing difficulties in operating the web-based system due to telecommunication limitations were given digital copies of the surveys so that the data collected could be entered in the web-based system when conditions were favorable. A developer version of the website was created to facilitate refining through consulting with stakeholders to ensure the official version was user friendly. One type of participant account and three types of administration user accounts (researcher, OW, and implementing unit coordinator) were created. Participants were able to terminate their participation or withdraw from the study at any time, and these options were reflected in each webpage in the participant’s account.

The second data source involved routine outreach at implementing units, which included names (or pseudonyms) of FSWs, age, and information regarding the HIV care cascade (whether they were offered HIV testing, whether they agreed to test, whether they received testing, and whether ART was initiated for those who tested positive). In order to measure the proportional increase in FSWs who received HIV testing through the OFT in the intervention districts, data from both the website and implementing unit outreach will be combined. These data were collected as a quantitative measure to compare HIV care cascades between intervention and control districts.

Data Management

The intervention that included the web-based system was available to participants at no cost. The system was password protected, ensuring only those who were authorized had access, and participant privacy was maintained. Participants were also given user names to maintain their confidentiality. Only the investigators were able to access the full information, including surveys of each participant. OWs were only able to view the contact details and progress of the participants they reached, and implementing units were only able to view the contact details and progress of the participants in their districts. The funding agency was not given access to participant information.

The web-based data could also be downloaded as Excel spreadsheets only by investigators. A daily cascade was used to monitor data collection progress and aid analysis (Multimedia Appendix 9). Research staff verified all incoming data to ensure all the necessary information was obtained. They also clarified conflicting information with OWs and performed random checks with participants through WhatsApp messaging or phone calls to ensure the intervention was performed according to the procedure. Participants were also verified against implementing unit outreach data to ensure that there was no documentation

of accessing HIV blood testing services within the past 6 months. A second check against implementing unit outreach data was also performed by the data manager after participants were verified by the research staff. After all data were verified, participants were given their incentives.

Data Monitoring

An independent data monitoring committee was not established as the trial aims to understand the acceptance of a test kit that is already widely used in other parts of the world. Progress and challenges in data collection were communicated and resolved between the research team and stakeholders continuously. The recruited sample size was constantly monitored to evaluate kit redistributions, recruitment decisions, and termination of data collection. Decisions were made based on consultations with the principal investigators, funding agency, and implementing partners. Researchers also monitored the progress of each participant and notified OWs to follow up with participants who had not completed their intervention process and to directly communicate with participants who enrolled through social media.

Undesired events related to the testing process were communicated among OWs, research staff, and principal investigators. These events included participants who encountered difficulties in proceeding with the testing process, duplicate enrolments, and participants found to be ineligible. Decisions regarding follow-up actions were consulted and made with the principal investigators and implementing partners.

Outcome Measures and Statistical Methods

Primary Outcomes

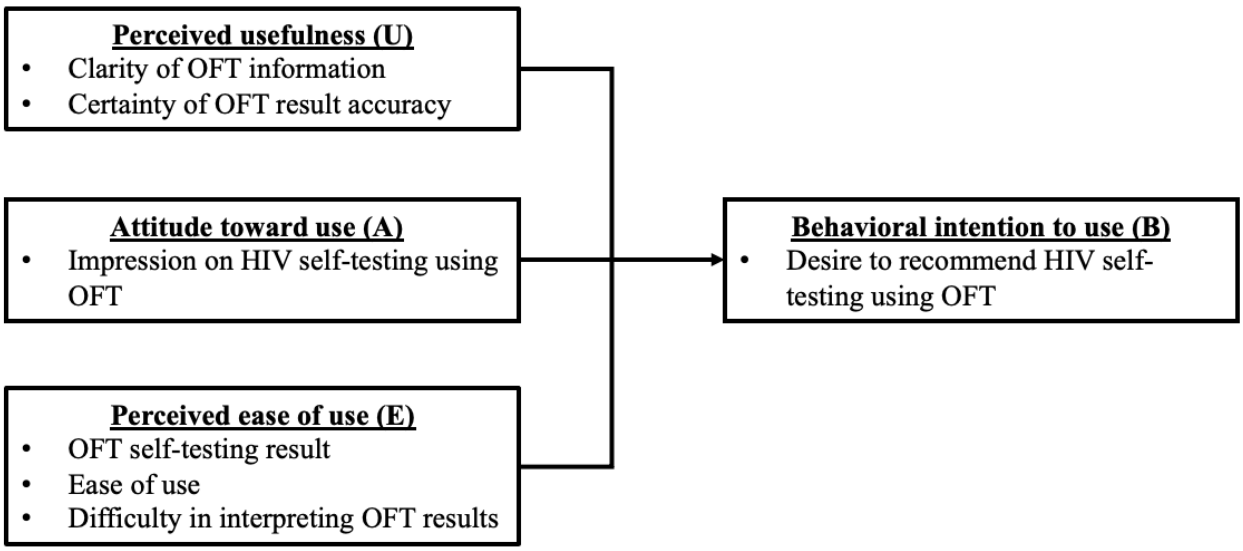
To measure the differences between control and intervention districts, two proportion *t* tests will be performed to compare the primary outcomes of this study, which are HIV testing uptake, HIV positivity rate, and ARV initiation rate. Specific daily quantitative data collected to answer the primary outcomes can be found in Multimedia Appendix 9, which outlines the different information that could be gathered from participants in control and intervention districts.

Secondary Outcomes

The secondary outcomes examine characteristics and behaviors among FSWs accepting the assisted and unassisted OFT and the perception of these approaches. Questions on demographic characteristics, condom use, client base, history of sexually transmissible infections, and Bahasa Indonesia version of the 12-item short HIV stigma scale [49] were present in the baseline survey. Additionally, perception of the experience of OFT use was present in the posttest survey (Multimedia Appendix 10). Chi-square analyses will be used to evaluate the secondary outcome measures.

Analysis on the perception of OFT use will be performed using an adaptation of the Technology Acceptance Model (TAM) Framework [50]. Questions on the posttest survey were separated into TAM categories of perceived usefulness, attitude toward use, and perceived ease of use to determine the behavioral intention of using the OFT in the future (Figure 4). Each question can be answered using a Likert scale with a score range from 1 to 5 (1 indicating extreme disagreement with the statement and 5 indicating extreme agreement with the statement).

Figure 4. Adapted Technology Acceptance Model framework for analysis of the perception toward oral fluid test (OFT) use.



Ethics Approval

The study protocol was reviewed and approved by the Faculty of Medicine, Udayana University-Sanglah General Hospital Ethics Committee with the number 612/UN14.2.2.VII.14/LT/2020. Research permission was granted by the Department of Internal Affairs, Republic of Indonesia with permit number 440.02/145/DV, which was subsequently referred to the licensing office in each province and priority district. This study has been registered with

ClinicalTrials.gov (NCT04578145). No amendments to ethics were made during the trial.

During the trial, a need for qualitative process evaluation was identified by key stakeholders. The qualitative study was performed separately by separate researchers under a different ethics approval. Procedures within the qualitative study will not be discussed under this protocol.

Results

Commencement of CBS coincided with the emergence of the COVID-19 pandemic, which prompted changes to alternate modes of OW training, outreach methods, data verification, and participant recruitment, fully utilizing virtual communication technologies. Initiation of data collection was staggered through 15 intervention districts between April 20, 2020, and May 29, 2020, to accommodate different timings in OW virtual training. Data collection in control districts commenced simultaneously in April 2020. All data collections ended on October 31, 2020.

The shift to a virtual modality in training OWs and monitoring of study implementation was conducted with great success. All OWs involved in the study attended the virtual trainings prior to the study initiation and were given guidance by research staff on the web-based system and relevant study procedures throughout the data collection period. The outreach effort using social media was also able to facilitate participant recruitment such that the targeted sample size in the intervention district was fulfilled. Furthermore, promoting the intervention through social media allowed the information to reach a wider audience in addition to utilizing the network of OWs.

In the intervention districts, 1907 FSWs completed the informed consent and 1545 opted to undergo the OFT (1516 assisted and 29 unassisted), with an overwhelming number (n=1518) enrolled through OWs, 27 enrolled independently through social media, and none enrolled through SPOT. There were 428 people who attempted to register independently through social media, but not all identified as FSWs; hence, many were ineligible for the trial. A number of these participants registered using names that are typically assigned to males in Indonesia; however, because the questionnaire did not have the option of choosing sex, it was not possible to definitively conclude that these participants were male. Furthermore, there were registrants who reached out to the research team after they were deemed ineligible by the questionnaire. Some reported being sexually active with their partners but did not participate in sex work.

The use of SPOT and virtual outreach by OWs were attempted to harness the strengths of conventional outreach that have been successful in the past. As such, this method of recruitment was not promoted on the study's official social media channels. Surprisingly, however, no participant was recruited through SPOT despite it being a location identified to be frequented by local FSWs.

In the control districts, data were routinely submitted at the end of each month. The completeness of the data was verified by research staff with the assistance of implementing unit coordinators. As control districts maintained their practices in the HIV program, only quantitative data were relevant for the purposes of answering the primary objectives in this trial.

Three forms of research dissemination are planned as follows: (1) a detailed report for the study sponsor, (2) presentations for stakeholders, and (3) a research article to be submitted to an open-access peer-reviewed journal. A brief version of the study protocol was uploaded to the implementing organization's website. The data generated will be disseminated to each implementing unit.

Discussion

Preliminary Insights

The trial was able to recruit the required sample size. Preliminary results indicated that uptake of HIV testing at health facilities among FSWs in the intervention districts was slightly higher compared to the control districts. The HIVST strategy using the OFT was well received and was able to recruit participants through social media. This indicates the feasibility and acceptability of a web-based HIVST strategy to increase testing uptake among FSWs in Indonesia.

This study demonstrated cutting-edge implementation research to assess possible scaling up of HIVST using the OFT at the national level. This study is performed at a larger scale than former studies on FSWs in Indonesia, and the processes of training, implementation, and monitoring were performed almost entirely online. This indicates that telecommunication infrastructure in urban areas is adequately developed and the use of smartphones is widespread, and points to the readiness for implementing telehealth at a larger scale. The wide reach and utilization of courier services, whether through regular postal services or rideshare companies with delivery services, are recognized. This opens the possibility for fully online modalities of test and treat services, which has never been previously attempted in Indonesia. Learning from recent key population-led initiatives in Bangkok, Thailand, adaptations were made to service delivery in light of COVID-19 [51]. These included the introduction of telehealth, self-sampling and testing for HIV and sexually transmissible infections, and pre-exposure prophylaxis medication delivery using courier services [51].

The study design was also appropriate because it allowed FSWs to perform assisted or unassisted testing and test at their convenience, as many clinics and community health centers were operating at limited capacity in addition to social restrictions at some of the intervention districts. The social media campaigns and web-based data collection methods were innovative approaches to supplement conventional outreach. As FSWs in Indonesia shift toward online methods to obtain clients [5], utilizing social media and web-based data collection can potentially capture previously unreached or hard-to-reach FSWs. Similar study designs that utilize internet-based interventions for self-testing were used mostly among MSM [34,36,52,53] and indicated the promising potential of using this approach to increase HIV uptake [52-54]. However, similar study designs for FSWs are yet to be implemented, which makes this study crucial in understanding the feasibility and acceptance of similar approaches in increasing HIV uptake among FSWs.

Limitations

Despite the multifaceted approach in recruiting FSWs, an overwhelming number of participants were recruited by OWs as opposed to registering independently through social media, which was likely due to the relatively late preparation and initiation of professional digital marketing efforts. However, this is consistent with findings from an HIVST trial among men and adolescents, where the majority of participants (82.7%) were recruited through community-based distributors [55], pointing to the crucial role of OWs in outreach. Additionally, the unknown digital footprint of FSWs posed a great challenge for creating targeted advertisements and social media campaigns. However, there was a notable increase in independent enrolment, although not all were eligible for the trial. Although the involvement of OWs was not systematically embedded in the study's social media campaign, it is important to note that OWs routinely utilized other social media platforms to engage with FSWs. Similarly, another HIVST trial among key populations, including FSWs, also found that 77.6% of participants opted for lay-provider testing instead of self-testing [25], which translates roughly to assisted and unassisted methods in our study. Given the covert nature of sex work, even online [45], further digital marketing research and strategies involving OWs must be incorporated to tailor messaging and engagement with FSWs in Indonesia.

The recruitment process through SPOT was unsuccessful, possibly due to business and mobility restrictions in Jakarta, which limited activities at nonessential establishments. Promotion of HIVST through SPOT relied solely on the person-in-charge's personal networks and may have narrowed the possible reach of the information. Since SPOT was not trialed in other districts with fewer restrictions, it was not possible to systematically assess the effectiveness of this method in this trial.

An additional limitation was the eligibility criteria applied in this study, which required participants to have exchanged sex for reward within the past month. This parameter may have ruled out FSWs who have had challenges obtaining customers during the COVID-19 pandemic. During the pandemic, many people lost their jobs and had to return to their hometowns [56]. Likewise, as the intervention measures were implemented in certain priority districts, FSWs who left these areas to return to their hometowns were unable to receive the intervention provided through this study.

Furthermore, as our study maintained a "business as usual" approach to the programs in control districts, the data collected were limited. For intervention districts, only those who were eligible filled out surveys, while other FSWs also received standard of care. Therefore, data are limited because demographic information, risk behavior information, and perception of stigma toward HIV/AIDS were only collected from those who fulfilled the eligibility criteria. As such, we will not be able to make comparisons between the characteristics of FSWs in the intervention and control districts.

Further Research Needs

The combination of innovative approaches offered a timely response to Indonesia's evolving sex work industry in an increasingly digitized nation. This study is the first to employ a combination of outreach and recruitment methods, as well as data collection methods, to ensure service delivery for HIV testing stays relevant and accessible in the digital era. The CBS protocol provided a holistic approach in reaching FSWs across Indonesia. Furthermore, CBS also increased the implementation sites to 15 intervention and eight control districts, providing insights that represent different urban settings across the archipelago, compared to a previous OFT study among key populations, which was implemented in three major urban centers in Java [28]. Given that there were no documented social media campaigns targeting FSWs for study recruitment in Indonesia, CBS successfully pioneered a large-scale targeted virtual outreach in Indonesia for this population that potentially lays the foundation for the future of HIV prevention outreach among FSWs.

Just as interesting is the finding that there were people who did not identify as FSWs but registered independently through the study's social media campaign. This suggests that the OFT is not only a tool that can increase testing among FSWs, but also a tool that captures the interest of those who perceive they are at risk for HIV due to sexual practices. The reach of social media also goes on to demonstrate the possibility to reach FSW and non-FSW populations who are not reached through conventional HIV program outreach.

Conclusion

This trial indicated that utilizing virtual methods in training OWs, utilizing outreach on social media, and adding the OFT to the standard of care in HIV programs are feasible. It also highlights the important role of OWs in facilitating access to online services and in using OFT kits. Likewise, it is important to understand how to better engage and reach the target population through social media. However, since most participants were recruited through OWs and opted for an assisted OFT, it will be challenging to understand differences between FSWs who were recruited through different methods and who opted for different testing methods. Regardless, the large number of participants opting for the OFT and the success in attaining the required sample size through combined traditional and virtual outreach point to the possibility of promoting routine testing with this modality.

The multidimensional and interdisciplinary approach aims to optimize the effectiveness of HIVST in increasing testing uptake and seeks to provide information on the profile of participants who access the OFT and preferred methods of testing. The administration of posttest surveys also acts as user feedback regarding satisfaction on specific aspects of OFT delivery and its potential to increase testing and linkage to care. The results from this study as a randomized community trial will provide robust and valuable evidence that can be used in advocating and planning for significant scaling up of HIVST among FSWs in Indonesia over the next few years.

Acknowledgments

This paper is dedicated to our co-principal investigator Professor Dewa Nyoman Wirawan, who passed away during the drafting of this paper. He was heavily involved in the conceptualization of this protocol and in advising the implementation of the study. We additionally acknowledge Dinar Lubis and Made Ady Wirawan for their contributions to the conceptualization of this study protocol, and the finance and administrative staff Ni Made Resti Wusadi, Putu Dian Andryani, and Anak Agung Bagus Adijaya, who ensured incentives to outreach workers and participants were given. We would like to thank the Ministry of Health, Ministry of Home Affairs, Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) sub-subrecipients, implementing units, outreach workers, and female sex workers who were involved in the study. This study was funded by United Nations Population Fund (UNFPA), country subrecipient of the GFATM. The article processing charge was funded by the researchers.

Authors' Contributions

Conceptualization: AASS, PPJ, IAN, OSM, AW, RM, and DNW; Formal analysis: IGAAM; Funding acquisition: PPJ and DNW; Methodology: AASS, PPJ, IGAAM, RM, and DNW; Project administration: JOY and IGAAM; Resources: IAN; Supervision: AASS, PPJ, OSM, AW, and DNW; Writing – original draft: JOY; Writing – review and editing: JOY, AASS, PPJ, OSM, AW, and RM. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

Principal investigators and research staff were sponsored by the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) to perform the study independently. None of the personnel involved in this study received financial compensation from the OFT kit manufacturer.

Multimedia Appendix 1
Logo of the trial used for branding in the intervention arm.
[PNG File , 21 KB - resprot_v10i7e27168_app1.png]

Multimedia Appendix 2
Screenshot in the instructional video for the oral fluid test showing the contents of the study kit.
[PNG File , 341 KB - resprot_v10i7e27168_app2.png]

Multimedia Appendix 3
A study kit with the study logo and kit ID bearing the district code and kit number.
[PNG File , 1742 KB - resprot_v10i7e27168_app3.png]

Multimedia Appendix 4
Instructional video on the use of the website and oral fluid test for study participants.
[MP4 File (MP4 Video), 90032 KB - resprot_v10i7e27168_app4.mp4]

Multimedia Appendix 5
Formula for calculating sample size.
[PNG File , 127 KB - resprot_v10i7e27168_app5.png]

Multimedia Appendix 6
Screenshot of the study website's homepage with informative articles on HIV, women's health, and sexual reproductive health.
[PNG File , 376 KB - resprot_v10i7e27168_app6.png]

Multimedia Appendix 7
Screenshot of the information page on the study's website with an instructional video, clinic locations, and relevant study information.
[PNG File , 267 KB - resprot_v10i7e27168_app7.png]

Multimedia Appendix 8
Text of questionnaires on the study website.
[DOCX File , 39 KB - resprot_v10i7e27168_app8.docx]

Multimedia Appendix 9

Quantitative data monitored in the daily cascade.
[PDF File (Adobe PDF File), 34 KB - resprot_v10i7e27168_app9.pdf]

Multimedia Appendix 10
Data collected for the primary and secondary outcomes.
[PDF File (Adobe PDF File), 18 KB - resprot_v10i7e27168_app10.pdf]

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Abbreviations

ART: antiretroviral therapy
CBS: community-based HIV screening
FSW: female sex worker
HIVST: HIV self-testing
MSM: men who have sex with men
OFT: oral fluid test

OPSI: Organisasi Perubahan Sosial Indonesia
OW: outreach worker
SPOT: Satelit Pengambilan Kit OFT (Satellite OFT Pickup Point)
TAM: Technology Acceptance Model
WHO: World Health Organization

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Protocol

Virtual Interactive Surgical Skills Classroom: Protocol for a Parallel-Group, Noninferiority, Adjudicator-Blinded, Randomized Controlled Trial (VIRTUAL)

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Abstract

Background: Traditional face-to-face training (FFT) for basic surgical skills is inaccessible and resource-intensive. Noninteractive computer-based learning is more economical but less educationally beneficial. Virtual classroom training (VCT) is a novel method that permits distanced interactive expert instruction. VCT may optimize resources and increase accessibility.

Objective: We aim to investigate whether VCT is superior to computer-based learning and noninferior to FFT in improving proficiency in basic surgical skills.

Methods: This is a protocol for a parallel-group, noninferiority, randomized controlled trial. A sample of 72 undergraduates will be recruited from 5 medical schools in London. Participants will be stratified by subjective and objective suturing experience level and allocated to 3 intervention groups at a 1:1:1 ratio. VCT will be delivered using the BARCO weConnect software, and FFT will be provided by expert instructors. Optimal student-to-teacher ratios of 12:1 for VCT and 4:1 for FFT will be maintained. The assessed task will be interrupted suturing with hand-tied knots.

Results: The primary outcome will be the postintervention Objective Structured Assessment of Technical Skills score, adjudicated by 2 experts blinded to the study and adjusted for baseline proficiency. The noninferiority margin (δ) will be defined using historical data.

Conclusions: This study will serve as a comprehensive appraisal of the suitability of virtual basic surgical skills classroom training as an alternative to FFT. Our findings will assist the development and implementation of further resource-efficient, accessible, virtual basic surgical skills training programs during the COVID-19 pandemic and in the future.

Trial Registration: International Standard Randomized Controlled Trial Number ISRCTN12448098; https://www.isrctn.com/ISRCTN12448098

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KEYWORDS

digital education; digital health; education; surgery; surgical skills; surgical training; surgical; suturing; telemedicine; virtual classroom; virtual training

Introduction

Background and Rationale

Basic surgical skills are essential to a wide range of medical professionals and aspiring surgeons. Recent advances in technology have facilitated the development of novel virtual training methods. Virtual classroom training (VCT) permits socially distanced interactive expert instruction via live video communication supplemented by concurrent feedback, graphical aids, and polling [1]. We aim to validate VCT as a modality of high-quality surgical skills education by evaluating its efficacy relative to that of the current alternatives.

Choice of Comparators

The General Medical Council stipulates safe basic wound closure under supervision as a procedural skill–learning outcome for undergraduate medical students [2]. Despite this, wound closure has not been sufficiently incorporated in university curricula, resulting in a deficiency in graduate competence in recent years [3,4]. Student-led surgical societies can deliver extracurricular tutorials on surgical skills; however, accredited, high-quality training can only be attained by professionally run face-to-face training (FFT) courses [5]. FFT is logistically complex, inaccessible, and resource-intensive. Furthermore, the requirement for social distancing during the COVID-19 pandemic has led to the suspension of nonessential FFT programs [6]. Noninteractive computer-based learning (CBL) is a cost-effective alternative. It can be completed independently by students, with the sole requisite of access to equipment and prerecorded training material. CBL is cheaper and more accessible than FFT; however, it does not offer live demonstration, interaction, or feedback. Therefore, it may be less educationally beneficial [7]. VCT may optimize resources and increase training accessibility while retaining the quality of FFT. VCT has the potential to improve the global availability and accessibility of basic surgical skills training; however, its efficacy has not yet been firmly established [8,9].

Objectives

This trial is designed to assess the effect size of the 3 interventions and test both the superiority of VCT to CBL and its noninferiority to FFT. We hypothesize that the efficacy of VCT will be greater than that of CBL and similar to that of FFT. We also aim to assess and compare the feasibility and accessibility of the 3 training modalities.

Trial Design

This is a parallel group, adjudicator-blinded, randomized controlled trial. Participants will be divided into 3 groups with an allocation ratio of 1:1:1. Group 1 will undertake noninteractive CBL, group 2 will receive VCT, and group 3 will receive FFT.

Methods

Participants, Interventions, and Outcomes

Study Setting

Participants will be recruited from across all year-groups within 5 medical schools in London, United Kingdom, to reduce travel requirements during the COVID-19 pandemic. The participating universities include the following: University College London (UCL), Imperial College London, King's College London, St George's University of London, and Barts and the London School of Medicine and Dentistry. The opportunity for students to participate will be advertised on the internet by the official student-led surgical societies that represent the 5 medical schools. Eligible individuals will be invited to volunteer through an electronic application form, which will contain a participant information leaflet (PIL), which includes employed methods of data handling and anonymization. The form will request the provision of informed consent and personal data that comprise name, age, sex, university, year of study, and email address for correspondence. The PIL and consent form are attached in Multimedia Appendix 1.

Eligibility Criteria

The criteria for inclusion will be current medical student status, availability on specified trial dates, and the ability to access both a PC with an integrated camera and a smartphone with an integrated camera. Outcome adjudicators will have membership of the Royal College of Surgeons degrees and Basic Surgical Skills certification [10].

Interventions

Expenses associated with the coordination of the interventions are listed in Table 1. All participants will be provided with a suture pad that contains a 5-cm incision, needle holder, surgical scissors, toothed and nontoothed forceps, a 70-cm-long nylon cord, and 5 silk suture packs. Interventions will have a 2-hour duration. All participants will view a 6-minute noninteractive instructional video that demonstrates the correct interrupted suturing and hand-tying technique with annotations before beginning the intervention.

Individuals in the CBL group will participate in the study from a location of their choice. They will practice independently under self-direction with continued access to the instructional video. They will be continuously monitored by a trial coordinator via the videoconferencing platform Zoom [11]. The VCT group will remotely attend a virtual classroom led by 2 expert instructors using the BARCO weConnect platform [1]. The VCT control room will be located at UCL, and students will log in from a location of their choice from a PC. Participants will be trained with an instructor-to-student ratio of 1:12. A proficiency-based progression model will be followed. Instructors will have a live view of all participants and will utilize graphical instructional aids, annotations, and interactive

polling to deconstruct the task and define its key maneuvers. Students will display their own hands while practicing, allowing the instructors to provide them with concurrent feedback and guidance. The FFT group will physically attend a socially distanced classroom at UCL, in line with national government and institutional COVID-19 guidelines. The group will be divided into 6 subgroups (n=4 students each), and each subgroup will be trained by a single instructor and will have an instructor-to-student ratio of 1:4. This ratio has been shown to optimize the educational benefit of FFT [12]. A proficiency-based progression model will again be followed, and instructors will perform a live demonstration of the correct technique and verbally deconstruct the procedure and define its key maneuvers. Students will also receive concurrent feedback and guidance from the instructor while they practice. The same instructors will deliver all 3 interventions; they will provide the video for CBL and implement the training for both the VCT and FFT arms.

Table 1. Financial costs associated with the coordination of the intervention.

Item or service	Cost (GB £)
Subscription to the Barco WeConnect platform	186.24
In-person training venue fees	510.00
Suturing equipment	988.41
Personal protective equipment	113.09
Zoom videoconferencing plan	11.99
Total cost	1809.73

Outcomes

Baseline characteristics will be collected to facilitate the identification of systematic differences between intervention groups that may increase the risk of bias. Age, year group, sex, and hand dominance will be elicited through a preintervention questionnaire. The primary outcome will be postintervention suturing and hand-tying proficiency, adjusted for preintervention proficiency. After the initial instructional video and again immediately after the intervention, participants will complete an assessment task. The task will include placing 3 interrupted sutures with hand-tied knots by using a single silk suture, with a time limit of 4 minutes. Proficiency will be measured using a validated Objective Assessment of Surgical and Technical Skills (OSAT) used by the Royal College of Surgeons [10]. Scores will be adjudicated by 2 experts blinded to the study design. Proficiency will be defined as the mean value of both adjudicator scores.

Secondary outcomes will be the students' subjective suturing and knot-tying confidence, perceptions of the intervention, and expenses associated with session attendance. Subjective confidence and perceptions will be elicited through a postintervention questionnaire and measured on a 5-point Likert scale. Expenses will be self-reported by participants.

Participant Timeline

Recruitment will begin in November 2020. Randomization and allocation will commence in January 2021. Interventions, data collection, and data analysis will be completed by May 2021, depending on governmental and institutional COVID-19 guidelines.

Sample Size

The effect of VCT on OSAT-measured proficiency is not reported in the existing literature. The VCT technology implemented by this trial has been optimized for 24 attendees. A total sample size of 72 individuals (n=24 per intervention group) was therefore selected. A sensitivity power analysis was performed using a 2-tailed dependent samples *t* test. With an α and β error probability of .05, a minimum detectable effect of 0.769 was computed.

Recruitment

The application window will be open for 31 days after advertisement. Applicants will be informed of the outcome within 1 week after its closure. From the pool of applicants, a sample of 72 will be selected to participate in the trial. To ensure substantial representation from all 5 centers, 8 participants will be selected at random from each of the medical schools. Further, 32 participants will then be selected randomly from the remaining applicant pool.

Assignment of Interventions

Allocation

A web-based questionnaire will be distributed to the participants to elicit their subjective confidence in their own suturing ability and the quantity of formal (expert-led) and informal (peer-led or independent) suturing training they have previously received. Participants will then be stratified by subjective suturing confidence—measured on a 5-point Likert scale—and objective previous suturing training experience—measured to the nearest hour. Permuted block randomization (block size=3) will be carried out to allocate the participants within each stratum to 1 of the 3 intervention groups. Permutations will be selected by a random number generator. Comprehensive instructions and guidelines to be followed before and during the training sessions will also be provided. Participants who do not want or are unable to participate will be replaced through random selection from the remaining list of applicants where possible.

Blinding

Outcome adjudicators alone will be blinded to intervention assignment. When recording the assessment task video, desk surfaces will be covered with plain white paper, and participants will not be visible above the elbow. Video files will be renamed

and reordered through random number generation prior to adjudicator review.

Data Collection, Management, and Analysis

Data Collection

Applicants will complete a questionnaire that elicits personal data, which will be used for correspondence. Participants will complete a questionnaire immediately before and after the intervention. All questionnaires will be administered using Jisc Online Surveys [13]. Participants will record the assessment tasks by using a personal device with an integrated camera. Framing specifications will be provided in advance. Video files will be shared with trial coordinators securely via WeTransfer [14].

Data Management

All data will be stored on encrypted hard-drives under password protection. Personal data collected from applicants will be accessed by trial coordinators only to permit the collection of nonidentifiable information from participants. Participants will be assigned anonymous numeric IDs, which will be used to identify their video recordings and questionnaire responses.

Statistical Methods

Within-group proficiency improvements after the interventions will be analyzed using the dependent *t* test. Between-group postintervention proficiency will be assessed through analysis of covariance with baseline proficiency as a covariate in the regression model. Post hoc analysis will be performed using the Fisher test of least significant difference. The combined hypothesis that VCT is both superior to CBL and noninferior to FFT will be tested at a 95% significance level. The noninferiority margin (δ) was defined on the basis of historical data. An observational study investigated the effect of FFT on OSAT scores, with a reported difference of 3.7 (95% CI 2.7-4.7) in mean values [15]. A δ of 0.675 was selected to ensure a preserved fraction of 3/4.

Monitoring

Data Monitoring

There will be no data monitoring as data collection will not be continuous; instead, all data will be collected simultaneously, with no interim analysis.

Harms and Auditing

Harms and auditing will be performed with ethical approval and participant consent form (Multimedia Appendix 1).

Ethics and Dissemination

Research Ethics Approval

The study has received ethical approval from the UCL Research Ethics Committee (REC) (ID: 19071/001). National and institutional COVID-19 guidelines will be followed and have been discussed and agreed upon with the UCL REC.

Protocol Amendments

Amendments to the protocol will be submitted to the UCL REC for consideration. Deviations in the statistical plan will be described and justified in updated versions of the protocol.

Consent

Informed consent will be obtained using the PIL and consent form, which are provided in Multimedia Appendix 1.

Confidentiality

Identifiable data will be collected from participants solely for the purposes of correspondence. They will be stored separately from nonidentifiable data and destroyed on completion of the study.

Data Access

The final anonymized data set will be accessed by the statistician alone. All other data will be destroyed on study completion.

Ancillary and Posttrial care

In accordance with the consent form, harms are not expected and risks are expected to be low, and data can be withdrawn by the participant up until the point of data analysis.

Dissemination Policy

The findings of this trial will be submitted for local, national, and international presentation and publication in a peer-reviewed journal. Authorship will be in accordance with the ICMJE (International Committee of Medical Journal Editors) guidelines. The anonymized participant data set and statistical code will be made available to the journal for peer-review on request.

Results

The study was fully funded in December 2020 and approved by the UCL REC in December 2020. The study is currently underway, and data collection has started. Data analysis and publication of results are expected in August 2021.

Discussion

Expected Findings

This randomized trial will be a comprehensive analysis of the suitability of virtual basic surgical skills classroom training as an alternative to FFT and CBL. Our findings will allow for the development and implementation of further resource-efficient, accessible virtual training programs during the COVID-19 pandemic and in the future.

Strengths and Limitations

We plan to conduct a 3-arm randomized controlled trial that will investigate the effect of VCT. Comparator groups will be noninteractive CBL and FFT. We will use a validated OSAT score to assess proficiency. We shall use optimal teaching methods and follow COVID-19 guidelines.

Acknowledgments

We acknowledge UCL and the Royal College of Surgeons for agreeing to finance the purchase of equipment, venue fees, and VCT technology expenses. Our study has received no nonfinancial support. This study is sponsored by the UCL Division of Surgery and Interventional Sciences, London. The funders have had no involvement in the design of the study and will not participate in the collection, analysis, or interpretation of the collected data. Funders will not be involved in drafting the manuscript or in decisions regarding its publication. The National Surgical Teaching Society and the VIRTUAL Study Group, which comprises the authors of this paper, were responsible for all elements.

Authors' Contributions

AN, MF, MG, SP, MKH, and NH designed the study. AN, MF, MG, SP, MKH, AA, AS, WM, and JS collected the data. AN and MF analyzed the data and drafted and critically revised the manuscript. AN, BWL, JK, AS, and JC supervised the study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Participation information leaflet and participant consent form.
[DOCX File , 22 KB - resprot_v10i7e28671_app1.docx]

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Abbreviations

CBL: computer-based learning
FFT: face-to-face training
OSAT: Objective Structured Assessment of Technical Skills
PIL: participant Informal leaflet
REC: Research Ethics Committee
UCL: University College London

VCT: virtual classroom training

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Protocol

A Mobile Peer Intervention for Preventing Mental Health and Substance Use Problems in Adolescents: Protocol for a Randomized Controlled Trial (The Mind Your Mate Study)

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Abstract

Background: Anxiety, mood, and substance use disorders have significant social and economic impacts, which are largely attributable to their early age of onset and chronic disabling course. Therefore, it is critical to intervene early to prevent chronic and debilitating trajectories.

Objective: This paper describes the study protocol of a CONSORT (Consolidated Standards of Reporting Trials)-compliant randomized controlled trial for evaluating the effectiveness of the Mind your Mate program, a mobile health (mHealth) peer intervention that aims to prevent mental health (focusing on anxiety and depression) and substance use problems in adolescents.

Methods: Participants will consist of approximately 840 year 9 or year 10 students (60 students per grade per school) from 14 New South Wales high schools in Sydney, Australia. Schools will be recruited from a random selection of independent and public schools across the New South Wales Greater Sydney Area by using publicly available contact details. The intervention will consist of 1 introductory classroom lesson and a downloadable mobile app that will be available for use for 12 months. Schools will be randomly allocated to receive either the mHealth peer intervention or a waitlist control (health education as usual). All students will be given web-based self-assessments at baseline and at 6- and 12-month follow-ups. The primary outcomes of the trial will be the self-reported use of alcohol and drugs, anxiety and depression symptoms, knowledge about mental health and substance use, motives for not drinking, and willingness to seek help. Secondary outcomes will include positive well-being, the quality of life, and the impact of the COVID-19 pandemic. Analyses will be conducted using mixed-effects linear regression analyses for normally distributed data and mixed-effects logistic regression analyses for categorical data.

Results: The Mind your Mate study was funded by an Australian Rotary Health Bruce Edwards Postdoctoral Research Fellowship from 2019 to 2022. Some of the development costs for the Mind your Mate intervention came from a seed funding grant from the Brain and Mind Centre of the University of Sydney. The enrollment of schools began in July 2020; 12 of 14 schools were enrolled at the time of submission. Baseline assessments are currently underway, and the first results are expected to be submitted for publication in 2022.

Conclusions: The Mind your Mate study will generate vital new knowledge about the effectiveness of a peer support prevention strategy in real-world settings for the most common mental disorders in youth. If effective, this intervention will constitute a scalable, low-cost prevention strategy that has significant potential to reduce the impact of mental and substance use disorders.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12620000753954; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=379738&isReview=true

International Registered Report Identifier (IRRID): DERR1-10.2196/26796

(JMIR Res Protoc 2021;10(7):e26796) doi:10.2196/26796

KEYWORDS

prevention; mental health; substance use; peer support; depression; anxiety; help-seeking; mobile phone

Introduction

Background

By 2030, the global health care costs associated with mental illness and substance use are predicted to be more than the pooled costs attributed to cancer, diabetes, and respiratory diseases [1]. Although the provision of widespread treatment is essential, if we are to significantly affect population health, effective prevention is also critical. Recent population data show that mental health problems among adolescents are rising [2], indicating that current prevention approaches do not prevent population level increases. Both mental health symptoms and substance use, begin and escalate during adolescence [3], with even small elevations in adolescence increasing the likelihood of developing a full-blown mental disorder later in life [4]. From the ages of 13 to 24 years, there is an increased susceptibility to the development of mental illness and substance use problems, with longitudinal life course studies indicating that transitions from childhood to adolescence and from adolescence to young adulthood are marked by significant increases in mental and substance use disorders [3]. This makes adolescence a critical time to intervene and prevent these problems using scalable and novel prevention approaches.

The social network theory has demonstrated that peers have a powerful influence on health behaviors, including mental health [5] and substance use [6]. Studies using social network analysis are beginning to uncover the mechanisms by which health behaviors, such as mental health symptoms and alcohol use, diffuse and spread through peer groups [7-9]. This approach is currently used to better understand the development and prevention of these problems. Several studies using a large nationally representative US data set (AddHealth) found that both friendship connections and peer influence function are causal factors that influence adolescents' health risk behaviors [10,11]. The size of this influence is substantial, with a 10% increase in the proportion of adolescent peer group members who drink alcohol, resulting in a 4% increase in individual drinking [12]. Furthermore, social connections among peers are important determinants of behavior, with a one SD increase in (1) friends' prior drinking increasing the odds of an adolescent binge drinking by 30% and (2) friends-of-partner drinking increasing the odds of binge drinking by 81% [13]. Research has also started to uncover the role of peer groups in the etiology of mental health symptoms, with processes such as corumination between peers actively increasing the risk of developing poor mental health, such as depression [14,15]. Conversely, it has recently been speculated that interventions providing positive support and scaffolding through the power of peers to develop prosocial, healthy behaviors during adolescence could have significant benefits for adolescent health and development [16].

Current prevention programs for adolescent mental health and substance use typically show modest effect sizes and limited implementation [17]. Universal school-based programs delivered to all adolescents, regardless of the level of risk, have been shown to demonstrate small to moderate effects in reducing alcohol misuse [18,19] and levels of anxiety and depression [20,21] and increasing mental health literacy [22]. As many current mental health prevention approaches largely represent adaptations of treatment approaches that were originally designed for adults, it is unclear how the unique developmental needs of adolescents have been taken into account in the design of these programs [23]. Adolescents are hypersensitive to social stimuli and are more susceptible to peer feedback on decision-making. Therefore, it is critical to consider the substantial role of peers in designing effective prevention strategies [23]. Furthermore, a recent review [17] of mental health interventions in schools in *The Lancet* identified the development and evaluation of peer-led models as a significant gap in the field.

In addition to influencing behavior, peers play an important role in identifying and facilitating access to support for friends with mental health and substance use issues. Currently, most young people experiencing difficulties with mental health and/or substance use will not seek help [24]. One study found that approximately only 20% of adolescents (aged 14-15 years) sought help for depression, whereas only 3% sought help for alcohol or other drug problems [25]. Those who sought help for substance use cited that friends were their main source of support, followed by parents or health professionals as reported by a much smaller proportion [25]. However, adolescents may not be equipped with the knowledge, skills, or awareness of appropriate referral services to provide adequate support to their peers when mental health and substance use problems arise. Thus, empowering adolescents to help their peers is not only critical to ensure that the advice and support received is appropriate, but can also facilitate help seeking for those providing support [25].

One existing, evaluated peer training program for adolescents is Teen Mental Health First Aid. Developed in Australia, this program includes three in-school sessions with trained facilitators to increase mental health literacy and reduce stigma, with separate courses for students in years 7-9 (ages 12-14) and years 10-12 (ages 15-17) [26,27]. These programs have shown promising effects in increasing help-seeking intentions and confidence to support friends and reducing stigma around mental health [26,27]. However, the program's impact on mental health symptoms has yet to be evaluated and it uses face-to-face delivery from external trainers, potentially limiting its scalability.

Current adolescents have grown up in a world with unequivocal access to technology and information. In Australia, 91% of teenagers (aged 14-17 years) own a mobile phone, and 94% of these phones are internet-connected smartphones [28]. One key opportunity for the prevention of mental disorders is the possibility of harnessing such mobile technology to deliver easily accessible prevention strategies that can be widely implemented at low cost, in a format that is acceptable to and engaging for adolescents. Adolescents use their phones to

communicate with their peers daily and regularly access web-based information. In a US survey, 89% of teenagers reported being on the web *several times a day* to *constantly* [29], with SMS text messaging as the dominant form of communication among peers on a daily basis [30]. Despite the recognition of the key role that peers play in health behavior and the frequent use of digital technologies by adolescents, scientifically evaluated digital peer interventions are lacking, with limited evaluations of current web-based or mobile programs available for adolescents.

To address these gaps, the Mind your Mate intervention was developed, a novel mobile health (mHealth) intervention aimed at upskilling and empowering adolescents to better support their peers on issues related to mental health, alcohol, and other drug use.

Aims, Objectives, and Hypotheses

This study aims to evaluate the effectiveness of Mind your Mate program among adolescents through a cluster randomized controlled trial (RCT) conducted in partnership with secondary schools. We hypothesized that the Mind your Mate intervention will be more effective than the active control group (health education as usual) in (1) delaying the uptake of alcohol and other drugs; (2) reducing anxiety and depression symptoms; (3) increasing knowledge about mental health, alcohol and other drugs; and (4) increasing help-seeking behavior.

Methods

Ethics Approval and Consent to Participate

The study was approved by the University of Sydney Human Research Ethics Committee, Australia (project number: 2020/054). Both active parental consent and active participant (student) consent were required before students could participate in the study.

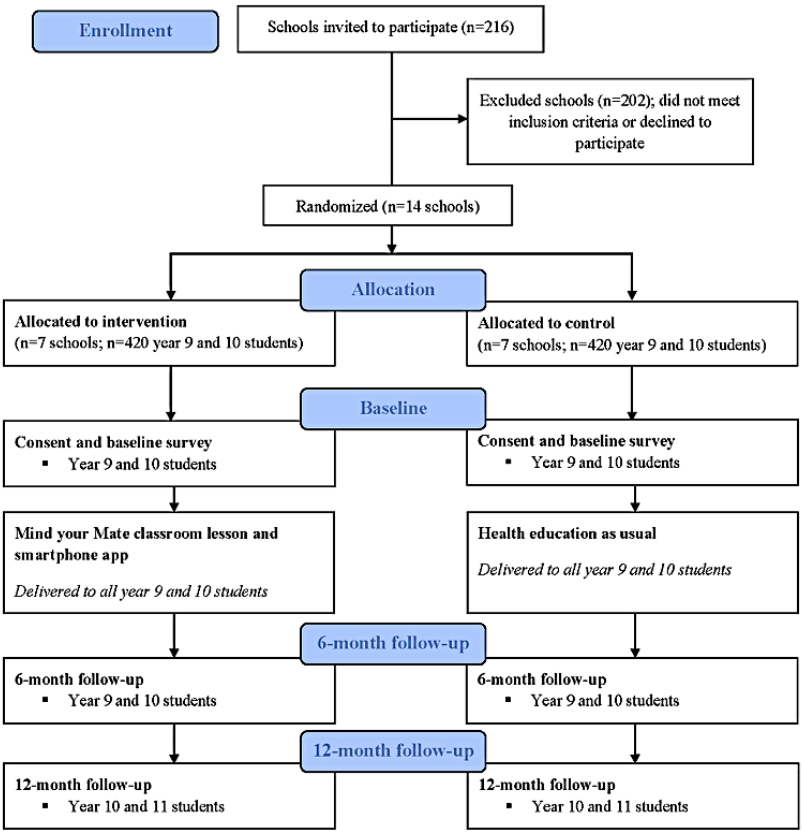
Access to schools was granted by the New South Wales (NSW) Department of Education and Communities (State Education Research Applications Process 2020130).

Study Design

This trial is registered with the Australian New Zealand Clinical Trials Registry (trial number: ACTRN12620000753954).

To determine the effectiveness of the Mind your Mate intervention, a cluster RCT will be conducted among year 9 or year 10 students (aged approximately 14 years) at 14 independent and public secondary schools in NSW from 2020 to 2021. Cluster randomization will be used to avoid contamination of the controls by the intervention group through student communication. Schools will be randomly allocated to either the Mind your Mate intervention condition or the active control condition (health education as usual). Figure 1 summarizes the anticipated recruitment, randomization, and assessment of the participants.

Figure 1. Anticipated recruitment, randomization, and assessment of participants based on the CONSORT (Consolidated Standards of Reporting Trials) guidelines.



Sample Size Calculations

This trial is powered to detect intervention by time interactions in longitudinal cluster RCTs. To allow for comparisons between the two conditions, 6 schools (with at least 60 students) in each of the 2 intervention groups were required, giving a total of 12 schools (with at least 720 students). This would achieve 80% power to detect a standardized between-group mean difference of 0.2 in outcomes at the end of the trial with three measurement occasions (P=.05). An effect size of 0.2, which is comparable with previous trials of anxiety, depression, and substance use prevention programs [20,21,31-34], would have substantial benefits at the population level according to economic modeling [35]. It is anticipated that the majority of students in the year group of participating schools will take part in the study, based on participation rates found in previous school-based trials conducted by the research team [36-39]. To account for school dropouts during the trial, which are expected to be approximately 10% based on similar previous school-based trials [40], this study will recruit 14 schools (with at least 840 students).

Procedure

Inclusion and Exclusion Criteria

Eligible participants will be all year 9 or year 10 students (aged approximately 14-15 years) attending participating schools that own a smartphone. Providing smartphones or laptops to study participants with technological barriers was not possible because of time and budget constraints. Mobile and internet literacy will be assumed. Students will be required to provide active informed consent, and only students with active parental consent will be eligible to participate.

Recruitment of Schools

A random selection of independent and public schools across the NSW Greater Sydney Area (Greater Capital City Statistical Area, 1 Greater Sydney) [41] will be approached through publicly available contact details. The study will be advertised through the researchers' networks and the Matilda Center's social media sites. Schools that took part in focus groups for feedback on mobile app development, as part of the Mind your Mate Development Study (University of Sydney Ethics Approval 2019/723) will also be approached. School principals will be sent an invitation letter via email outlining the aims of the study and seeking permission to implement the study in their school. Schools will then be followed up through phone calls by the research team.

Schools principals who consent to their school taking part will be asked to identify an appropriate staff member and inform the research team on how to liaise with this staff member with regard to the trial.

Randomization

Following the school principal's approval, randomization and stratification according to gender will be conducted by a biostatistician external to the research team using the blockrand function in R (R Core Team). The school gender mix for stratification will be coeducational, predominately male, or predominately female, and the threshold for predominately male or predominately female will be at >60%. Half of the schools (n=7) will be randomly allocated to the Mind your Mate intervention condition and half (n=7) to an active control group (health education as usual). Similar to school-based interventions of this kind, students and teachers will not be blinded to intervention allocation.

Informed Consent

Participating schools will be asked to send information and active (opt-in) consent forms to parents or guardians of year 9 or year 10 students via hard copy or electronically. Students who receive parental consent will be provided with a web-based participant information statement and consent form and will be required to actively consent before beginning the study. Students who do not consent or who do not receive parental consent to participate in the research trial will still be offered access to the content of the program; however, they will not be prompted to complete assessment surveys, and no data will be collected from those individuals.

Intervention

Overview

The Mind your Mate intervention was collaboratively designed by young people and experts in mental health and substance use prevention. Focus groups were conducted with year 10 students (n=23) from 2 independent secondary schools in Sydney to inform them of the critical components of the development of the mobile app and design. The Matilda Centre's Youth Advisory Board, a group of young adults who provide feedback on youth-focused projects, guided the initial development and design of the app. Furthermore, each educational module within the app was reviewed by 2 psychologists with expertise on mental health and substance use. The wide range of input from a variety of ages and backgrounds was intended to ensure that the intervention is inclusive and tailored to the needs of adolescents.

Mind your Mate is an mHealth program aimed at upskilling and empowering adolescents to better support their peers about issues on mental health, alcohol, and other drug use. The intervention will include 1 introductory classroom lesson, led by a teacher but delivered on the web, and a downloadable mobile app. It is anticipated that the app will be made available to schools free of charge following the intervention.

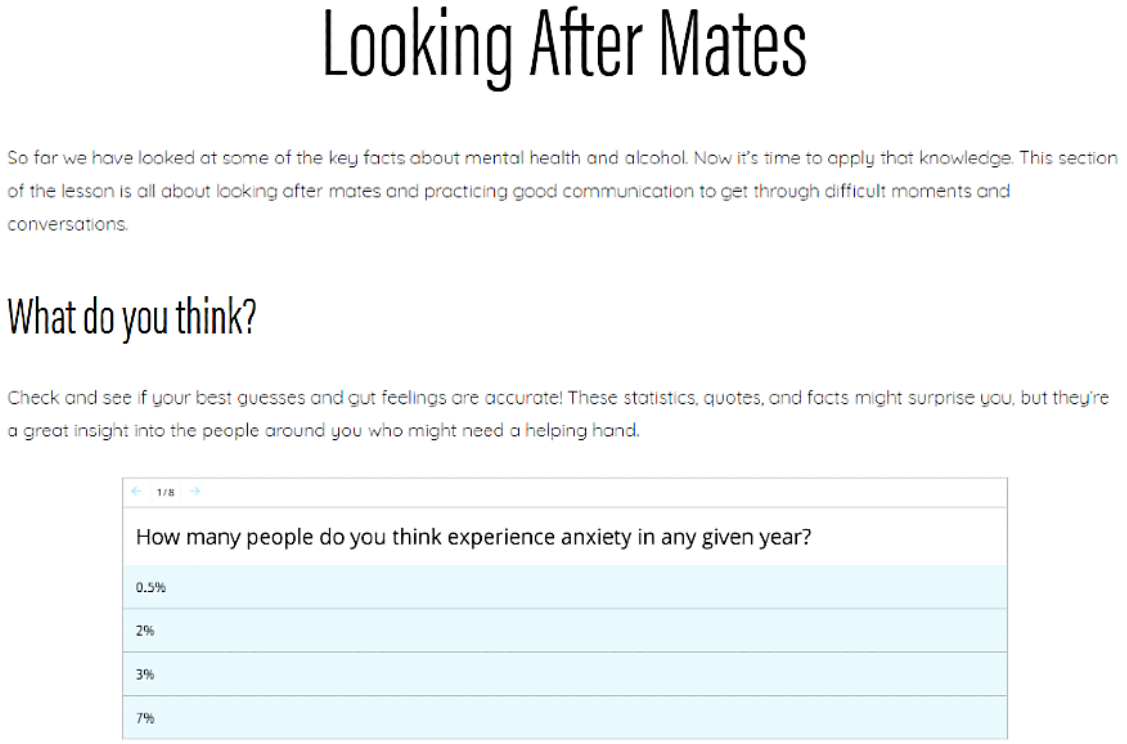
Classroom Lesson

The Mind your Mate classroom lesson will be web-based through the study website by teachers of the participating schools. Teachers will be provided with an implementation guide containing instructions for accessing the survey, classroom lessons, and an outline of the content links to the NSW Personal Development, Health, and Physical Education Syllabus.

The classroom lesson will take approximately 40 minutes to complete and will be conducted after the students have completed the baseline survey. The lesson introduces common mental health and substance use problems encountered by young people and discusses the concept of supporting peers through animated examples, quizzes, and interactive activities (Figure 2 for example screenshots of these components). The lesson

concludes with a video tour of the app's features and instructions for students to download the app onto their mobile device. Students were instructed to use the mobile app as needed over the following 12-month period.

Figure 2. Screenshot of the Mind your Mate classroom lesson.



Mobile App

The Mind your Mate app aims to facilitate discussions among peers and provide key mental health literacy information about anxiety, depression, and substance use (Figure 3). It provides communication tools, educational modules, and suggested activities to engage in conversations and provide support for peers, including the ability to schedule conversations, follow-up, and example messages to send to peers. Several features were included to maintain engagement with the app based on feedback from the focus groups. These included emphasis on visual content such as infographics and videos rather than text, user experience customization through avatar selection and color scheme, gamification of content, and interactive features such as mood tracking and customized self-care activities. Automated pop-up reminder notifications were programmed to maintain their engagement. The reminders appear on the user's phone home screen and are related to scheduled conversations with friends and the completion of the education modules. Digital metrics will be collected to measure engagement with the app, including uptake, frequency of usage, time spent in the app, and the features and modules that were accessed.

An overview of the Mind your Mate app content is provided in Table 1. The app is self-paced and only accessible to the participants in the intervention group in this study. Within the app, it is emphasized that students are not responsible for their friends or their friends' choices. Students are encouraged to contact a responsible adult or health professional if they are concerned about their friends. Crisis helpline numbers are easily accessible on the home screen and under support options.

Figure 3. Screenshot of the Mind your Mate mobile app.

Table 1. Overview of the educational module content of the Mind your Mate smartphone app.

Module name	Key content covered	Related features
Mental health	• Anxiety and depression literacy	• Animated videos featuring personal stories • Symptom diagrams • Myth buster
Stressful times	• Management of well-being • References to COVID-19 pandemic and bushfires	• Links to trusted external resources for self-help and emergencies
Alcohol and drugs	• Substance use literacy, normative use, and standard drinks	• Animated videos • Symptom diagram • Quiz question • External link to standard drinks calculator
Listen up	• Active listening skills • Tips and tools to start conversations with friends	• Scheduling conversations that link directly into calendar • Example text to send to friends
Keeping friends safe	• Harm minimization for substance use and supporting disclosure to parents or professionals	• Recovery position diagram • Video challenging fears of responsibility for a mate • Harm minimization and emergency response video
Tricky conversations	• Active questioning, motivational interviewing, and communication skills	• Conversation preparation checklist and template • Template messages to send to friends when reaching out • Emotion dictionary
Checking in	• Following up with friends and conversation tips	• Scheduling follow-up conversations with friends directly into calendar • Support links • Profiles for friends to reference upcoming and past conversations
What next?	• Challenges notion of having sole responsibility for another's well-being and supporting disclosure to parents or professionals	• Template to review conversation with friend • Interactive checklist • Textbox for reflection
Support options	• Provision of formal and informal support options such as school counsellor, parent, free web-based resources, and general practitioners	• Template messages to send to friends when reaching out • Links to trusted external educational sites, resources, and support
Looking after yourself	• Self-care • Emotion regulation skills	• Personalization of self-care activities list • Ability to add custom activity • Mood tracker

Active Control Group

Control schools will be asked to continue to implement their usual health and physical education classes for the 12-month trial period. The year 9 and year 10 Health and Physical Education curriculum mandates that content on alcohol and other drug use and well-being be implemented. As such, all control schools will implement curriculum-based health education during the trial. This group will serve as the *active control*. Although no app component will be offered to control schools during the trial, complimentary use of the intervention at the end of the study, if effective, will be available.

Assessment Occasions

All students (intervention and control conditions) will be asked to complete a web-based self-report survey in a supervised classroom setting at baseline and 6 and 12 months after baseline. Students completing web-based surveys will be assigned a unique participant identifier generated in REDCap (Research Electronic Data Capture; Vanderbilt University), a secure web-based data collection system. This identifier will be used to email students with personalized survey links that they will use to complete each survey. This unique code links student data over time while maintaining confidentiality. Absent students will be contacted by the research team (using details provided upon registration) and invited to complete the survey at a later date. Students will be made aware that all the contact information they provide will be kept strictly confidential and secure, separate from their survey responses. After each survey, students will be incentivized with entry into a draw for 1 of 5 Aus $50 (US $38) Prezzee gift vouchers (5 vouchers per assessment occasion).

Measures

Overview

Demographic data, including age, sex, gender, home postcode, and country of birth, will be obtained to determine the baseline equivalence of the groups. To assess academic performance, students will nominate the range that their grades usually fall into (ie, <49%, 50%-59%, 60%-69%, 70%-79%, 80%-89%, and 90%-100%). Truancy will be measured by students reporting the number of days that they had off from school in the previous year without their parents' permission.

Primary Measures

Knowledge

Mental health and substance use knowledge specific to content within the mobile app will be assessed using a questionnaire developed by the research team (Multimedia Appendix 1). General mental health literacy will be assessed using questions adapted from the Mental Health Literacy Questionnaire [42].

Alcohol and Other Substance Use

Drinking behavior in the past 6 months will be assessed by using questions adapted from the School Health and Alcohol Harm Reduction Project Patterns of Alcohol index [43] and reflect those used in previous trials the team has led [44]. Students will be asked to report the frequency and quantity of alcohol consumption in standard drinks, proportion of friends who drink, and intentions to try alcohol. A pictorial standard drink chart will be supplied within the survey to assist students in identifying what constitutes a standard drink in common portions and the types of alcohol [45].

The reasons for not drinking alcohol will be assessed using the Motives for Abstaining from Alcohol Questionnaire [46]. Students will be asked to rate how important each statement is to them personally, with response options ranging from *not at all important* to *extremely important*.

Other substance use will be assessed using questions adapted from the Australian Institute of Health and Welfare: National Drug Strategy Household Survey [47]. Students will be asked to indicate whether they have ever tried tobacco, vaping, cannabis, ecstasy, cocaine, or methamphetamines; the nonmedical use of prescription drugs; or a combination of drugs at the same time. Students will further be asked how likely it is that they will try any of the listed drugs in the future and the proportion of friends and acquaintances who use drugs.

Mental Health Measures

Psychological distress in the past month will be assessed using the Kessler 6 scale [48]. Depression and anxiety symptoms during the past 2 weeks will be measured using the Patient Health Questionnaire 8 [49] and the Generalized Anxiety Disorder 7-item scale [50], respectively.

Help-Seeking Measures

The General Help-Seeking Questionnaire [51] will be used to assess future help-seeking behavioral intentions from various sources. A list of potential sources of help will be shown. Students will first be asked to indicate how likely it is that they would seek help from each of these sources for personal or emotional problems, then how likely it is that they would seek help from each of these sources if they were experiencing suicidal thoughts. Responses will be given using a 7-point scale ranging from *extremely unlikely* to *extremely likely*.

Recent help-seeking behavior in the past 2 weeks will be measured using the Actual Help-Seeking Questionnaire [52] and questions adapted from the Mission Australia Report, 2018 [53]. Students will be asked to indicate whether they have sought help from a list of sources in the past 2 weeks. If they select *yes*, they will be asked to briefly describe the type of problem that they sought help for.

Secondary Measures

Positive Well-being

The impact of the intervention on positive well-being will be assessed using measures adapted from the Warwick-Edinburgh mental well-being scale [54]. Students will be asked to read three statements, such as "I have been feeling good about myself," and tick the response that best reflects their experience of that statement in the past 2 weeks. Response options range from *none of the time* to *all of the time*.

Quality of Life

The Pediatric Quality of Life questionnaire [55] will be used to measure participants' self-reported quality of life. Students will be asked to complete the questions from the perspective of their own health that day, such as "I don't feel worried today."

Impact of COVID-19 Pandemic

The impact of the COVID-19 pandemic on physical and mental health will be assessed using measures adapted from the Australian National COVID-19 Mental Health, Behaviour and Risk Communication Survey [56].

Fidelity and Implementation Log

Students in the intervention group will be asked to provide feedback on their experience and the use of the mobile app, as well as suggestions they may have for improvement, at the 6- and 12-month follow-up occasions. In addition, one teacher at each participating school will be asked at the 12-month follow-up to complete a logbook documenting any additional mental health or alcohol and drug education that was implemented over the course of the study. The logbook will be used to control for the effects of additional well-being programs. Digital metrics of mobile app engagement will also be collected.

Statistical Analysis

Analyses will use an intention-to-treat approach, including all available measurements for all students, in the groups in which they were randomized. Baseline equivalence and attrition between groups will be examined using single-level analyses, one-way analyses of variance to examine normally distributed data, chi-square analyses to examine binominal data, and Mann-Whitney *U* tests to examine nonnormally distributed data. The baseline data of the primary outcomes will be used as covariates to ensure that any differences between groups at baseline are accounted for. To examine intervention by time interaction–effects, mixed-effects regression will be used

because of the multi-level nature of the data (students nested within schools). Hypothesized intervention effects will primarily be examined using mixed-effects linear regression analyses for normally distributed data and mixed-effects logistic regression analyses for categorical data. Bonferroni adjustments will be made for multiple comparisons where appropriate. Multiple imputation and regression weighting strategies will be used to examine the impact of attrition. Sensitivity analyses will be used to assess the effect of attrition on inferences drawn from the target parameters in the statistical analyses**.**

Results

This study was funded by an Australian Rotary Health Bruce Edwards Postdoctoral Research Fellowship from 2019 to 2022. Some of the development costs for the Mind your Mate intervention came from a seed funding grant from the Brain and Mind Centre, The University of Sydney. The enrollment of schools began in July 2020, with 12 of 14 schools enrolled at the time of submission. Baseline assessments are currently underway, and the first results are expected to be submitted for publication in 2022.

Discussion

Principal Findings

This protocol outlines the design of a cluster RCT to evaluate the effectiveness of an mHealth peer intervention for preventing mental health symptoms and alcohol and other drug use and promote help seeking and knowledge among adolescents. To our knowledge, the proposed intervention is the first peer-prevention program delivered via a mobile app facilitated through the school system. If effective, it has the potential for widespread implementation at a relatively low cost, as it uses a delivery method that is both acceptable and easily accessible to adolescents.

Strengths and Limitations

The key strengths of the proposed effectiveness study are the intervention's focus on fostering peer support among adolescents and the use of digital technology. The principle of peer support embedded within the intervention aims to strengthen and foster adolescents' social connections both within their peer groups and with trusted adults. Social connection is known to be a key protective factor for mental health problems [57,58]. Furthermore, help seeking for mental health, drug, and alcohol concerns has long been plagued by surrounding stigma and a lack of knowledge of relevant support services; thus, most young people do not seek support when it is needed [24,59]. The provision of easily accessible information in the Mind your Mate smartphone app that destigmatizes common mental health challenges and provides support options might help overcome some of these barriers and encourage early help seeking in adolescents. Indeed, programs aimed at reducing mental health stigma are associated with increased confidence among young people in supporting peers [27]. Future research may more closely examine the interaction between stigma and peer-based processes.

Web-based delivery and the use of a mobile app means that the intervention is easily accessible and uses a delivery platform with which adolescents are familiar and comfortable. It also provides the potential to deliver the intervention widely at a relatively low cost, as no teacher training is required. The app itself is self-paced and can be used by students in their own time, with only a short time requirement anticipated for teachers. Furthermore, the web-based mode of delivery of the intervention ensures the fidelity of high-quality information and facilitates ease of access.

Another benefit of the program is its links to existing school health and physical education curricula, meaning schools could act as key delivery partners to roll out the intervention if found to be effective. Finally, the intervention was collaboratively designed with young people, meaning it is more likely to be acceptable and engaging for young people, an important outcome not only within the context of the current trial but also for future efforts to take the program to scale.

One limitation of the study is the reliance on participant self-report to collect data for the primary outcomes of this trial. Although these were chosen due to ethical and feasibility considerations and these are standard practices in school-based trials of mental health and substance use prevention [20,60], it is possible that measures of mental health and/or substance use could be subject to underreporting or overreporting. To mitigate these effects, students are reminded of the confidentiality of their responses at each survey occasion and encouraged to be as honest as possible, thereby reducing the risk of bias or concealment. Owing to time and budget constraints, the study was unable to provide smartphones to students who did not own them. Future research may adapt the intervention to be suitable for a range of groups, including adolescents living in rural and regional areas and adolescents experiencing technology barriers such as lack of access to smartphones and computers. Furthermore, although there is some evidence that digital tools may be more effective for certain users when human support is included compared with standalone tools [61], this was beyond the scope of this study because of time and budget constraints. Future research may explore the addition of human support or check-ins for peer-led mHealth programs and their impact on outcomes and user engagement. Finally, given the age of the students in the study (14-15 years old), we may be limited in our ability to assess change in substance use over the period of the trial, as the proportion of students using substances at this age may be small and typically tends to increase in later adolescence. Nonetheless, the Mind your Mate intervention was developed as a prevention approach because of the importance of early intervention, before thoughts and behaviors have become entrenched.

Conclusions

The development of a novel mHealth tool for young people to support their peers and improve their own mental health represents an innovative applied approach to the prevention of mental disorders in a real-world setting. If effective, the intervention is low cost and will link to the existing high school syllabus, with the potential for widespread implementation and significant impact.

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Authors' Contributions

LB, NCN, and CC conceptualized and designed the study and obtained funding for the study. AFB and LB obtained ethical approval for the study and were responsible for recruitment and follow-up. LB, AFB, CC, and NCN drafted the manuscript, and all authors approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
App-specific knowledge questionnaire.
[DOCX File , 26 KB - resprot_v10i7e26796_app1.docx]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
mHealth: mobile health
NSW: New South Wales
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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Protocol

Investigating the Mechanisms of Graded Sensorimotor Precision Training in Adults With Chronic Nonspecific Low Back Pain: Protocol for a Causal Mediation Analysis of the RESOLVE Trial

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Abstract

Background: Chronic low back pain (CLBP) is a global health problem associated with an increasing burden on individuals, health care systems, and society. Common treatments for people with CLBP produce, on average, small short-term improvements in pain and function compared with minimal care. The RESOLVE trial randomly allocated 276 people with CLBP to a new complex treatment strategy, pain education integrated with graded sensorimotor precision training (RESOLVE), or a sham control. The RESOLVE treatment was developed within a theoretical framework to target possible treatment mechanisms associated with CLBP development and persistence.

Objective: This protocol describes the planned evaluation of these proposed treatment mechanisms. Improved understanding of the mechanisms underpinning the RESOLVE treatment may guide its refinement and implementation.

Methods: We will use causal mediation analysis to evaluate the proposed treatment mechanisms, including pain self-efficacy, back beliefs, pain catastrophizing, kinesiophobia, back perception, tactile acuity, and movement coordination. The primary outcomes are pain intensity and function at 18 weeks following allocation. Data were collected blind to allocation and hypotheses at baseline (mediators, outcomes, confounders), end of treatment (mediators), and at 18 weeks following allocation (outcomes). We will test the robustness of our findings by conducting planned sensitivity analyses.

Results: Ethical approval was granted by the University of New South Wales Human Research Ethics Committee (HC15357). A total of 276 participants have been recruited from primary care practices and the community in Sydney, Australia.

Conclusions: The RESOLVE treatment constitutes a new paradigm for CLBP management with potentially wide-reaching implications. This mechanistic evaluation will provide evidence for the hypothesized treatment mechanisms and help explain why the treatment strategy did or did not have an effect on patient-reported outcomes. These results will help guide the treatment refinement and implementation.

Trial Registration: Australian and New Zealand Clinical Trials Registry ACTRN12615000610538; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=368619&isReview=true

International Registered Report Identifier (IRRID): DERR1-10.2196/26053

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KEYWORDS

chronic low back pain; mediation analysis; mechanism evaluation; protocol

Introduction

Low back pain (LBP) is a global health problem [1,2]. The associated personal and societal burden continues to increase, despite the increasing amount of health care resources devoted to LBP treatment [3,4]. Although many recover from a new episode of LBP, recurrence is common, and for a small proportion pain becomes persistent and significantly disabling [5-7]. Individuals who develop chronic low back pain (CLBP) have a reduced chance of recovery and experience substantial functional limitations and poor quality of life [8,9].

People with LBP perceive recovery as a complex interaction of decreased pain, improved function, and reduced symptom interference with daily life [10]. Common treatments provide mostly small short-term improvements in pain and function, when compared with minimal care [11,12]. Demand for improved treatment effects is pressing. There is a limited understanding of why common treatments are ineffective and a lack of high-quality evidence on promising new treatment targets [13]. Better evidence regarding the mechanisms of treatments can help address these problems and has been identified by pain researchers as one of the highest research priorities [14].

A clearer understanding of the biopsychosocial influences on pain has promoted the development of new explanatory models for CLBP [15] and new treatment strategies [16-19]. Accumulating evidence demonstrates structural, functional, and biochemical differences in the central nervous system between people with CLBP and people without pain [20], many of which appear related to the CLBP experience [21-23]. The RESOLVE trial is a randomized controlled trial (RCT) evaluating a new complex treatment strategy (pain education integrated with graded sensorimotor precision training) partly informed by evidence of central nervous system dysfunction against a sham control.

People with CLBP want improvements in pain and function [10], and the effects of the RESOLVE treatment on these key outcomes will be evaluated [24]. Yet these effect estimates will not elucidate the mechanisms through which the effects occurred. We present an a priori protocol for a secondary analysis of the RESOLVE trial to estimate the effects of the RESOLVE treatment on 7 proposed treatment mechanisms, and to estimate whether these mechanisms cause change in pain and function. The aim of this study is to evaluate these effects through a causal mediation analysis to guide treatment optimization and implementation.

Methods

Design

The study involves a causal mediation analysis of a 2-group participant and assessor-blinded RCT [24,25]. The RESOLVE trial was prospectively registered (ACTRN12615000610538) and approved by the University of New South Wales Human Research Ethics Committee (HC15357).

Participants

Participants were recruited from primary care practices and the community in Sydney, Australia. The eligibility criteria are comprehensively described in the trial protocol [25]. Briefly, the RESOLVE trial included people reporting nonspecific LBP [26] (intensity rated at least 3/10), with or without leg pain, that had persisted for at least 12 consecutive weeks. Participants were aged between 18 and 70, fluent in English, able to access the internet, and had a trusted person to assist with the home portion of the intervention. The RESOLVE trial excluded people with LBP due to serious pathology, and people with contraindications to physical activity, transcranial direct current stimulation, cranial electrical simulation, low-intensity laser therapy, or short-wave diathermy. Finally, the RESOLVE trial excluded people who were pregnant or had given birth in the previous 6 months, had undergone spinal surgery in the previous 12 months, were scheduled for major surgery in the next 12 months, or had an uncontrolled mental health condition that would impede participation.

Randomization

Eligible participants were randomly allocated in a 1:1 ratio to the RESOLVE treatment or the sham-control treatment. The allocation schedule was generated a priori by a scientist independent to the trial using blocked randomization. The allocations were printed and placed in 276 sealed, opaque, sequentially numbered envelopes. Participants and assessors were blind to both group allocation and study hypotheses throughout the trial and follow-up period.

Interventions

The treatments are comprehensively described in the trial protocol [25] and briefly here. Each treatment group received twelve 30-60-minute one-on-one treatment sessions with a clinician, scheduled approximately weekly over 12-18 weeks. The treatment sessions were supplemented with a home treatment component entailing 30 minutes of training 5 times per week. Concomitant interventions were allowed and recorded on a weekly treatment diary.

RESOLVE Treatment Group

The RESOLVE treatment comprised 4 treatment components delivered with a standard progression protocol. The components were pain education, graded sensory training, movement simulation training, and graded precision-focused feedback-enriched functional movement training. The intent was to help people in pain *understand* that it is safe and helpful to move, *feel* safe to move, and *experience* safety with movement as they progress toward reengagement with meaningful functional goals.

Pain education was delivered throughout the treatment period to improve the participants' understanding of pain and their CLBP problem, address maladaptive beliefs, improve engagement with treatment, and emphasize the value of movement and physical activity. The pain education was based on the *Explain Pain* model [27,28], delivered according to a standard curriculum, and individualized to the patients lived experience and CLBP narrative. The educational material was delivered by the study clinicians and included the use of graphical media, video, metaphor, and narrative [27,29,30].

Sensory precision training comprised tactile localization training, discrimination of sharp/blunt sensations, and graphesthesia training. The movement simulation component was grounded in graded motor imagery, developed for pathological limb pain [31], and included left–right recognition training using the Recognise software [32] and implicit and explicit motor imagery training using a series of custom-designed videos on low back movements.

Graded precision-focused feedback-enriched functional movement training included individualized movement training related to the patients' goals. Training progressed from part practice to whole task practice within a visual and proprioceptive feedback-enriched environment [33].

Sham Treatment Group

The sham treatment was composed of 3 treatment components to match for time and clinician interaction, individualization, and relevance [34]. These include passive discussion of the participant's back pain experience, detuned low-intensity laser therapy, and detuned short-wave diathermy. Participants also received a home training program of sham cranial electrical stimulation to control for the home training requirements of the RESOLVE treatment group.

Mediators, Outcomes, and Confounder

Overview

Patient characteristics, outcome measures, mediators, and potential confounders were assessed at baseline. Mediators were assessed again following the twelfth treatment session, approximately 12-18 weeks following allocation. Outcome measures were assessed again 18 weeks following allocation. Participants and outcome assessors were blind to group allocation and study hypotheses.

Outcomes

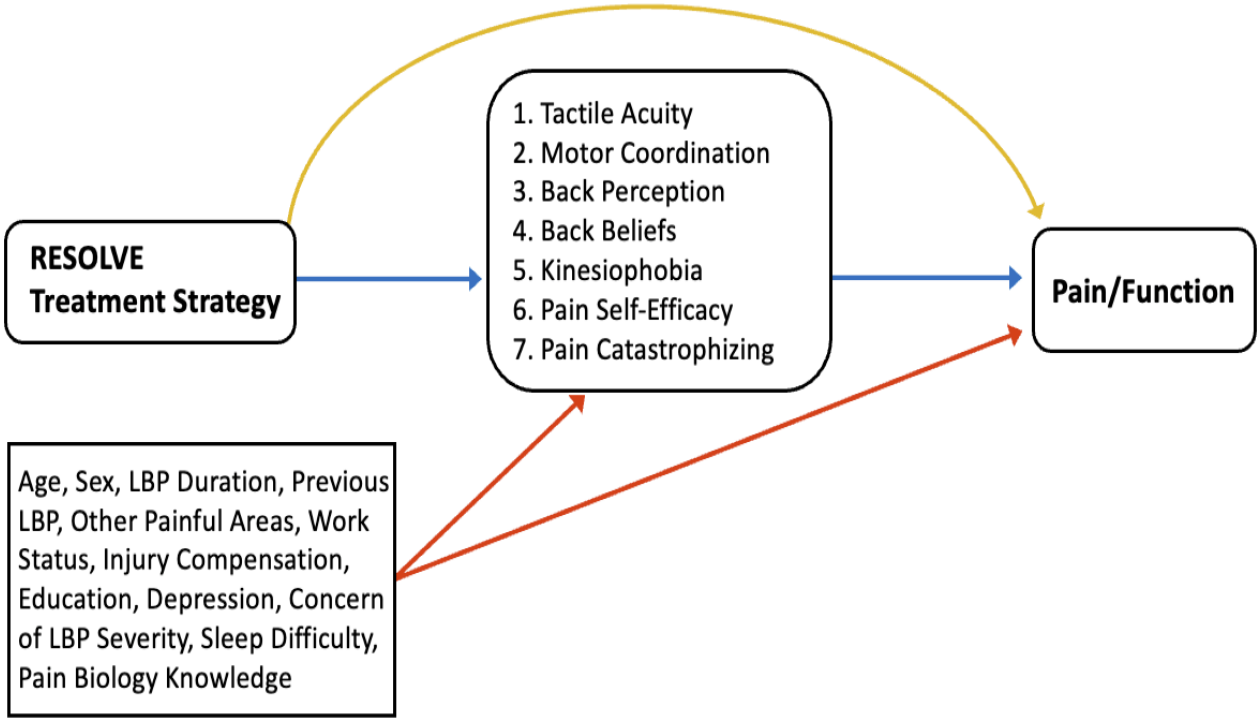
We will consider 2 primary outcome measures for this mediation study:

1. Average pain intensity over the past week, assessed using an 11-point Numeric Rating Scale (NRS; 0=no pain, 10=pain as bad as it could be) [35], considered a valid, reliable, and responsive measure of pain intensity [36].
2. Function, assessed using the 24-item Roland–Morris Disability Questionnaire [37], considered a valid and reliable measure of low back–related disability [38,39].

Mediators

We will investigate 7 hypothesized mediators. A simplified model of the hypothesized causal relationships between the effects of the RESOLVE treatment on the outcomes through the mediator(s) is presented in Figure 1.

Figure 1. Simplified causal pathways for the effect of the RESOLVE treatment on the outcomes, pain intensity and function, via the hypothesized mediators. The mediators are measured at the end of treatment. Outcomes are measured at 18 weeks after randomization. The potential confounders are measured at baseline. The diagram assumes independence of mediators. The treatment–mediator relationship is represented by the blue line from the RESOLVE treatment to the mediators. The mediator–outcome relationship is represented by the blue line from the mediators to the outcomes. The potential confounders of the mediator–outcome relationship are represented by the red lines. The direct effect of treatment on the outcome is represented by the yellow line.



The 7 mediators to be modeled are as follows:

1. Tactile acuity: measured using a digital caliper to establish 2-point discrimination thresholds over the lumbar region of most discomfort [40], considered a reliable measure of tactile acuity [41].
2. Lumbopelvic motor coordination: measured on a clinical scale assessing the ability to dissociate lumbopelvic movement from that of the thoracolumbar junction, considered a reliable measure of lumbopelvic control when assessed by an experienced clinician/assessor [42].
3. Back-specific body perception: assessed using the Fremantle Back Awareness Questionnaire (FreBAQ) [43]. The FreBAQ has 9 items, each scored on a 5-point scale (0=Never, 4=Always). The total score ranges from 0 to 36, with higher scores indicating higher body perceptual disturbance. The FreBAQ is considered a psychometrically sound method for assessing disruption of body image in people with CLBP [43].
4. Back beliefs: assessed on the Back Beliefs Questionnaire (BBQ) [44]. The BBQ has 14 items, including 5 distractors, each scored on a 5-point Likert scale (1=completely agree, 5=completely disagree). The total score ranges from 9 to 45, with lower scores indicating more pessimistic beliefs about the consequences of LBP. The BBQ is a valid and reliable measure to quantify beliefs about the consequences of LBP [45].
5. Fear of movement-related pain (kinesiophobia): assessed on the Tampa Scale for Kinesiophobia (TSK) [46]. The TSK has 17 items, each scored on a 4-item scale (1=strongly disagree, 4=strongly agree). The total score ranges from 17 to 68, with higher scores indicating greater levels of fear of movement-related pain. The TSK is a reliable and valid measurement tool that provides information on activity avoidance and pathological somatic focus [47].
6. Pain-related self-efficacy: assessed on the Pain Self-Efficacy Questionnaire (PSEQ) [48]. The PSEQ has 10 items, scored on a 7-point Likert scale (0=not confident at all, 6=completely confident). The total score ranges from 0 to 60, with higher scores indicating greater confidence in the ability to undertake activities despite pain. The PSEQ has adequate psychometric properties [49,50].
7. Pain catastrophizing: assessed on the Pain Catastrophizing Scale (PCS) [51]. The PCS has 13 items, scored on a 5-point scale (0=not at all, 4=all the time). The total score ranges from 0 to 52, with higher scores indicating an exaggerated perception of pain-related problems. The PCS is a reliable measure to assess catastrophic thoughts about pain [51,52].

Confounders

We assumed no confounding of the treatment–mediator and treatment–outcome relationships due to random allocation of treatment. We identified potential confounders of the mediator–outcome relationship using the disjunctive cause criterion [53,54]. This involved selecting measured pretreatment covariates that are hypothesized to be a cause of the mediator, outcome, or both. The minimum sufficient adjustment set includes age, biological sex, duration of LBP episode, number of previous LBP episodes, number of other painful areas, work status, injury compensation, education level, depression, concern

of LBP severity, sleep difficulty, and pain biology knowledge (refer to Multimedia Appendix 1 for details on potential confounders). We will also include pretreatment measures of the mediators and outcomes in the models [55].

Causal Mediation Analysis: Rationale

We will test the mechanisms of the RESOLVE treatment strategy for adults with CLBP by estimating the extent to which the 7 hypothesized mediators explain the effect of the treatment on the participants' pain and disability scores. Using causal mediation analysis, we will partition the total effect (TE) of the treatment into an indirect effect which operates through the mechanism(s) of interest, and a direct effect which operates through all other possible mechanisms [56,57].

The RESOLVE treatment strategy was designed around the Maladaptive Perceptions Model [58], an explanatory framework for the development and persistence of LBP that is grounded in a broad scope of literature concerning behavioral (eg, movement avoidance), neurobiological (eg, altered cortical representations), and cognitive (unhelpful and inaccurate beliefs about the biology of pain and the structural integrity of the back) characteristics of CLBP [20]. The RESOLVE treatment integrates contemporary understandings of pain with known features of best practice care to address the biopsychosocial contributors to the CLBP experience, including maladaptive conceptualizations of the pain problem [59-61], altered sensory function [62,63], altered motor function [64-68], and altered self-perception of the back [43].

While the causal mechanisms that underpin improvement or recovery from CLBP are not well established [13], the Maladaptive Perceptions Model [58] proposes several intermediary variables through which effects might occur. These are cognitions about the back, pain, and movement [69]; back-specific body representations [43]; fidelity and weighting of sensory information from the back [70,71]; and spinal control, movement coordination, and functional tolerance for meaningful activities [33,72]. Components of the RESOLVE treatment were designed to target these factors alongside pain and function.

We have chosen the proposed mediators, pain self-efficacy, back beliefs, pain catastrophizing, kinesiophobia, back perception, tactile acuity, and movement coordination, based on theoretical predictions from the Maladaptive Perceptions Model [58] and the results of pilot studies [33,69-71,73,74].

Effects of Interest

We will estimate the effect and corresponding uncertainty for the treatment–mediator relationship. This is the average unstandardized effect of the RESOLVE treatment on each independent mediator, compared with sham control. We will also estimate the effect and corresponding uncertainty for the mediator–outcome relationship. This is the average unstandardized effect of the mediator on the outcome (Figure 1).

If inference is considered feasible given the causal assumptions, we will also estimate natural (in)direct effects of the RESOLVE treatment on the outcomes considering (1) the mediators independently, while assuming independence of the mediators, and (2) the mediators simultaneously as a joint mediator.

Causal Model

The identification of natural (in)direct effects relies on several strong and untestable causal assumptions including (1) no treatment–outcome confounding, (2) no mediator–outcome confounding, (3) no treatment–mediator confounding, and (4) no mediator–outcome confounder that is itself affected by the treatment [75]. Adjustment for a sufficient set of observed confounders and correct specification of the statistical models may provide sufficient conditions to identify mediation effects and causal interpretation [76]. Assumption (4) may not hold because there are possible causal relationships between mediators. We will also assess the mediators simultaneously as a joint mediator which relies on weaker assumptions for identification [77,78]. The causal model is presented in Figure 1.

Statistical Analysis

Analyses will be performed in R (version 3.6.1; R Foundation for Statistical Computing) [79]. We will use the "mediation" package [80] to estimate independent mediated effects and the "medflex" package [78] to estimate joint mediated effects.

We will estimate effects for the treatment–mediator and mediator–outcome relationship with 2 regression models: the mediator model and the outcome model. We will specify the mediator model as a linear regression of the mediator (dependent variable) on treatment allocation and baseline values of the mediator. The outcome model will be specified as a linear regression of the outcome at 18 weeks (dependent variable) on the mediator at baseline and follow up, treatment allocation, and possible confounders of the mediator-outcome relationship, and a treatment allocation x mediator interaction term. We will also include an interaction term (treatment allocation × mediator) in the outcome models to increase model flexibility [57].

Independent Mediated Effects

A model-based inference approach developed by Imai et al [81] will be used to estimate independent mediated effects for each mediator. We will use the "mediate" function [80] to compute the average treatment effect, the average causal mediation effect (ACME), and the average direct effect (ADE). We will use 1000 bootstrapped simulations to estimate 95% CIs. We will interpret conditional estimates of the ACME and ADE separately if there is evidence for a significant (P<.05) intervention–mediator interaction. If there is no evidence for an interaction, we will interpret the average of the conditional effects for the ACME and ADE.

Joint Mediated Effects

An imputation-based approach using a class of natural effect models introduced by Lange et al [82] and Vansteelandt et al [83] will be used to estimate the joint mediated effect of all mediators simultaneously. We will use the "neModel" function [78] to compute the natural indirect effect (NIE), natural direct effect (NDE), and the TE. We will use 1000 bootstrapped simulations to estimate 95% CIs.

Missing Data

We will assess the proportion and patterns of missing mediator and outcome data. We will conduct all analyses on complete cases if the proportion of missing data is less than 15% for all variables in a given model. If missing data exceed 15%, we will impute missing data through multiple imputation by chain equations using the "mice" package [84] in R.

Sensitivity Analyses

We will conduct sensitivity analyses to determine the robustness of the estimated ACME to bias introduced by unmeasured pretreatment confounding in the independent mediated effect models [85]. We will use the "medsens" function [80] to estimate the magnitude of residual confounding that would cause the point estimate of the ACME to reach 0. The level of residual confounding is represented by the correlation between the residuals (error terms) in the mediator and outcome models, denoted ρ. By estimating the ACME, including point estimates and 95% CIs, at all possible levels of ρ (between the extremes of –1 and +1), we can determine how strong the effects of residual confounding would need to be to reduce the ACME to 0 (ie, no mediating effect).

We will conduct a sensitivity analysis to determine the robustness of the estimated NIE and NDE to possible unmeasured confounding in the joint mediated effect model [85]. The mediational E-value [86] will be used to assess the minimum strength of the relationship between an unmeasured confounder and the mediator, conditional on measured confounders, that would reduce the NIE and NDE to 0. A comparatively large E-value in relation to known confounders implies that considerable unmeasured confounding would be required to reduce the NIE and NDE to 0. A comparatively small E-value implies that little unmeasured confounding would be required to reduce the NIE and NDE to 0. We will use the "EValue" package [87] in R to estimate the mediational E-value.

If appropriate, we will conduct a sensitivity analysis to assess possible violations to the temporal ordering of the mediator–outcome relationship, excluding participants for whom the mediators and outcomes were assessed concurrently at 18 weeks.

Secondary Analyses

If there is evidence of a mediator–outcome effect, we will investigate the magnitude of change required in the mediator(s) to produce a minimally clinically important difference (MCID) in pain intensity (of 1 point out of 10) [88] and disability (of 2 points out of 24) [89].

Ethics Approval and Consent to Participate

The University of New South Wales Human Research Ethics Committee granted ethical approval (HC15357), and all participants provided written informed consent to participate.

Results

A total of 276 participants have been randomized into the RESOLVE trial. Follow-up data collection is underway with authors blind to study data.

Discussion

We present an analysis plan for a mechanism evaluation of a new complex treatment strategy combining pain education and graded sensorimotor precision training (RESOLVE), when compared with a sham treatment in people with CLBP. The RESOLVE treatment constitutes a new paradigm for CLBP management with potentially wide-reaching implications. This mechanism evaluation will provide evidence for the hypothesized treatment mechanisms. If the treatment is effective, this investigation will help explain how the treatment worked, and if the treatment is ineffective, it will help explain why the treatment did not work. These results will help adapt and refine the treatment and guide future implementation strategies.

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a European CRPS minimum standards of care summit. GLM has received support from Kaiser Permanente (USA); workers' compensation boards in Australia, North America, and Europe; Noigroup Australasia; the International Olympic Committee; Arsenal Football Club; and the Port Adelaide Football Club. The aforementioned funding bodies and organizations had no role in the conception or writing of the manuscript and there are no other relationships or activities that could appear to have influenced the submitted work.

Authors' Contributions

All authors contributed to the overall design of the study and are involved in the ongoing management of the trial. JM, BW, GLM, and TS procured funding. All authors contributed to developing the intervention and data collection protocols and materials, and reviewing, editing, and approving the final version of the paper. AC drafted the manuscript, and all authors subsequently contributed to the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

GLM receives royalties for books upon which some of the resources in the RESOLVE trial are based. GLM had no role in data collection and will have no role in data analysis. There are no other conflicts to declare. BW receives speakers' fees for talks on pain and rehabilitation.

Multimedia Appendix 1
Potential confounders.
[DOCX File , 17 KB - resprot_v10i7e26053_app1.docx]

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Abbreviations

ACME: average causal mediation effect
ADE: average direct effect
ATE: average total effect
BBQ: Back Beliefs Questionnaire
CLBP: chronic low back pain
FreBAQ: Fremantle Back Awareness Questionnaire
LBP: low back pain
MCID: minimally clinically important difference
NDE: natural direct effect
NIE: natural indirect effect
NRS: Numeric Rating Scale
PCS: Pain Catastrophizing Scale
PSEQ: Pain Self-Efficacy Questionnaire
RCT: randomized controlled trial
TE: total effect
TSK: Tampa Scale for Kinesiophobia

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Protocol

The Efficacy of the Dyson Air Purifier in Improving Asthma Control: Protocol for a Single-Center, Investigator-Led, Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Background: Indoor air quality has been shown to influence asthma control and outcomes. Air purifiers and high-efficiency particulate air filtration devices can improve indoor air quality by reducing the indoor levels of air pollution and allergens. However, the influence of this improved indoor air quality on asthma control remains unclear; hence, randomized controlled trials are needed to further elucidate this phenomenon.

Objective: This study aims to investigate the effect of reducing the levels of allergens and pollutants in the bedroom and living room through the use of Dyson air purifiers (Dyson Pure Cool) on asthma control.

Methods: This is an 18-month long, investigator-led, randomized, double-blinded, placebo-controlled, single-center trial. Subjects will be randomized in a 1:1 ratio to active or placebo Dyson filters. The primary outcome is the change in the scores of Asthma Control Questionnaire 6 and Asthma-specific Quality of Life Questionnaire from baseline. Secondary outcomes include changes in lung function (forced expiratory volume in one second, forced expiratory volume in one second/forced vital capacity ratio, and midexpiratory flows), peak expiratory flow measurements, airway hyperresponsiveness (assessed by methacholine bronchial challenge), fractional exhaled nitric oxide, and indoor air pollutant levels. The sample size will be 50 subjects, and all subjects will have a confirmed diagnosis of mild persistent to moderate persistent asthma along with an Asthma Control Questionnaire 6 score of >1.5.

Results: This study was approved by the West Midlands Research Ethics Committee (18/WM/0277). The study results will be published in peer-reviewed scientific journals; presented at relevant scientific conferences; and shared in plain English with participants in our newsletters, in our clinics, and via the David Hide Asthma and Allergy Research Centre website. Our trial began in September 2019 and is expected to end in August 2021.

Conclusions: This is a double-blinded, placebo-controlled, randomized, investigator-led study to investigate the efficacy of a novel air purifier in improving asthma control in adults. The trial period of 18 months will facilitate the collection of robust data and will therefore generate clear signals. However, this extended trial duration may lead to patient withdrawal. Furthermore, this trial is conducted at a single center and in a location with a homogenous cohort of people, which may affect translatability. Nonetheless, it is hoped that the findings of this trial may help further inform clinicians regarding the utility of this novel device as an adjunct in asthma care.

Trial Registration: ClinicalTrials.gov NCT04729530; https://clinicaltrials.gov/ct2/show/NCT04729530

International Registered Report Identifier (IRRID): DERR1-10.2196/28624

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KEYWORDS

air purifier; asthma; clinical trial; air pollution; allergens; respiratory function tests; bronchial provocation tests

Introduction

Background

The last few decades have been witnessing an ongoing *asthma epidemic*, whereby there is an increasing prevalence of asthma in the Western world and beyond [1]. The precise cause of this phenomenon is not fully understood, but it has coincided with changes in the quality of indoor air, which contains increased levels of allergens and pollutants [2]. The indoor environment contains other biological materials (such as microbiome and endotoxin) and pollutants (gases and particulate matter [PM]), which can adversely affect the development and morbidity of asthma [3]. Indoor pollutants also include smoke from cigarettes and wood, coal or gas fires, particulate materials associated with biofuel combustion, chemical vapors, gases including nitrogen dioxide (NO_2), formaldehyde, and volatile organic compounds (VOCs). The latter may come from sources such as building products, cleaning agents, and paints. One such VOC is formaldehyde, which can irritate both the upper and lower respiratory tracts [4]. Small PM (PM2.5) is particularly damaging as it penetrates the small airways of the lungs and may even enter the bloodstream. Major indoor sources of NO_2 and PM include gas stoves and cigarette smoke, but outdoor sources such as traffic and industrial pollution can also contaminate the indoor environment [5]. Among the indoor allergens, bedroom exposure to dust mite has been linked to worsening asthma symptoms and increased bronchial responsiveness [6]. In places where dust mites cannot thrive, allergens from cats, cockroaches, and Alternaria assume importance [7]. High indoor temperatures and humidity may increase the allergenic burden, particularly the proliferation of house dust mites and molds [7]. Therefore, modern living conditions are associated with a higher risk of allergen exposure, which causes an increase in the sensitization and symptoms of asthma.

It has also been suggested that exposure to pollutants can potentiate the effects of allergens [8]. Indeed, a combination of high levels of indoor pollution and allergens is related to the development and severity of asthma [9]. Allergens, microbiome, and pollutants can interact with each other to augment the immune response, further leading to harmful effects on the airways [10,11].

Thus, indoor air pollution (both chemical and biological) is a considerable environmental trigger for the acute exacerbation of asthma, which leads to increasing symptoms, emergency department visits, hospital admissions, and even mortality [3,9,12]. Therefore, maintaining a high air quality with lower levels of allergens and pollutants is important for improving the health of individuals with asthma and other respiratory diseases. A feasible and practical intervention that can reduce allergen and pollutant levels in indoor air should reduce morbidity and improve asthma control.

The National Institute of Health, United States, recently convened a workshop to examine the current status of the indoor environment in improving asthma control [9]. The workshop concluded that apart from the replacement of gas stoves with electric stoves and avoidance of indoor smoking, few methods are currently available for reducing indoor NO_2 and possibly other pollutants. Technological improvements have been made in improving the efficacy of high-efficiency particulate air (HEPA) particle filtration devices that are designed to remove the targeted indoor air pollutants, such as fine PM (PM2.5) [13]. Some studies have demonstrated a positive effect of using an air cleaner with HEPA and carbon filters on asthma symptoms [14-16]. Although most studies using air purifiers have shown a reduction in gases and PM, the overall effect on asthma control remains uncertain. Allergen reduction intervention studies have reported inconsistent results [10]. Therefore, novel intervention strategies are needed to reduce both allergens and pollutants in the indoor environment to the extent that can improve asthma control and reduce airway inflammation and hyperresponsiveness. Recently, nocturnal temperature–controlled laminar airflow technology has been investigated for treating atopic asthma with some benefits [17]. It has been suggested that this strategy of reducing indoor exposure to allergens and pollutants might be cost-effective [18]. However, this result was not observed in a recent large randomized controlled trial investigating this technology [19].

Objectives

The purpose of this study is to investigate the effects of reducing the levels of allergens and pollutants in the bedroom and living room, via a novel HEPA air purifier, on asthma control. Specifically, this study aims to investigate whether placing novel Dyson Pure Cool Towers [20], which have additional purification functions, in the bedroom and living room of subjects with asthma will improve their asthma control. The study hypothesizes that the addition of the Dyson air purifier to the standard treatment will improve asthma control, as assessed by the Juniper Asthma Control Questionnaire 6 (ACQ6) score [21], and improve the quality of life, as assessed by the Juniper Asthma-Specific Quality of Life Questionnaire (AQLQ) score [22], as a result of reducing indoor allergen and pollutant levels.

Methods

Study Design

This is an investigator-led, single-center, double-blinded, placebo-controlled, randomized controlled trial, with a 1:1 randomization ratio to an active or placebo filter. The David Hide Asthma and Allergy Research Centre (DHAARC), Isle of Wight National Health Service Trust, Isle of Wight, United Kingdom, will serve as the study site.

Sample Size

As the trial will be using a novel intervention, the estimates of effect size are not available for a sample size calculation. However, other studies have shown that clinical response can be demonstrated using a HEPA filter with as few as 15

participants in each group [16]. Hence, we decided on a sample size of 25 in each group, which is likely to indicate whether the Dyson air purifier improves asthma control.

Participants

We plan to recruit 50 participants from the David Asthma and Allergy Centre outpatient asthma clinics and primary care health centers, according to the inclusion and exclusion criteria (Textbox 1). All participants will be provided with oral and written information and adequate time to consider study enrollment. Written informed consent will be obtained by the research team.

Textbox 1. Inclusion and exclusion criteria.

Inclusion Criteria

- Participants aged between 18 and 75 years with a confirmed diagnosis of mild persistent to moderate persistent asthma (defined as: British Thoracic Society guidelines [23] steps *regular preventer therapy* to *additional add-on therapies*).
- Juniper Asthma Control Questionnaire 6 score >1.5.
- Participants must be able to provide written informed consent.

Exclusion Criteria

- Participants with significant chronic respiratory diseases, such as chronic obstructive pulmonary disease or bronchiectasis.
- Participants with any severe disease (such as cardiovascular disease or dementia) because of which adherence to the study protocol may induce unjustified stress.
- Participants who are being treated with allergen-specific immunotherapy.
- Participants with a history of significant alcohol or drug abuse.
- Participants who are taking an investigational drug for asthma.
- Participants who were unwilling, unlikely, or unable to comply with the study protocol, as assessed by the study team members.
- Participants who were likely to be started on biological therapies for asthma (omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab) during the study period.
- Pregnancy.
- Participants already using air purifiers in their dwellings.
- Participants planning to shift from their houses during the study period.

Intervention

The intervention studied will be the Dyson Pure Cool Tower, which will be installed in the living room and bedroom of study subjects. Dyson purifying fans sense particulates (PM10 and PM2.5) and gases (VOC and NO_2) and capture pollution (HEPA filtration 99.95% PM0.1 and Tris-impregnated carbon granules to capture gases such as formaldehyde, benzene, and NO_2). Then, they disperse purified air throughout the room through forward projection [20]. Study subjects can withdraw at any point and can continue to use their regular asthma medication.

Primary Outcomes

The primary outcomes are changes in ACQ6 and AQLQ scores from baseline. A change in ACQ6 (≥0.5) score on a 6-point scale is considered the minimal important difference, whereas a change in AQLQ score of ≥0.5 on a 7-point scale is considered clinically important.

These questionnaires have been extensively validated and are commonly used in asthma research for measuring asthma control and quality of life.

These standardized questionnaires will be delivered over the telephone, by post, or in person during center visits.

Secondary Outcomes

The secondary outcomes are as follows: (1) changes in airway responsiveness (assessed by methacholine bronchial challenge) from baseline, (2) changes in the indoor levels of pollutants (as measured by the Dyson purifier) from baseline, (3) changes in lung function assessed via spirometry (forced expiratory volume in one second [FEV_1], FEV_1/forced vital capacity [FVC] ratio, and midexpiratory flows) from baseline, (4) changes in peak expiratory flow (PEF) measurements from baseline, and (5) changes in airway inflammation (fractional exhaled nitric oxide levels [FeNO]) from baseline.

Spirometry

Spirometry will follow the American Thoracic Society guidelines [24] to ensure validity and reproducibility. As per the guidelines, the highest of three FEV_1 measurements within 5% of each other will be used. We will record FEV_1, FVC, MEF, and PEF values in liters and their values percent predicted for age, height, sex, and ethnic origin. The forced expiratory ratio (FEV_1/FVC) will also be calculated.

Bronchial Hyperresponsiveness

Bronchial challenge will be performed using methacholine as the stimulant [25]. Methacholine will be prepared according to a prespecified protocol using a checklist that follows a specific

standardized operating procedure consistent with the European Respiratory Society's technical standards [26]. A safety checklist will be completed before each participant performs a bronchial challenge. The test will then be conducted according to the aforementioned standardized operating procedure consistent with that performed in previous studies at this center [27]. In total, 600 µg of Salbutamol will be prescribed on a standard hospital drug chart for all participants for administration after the bronchial challenge test. The test will be conducted by a doctor or a registered trained nurse (with immediate access to a doctor for additional support if needed).

A dosimeter system will be used (Jaeger APS [aerosol provocation system] Vyntus system, Carefusion). An initial inhalation of 0.9% saline will be followed 1 minute later by spirometry recording to obtain a baseline value. Baseline FEV_1 will be required to be greater than 70% of the predicted value to proceed with the test. Subsequently, incremental methacholine doses from 1 mg to 32 mg will be administered. The dose causing a 20% decrease in FEV_1 from the postsaline value will be interpolated and expressed as PD_{20} FEV_1. A positive test is defined by PD_{20}<2 µg. A continuous dose-response slope measure of bronchial hyperresponsiveness will also be estimated by the least-square regression of percentage change in FEV_1 upon cumulative methacholine dose for each subject. The dose-response slope obtained will be transformed to satisfy normality and homoscedasticity. The results will be communicated to the participants' general practitioners by written letters.

To perform spirometry or methacholine bronchial challenge, subjects will be required to be free from respiratory infection for 14 days, not taking oral steroids, not taken short-acting β2 agonists for 6 hours and long-acting β2 agonists for 12 hours, and abstained from caffeine intake for at least four hours. To exclude pregnancy before undergoing bronchial challenge, premenopausal female participants will be asked to provide a urine sample for pregnancy testing.

By way of safety precautions, participants will be followed up by telephone following each visit involving a bronchial challenge to check whether the participant is well and had no adverse reaction to the methacholine. All adverse reactions will be reported via the institutions' local reporting system.

FeNO Measurements

Measurement of FeNO will be performed in all patients using a standardized methodology [28]. This will be performed during each subject's visit to the center.

PEF Measurements

Measurements of PEF will be performed in all patients at regular intervals, according to the standardized technique. These data will be collected during spirometry. It will also be collected using either SMART peak flow technology [29] or the Wright Peak Flow meter (Clement Clarke International Ltd), based on patients' preference.

Additional Assessments

Additional Questionnaires

The standardized and extensively validated Juniper Rhinoconjunctivitis Quality of Life Questionnaire [30] will be administered. At baseline, the International Study of Asthma and Allergies in Childhood questionnaires [31] will be used to assess asthma symptoms, morbidity, medication requirements, and the presence of other allergic diseases. International Study of Asthma and Allergies in Childhood environmental questionnaires will be used at baseline to evaluate the home environment and exposure to allergens and irritants. An asthma history questionnaire (Multimedia Appendix 1) will also be used to assess asthma symptoms, morbidity, and medication requirements.

Physical Examination

Physical examination will include the assessment of vital signs, a general examination, and chest auscultation. Height and weight will also be recorded.

Dust Sampling

Dust samples will be taken from the mattress and carpet in the bedroom and living room (same rooms where the purifiers will be located). Sampling will be performed over an area of 1 meter square, which would be vacuumed for 2 minutes. The nozzle of the sampler will be wiped and thoroughly dried between the samples. The collected samples will be refrigerated and frozen at −20°C as soon as possible.

Blood Sampling

Blood samples will be collected at baseline and at the end of the study and stored at −80°C. The following samples will be collected:

1. 2×Green Top (BD Lithium Heparin 10 ml Plus–Bunzle Health care–VS367526)
2. 1×Lavender Top (Vacutainer blood sample tube K3EDTA 4 ml–KFK042/368860)
3. 1×Gold Top (Blood Sample Tube Serum Plastic 5 ml Gold with gel SST11–KFK114/367954).

Skin Prick Test

Skin prick tests will be performed by experienced nurses using standard techniques [32] and protocols. Antihistamines will be withheld (if safe to do so) for 72 hours before the procedure. A panel of 12 common allergens will be tested: house dust mite (*Dermatophagoides pteronyssinus* and farina), grass pollen mix, tree pollen mix, cat and dog epithelia, hamster, poultry feathers, *Alternaria alternata*, *Cladosporium herbarum*, Aspergillus, *Penicillium notatum* plus histamine (positive control), and physiological saline (negative control; extracts from ALK-Abello). An allergen skin test reaction with a mean wheal diameter of at least 3 mm greater than the negative control will be regarded as positive and the subject considered as atopic.

Indoor Air Pollution Data

Dyson will continuously sense the indoor pollutant data. The machines are equipped with air quality and environmental sensors on-board. This system also comprises sensors for

measuring temperature, relative humidity, NO_2, VOC, and PM. From the PM sensor PM2.5, PM10 is obtained. From the sum of the gaseous sensing and PM sensing, Dyson deduces an air quality index that is also displayed. When the product is connected to a local Wi-Fi, the data from these sensors are automatically sent to the Dyson cloud services [20]. These data will then be processed and shared with the study team for analysis.

Randomization

Participants will be randomized to active (intervention) or placebo purifiers in a 1:1 ratio. The purifiers will be paired and randomized by Dyson using the random function in Excel (Microsoft), with the constraint that the two groups need to be equal. Each pair of machines will be allocated a number by Dyson. The study team will allocate a sequential DY number to the participants as they are recruited. Machine pairs will be allocated by number to the corresponding DY number.

Blinding

Dyson will provide identical looking purifiers and placebo or active filters. Two purifiers will be wrapped and delivered to the subjects, where one machine will be installed in the bedroom and the other in the living room of the individual participant. Only the project manager will be aware of the serial numbers of the active or placebo filters. Participants, Dyson, and the study team will be blinded to participant allocation, but not the project manager. In addition, apart from knowing that the participants met the eligibility criteria, Dyson will be blinded to all other participant details. When filters or machines need to be changed, the project manager will be provided with the participant identifier (DY number). The project manager will then issue the study team a new machine with a matching filter status from the spare machines provided by Dyson, thus keeping the study team blinded.

Data Management

Research participants will be seen at the DHAARC where all data will be gathered, processed, and stored securely for statistical analysis. Data management will follow a similar pattern used by a previous study [27]. An Access database (Microsoft), using the study number only for identification, will be set up. The current name and address will be entered into an Excel database. Study data will be stored in the Access database using the unique study number as the primary key, which will then be used to create separate analysis files in SPSS (IBM). The study number will link the subjects' clinical information to other data and collected samples. Source data will be held securely on the Isle of Wight National Health Service local area network with limited access. The files used for analysis will not contain any personal identifiable information. Double data entry will be used for questionnaire data, whereas lung function data will be exported directly from the Carefusion Impulse Oscillometry machine (Carefusion). Range checks will be performed to ensure data quality.

Data will be collected and retained in accordance with the 2018 General Data Protection Regulation. All essential documents, including source documents, will be retained for a minimum period of 15 years following the end of the study. A *DO NOT DESTROY* label stating the time after which the documents can be destroyed will be placed on the inner cover of the records of trial participants. All study documents will be stored securely at the study site: the DHAARC at St Mary's Hospital, Isle of Wight.

Anonymized data may be transferred to the University of Southampton, Faculty of Medicine, for further analysis. At the end of the trial, anonymized aggregated data will be shared with Dyson Technology Ltd for their review. We will establish a data-sharing agreement with both organizations. The sponsor will not make personal data, raw data, or any other results generated available to Dyson Technology Ltd or any third party, except for governance or audit by a regulatory authority.

Data Analysis Plan

Data will be analyzed blinded with SPSS 26 (IBM Corporation), GraphPad Prism 9 (GraphPad Software), and Stata, version 16 (StataCorp).

Baseline descriptive statistics for both allocated groups will be presented and assessed. Normally distributed continuous variables will be presented as mean (SD) and assessed using two-tailed *t* tests. In case of deviations from normality, data will be suitably transformed before applying two-tailed *t* tests for comparison between the groups. Skewed data will be presented with median (IQR) and assessed using Mann-Whitney *U* tests. Categorical variables will be presented as percentages (frequency) and assessed using chi-square or Fisher exact tests.

The primary and secondary outcomes will be analyzed on an intention-to-treat basis.

The data on both primary and secondary outcomes from this study are longitudinal data with measurements taken at several time points. The starting point of asthma status and the response to intervention or placebo is expected to vary in a subject-specific manner over time within the group and between the groups. Therefore, the response data will be analyzed by fitting a multivariable linear mixed model (random intercept and random slope model) using the maximum likelihood estimation method with exposure groups as the fixed effect and time as the random effect. Such a model is well suited for accommodating missing data. Adjustments will also be made for the relevant baseline covariates. The assumptions of the model, normal distribution of residuals and constant variance, will be checked. Per-protocol analysis will also be conducted by using samples with no missing data. Separate-adjusted models will be built using relevant baseline covariates (eg, age, sex, and lung function).

Patient and Public Involvement

Patients will not be formally involved in the study design. However, we sought the opinion of patients with asthma attending the clinic, and they had exceptional interest in obtaining evidence of the efficacy of Dyson air purifier in improving asthma control.

Adverse Events

This study did not involve procedures with a greater than minimal risk. The social and psychological risks of talking to

interviewers while completing questionnaires or documentation sheets are minimal. Skin prick testing may cause minimal discomfort and occasionally large localized swelling, but it rarely causes a systemic reaction [32]. Lung function tests and exhaled nitric oxide tests do not pose a significant risk of adverse effects. Bronchial challenge tests can cause wheezing and chest discomfort, but appropriate precautions will be taken to avoid this. Moreover, these symptoms can be treated with inhaled bronchodilators, which are routinely administered after the test. Very occasionally, nebulized bronchodilators may be required to treat more than mild wheezing and asthma symptoms that may have been provoked. Occasionally, patients with asthma can experience a severe episode of asthma following the test; hence, the test is always performed in the presence of a medically qualified and trained personnel and at well-equipped facilities for the immediate treatment of bronchospasm are at hand. The overall risk is similar to that of routine clinical care. If an adverse effect is reported at one of the regular contacts (center visit, home visit, and telephone interview) or during the study procedures, then all details will be recorded in the case report form and reported to the investigators if needed. Appropriate actions will be taken to eliminate or minimize the risk to the participant. In addition, participants will be provided with an emergency 24-hour telephone number to report any adverse effects. Any serious adverse events and adverse events will be tabulated. The study team will review safety data on an ongoing basis but specifically at their monthly meetings; moreover, all recorded adverse effects will be reviewed. The study team will be responsible for classifying, documenting, determining causality, and reporting. Adverse events will be recorded in accordance with Good Clinical Practice recommendations.

Results

Overview

The trial started in September 2019 and is expected to end in August 2021. A summary of the assessments and their intervals is presented in Table 1. An overview of the study design is shown in Figure 1.

Table 1. Trial assessment timepoints.

Study task or measurement performed	Screening or CV[a]1	HV[b]1, 0 week	TC[c]1, 6-7 weeks	CV2, 12-13 weeks	TC2, 18-19 weeks	TC3, 24-26 weeks	TC4, 30 weeks	TC5, 36 weeks	TC6, 42 weeks	TC7, 48 weeks	TC8, 52 weeks	CV3, 76-78 weeks	HV2, 76-78 weeks
Patient information and consent	✓[d]												
ISAAC[e] questionnaires	✓												
ACQ6[f]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
AQLQ[g]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
RQLQ[h]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Asthma history questionnaires[i]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Peak expiratory flow	✓	✓	✓	✓	✓						✓	✓	
Physical examination	✓			✓								✓	
Skin prick test	✓												
Spirometry	✓			✓								✓	
Bronchial challenge methacholine)	✓											✓	
FeNO[j]	✓			✓								✓	
Dust sample collection		✓										✓	✓
Blood sample	✓											✓	
Installation of air purifiers		✓											
Indoor air pollution data by Dyson purifiers		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Return of air purifiers													✓
Letter to general practitioner	✓											✓	

[a]CV: center visit.

[b]HV: home visit.

[c]TC: telephone call.

[d]Task or measurement is performed.

[e]ISAAC: International Study of Asthma and Allergies in Childhood.

[f]ACQ6: Asthma Control Questionnaire 6.

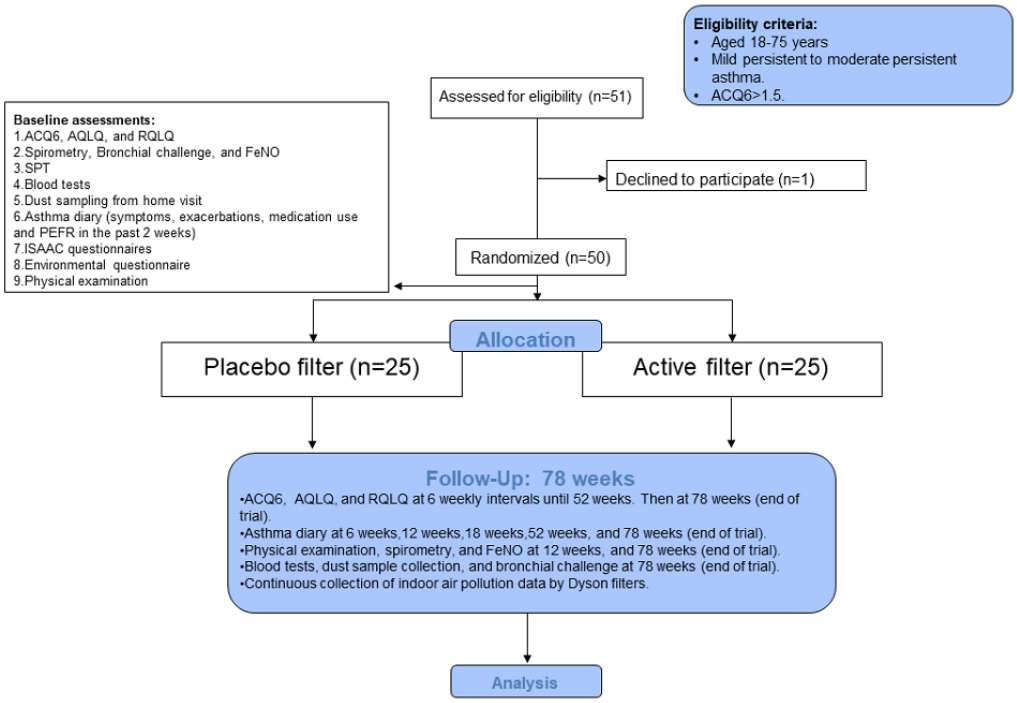
[g]AQLQ: Asthma-Specific Quality of Life Questionnaire.

[h]RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire.

[i]Asthma history questionnaire includes information on symptoms, medication use, and exacerbations in the past 2 weeks.

[j]FeNO: fractional exhaled nitric oxide.

Figure 1. Overview and CONSORT (Consolidated Standards of Reporting Trials) diagram of the study. ACQ6: Asthma Control Questionnaire 6; AQLQ: Asthma-Specific Quality of Life Questionnaire; FeNO: fractional exhaled nitric oxide; ISAAC: International Study of Asthma and Allergies in Childhood. PEFR: Peak Expiratory Flow Reading; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire; SPT: skin prick testing.



Ethics and Confidentiality

The study protocol was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials statement [33], and the trial will be reported according to the guidelines of the CONSORT (Consolidated Standards of Reporting Trials) statement [34].

The West Midlands Research Ethics Committee (REC; REC Reference, 18/WM/0277) and the local research and development department approved and reviewed this study. The study will be conducted in accordance with the principles of Good Clinical Practice. Any amendments to the protocol will be submitted to the REC and local research and development for review and approval.

All records, reports, and forms will be anonymized and identified in a manner that ensures participant confidentiality. Records will also be stored in a secure area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the sponsor, its designee, or the REC or as required by law. The investigators and study site staff involved in this study may not disclose or use, for any purpose other than the performance of the study, any data; record; or other unpublished, confidential information disclosed to the individuals in this study. Previous written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

Dissemination of Research Findings

The chief investigator will serve as the custodian of the data arising from this study, and the sponsor will be the owner of the data. The study findings will be used for publication in peer-reviewed scientific journals and presentations in scientific meetings. Summaries of the results will also be made available to investigators for dissemination within their clinics. The findings will also be shared in plain English with participants in our newsletters and via the DHAARC website.

Discussion

This protocol outlines a double-blinded, placebo-controlled, randomized, investigator-led study designed to investigate the efficacy of a novel air purifier in improving asthma control in adults. The trial period of 18 months will facilitate the collection of robust data and will therefore generate clear signals. However, this extended trial duration may lead to patient withdrawal and adherence challenges. Furthermore, this trial is conducted at a single center and is conducted in a location with a homogenous cohort of people, which may affect translatability. Nonetheless, it is hoped that the findings of this trial may help further inform clinicians regarding the utility of this novel device as an adjunct in future asthma care. In addition, the comprehensive air pollution data captured by the device along with the repeated characterization of subjects via subjective and objective measures will add to the understanding of the influence of indoor air pollution on asthma control.

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Authors' Contributions

SHA is the chief investigator, and RK is the coinvestigator. WCGF, SG, SP, TT, LK, KB, ML, FN, RK, and SHA contributed to the drafting and critical revision of the protocol and approved the final version of the manuscript.

Conflicts of Interest

FN is an employee of Dyson. Dyson provides financial support and air purifiers for this trial but will not be involved in the management, analysis, and interpretation of data; writing of the report; or the decision to submit the report for publication. All other authors declare no conflicts of interest.

Multimedia Appendix 1
Asthma history questionnaire.
[PDF File (Adobe PDF File), 352 KB - resprot_v10i7e28624_app1.pdf]

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Abbreviations

ACQ6: Asthma Control Questionnaire 6
APS: aerosol provocation system
AQLQ: Asthma-Specific Quality of Life Questionnaire
CONSORT: Consolidated Standards of Reporting Trials
DHAARC: David Hide Asthma and Allergy Research Centre
FEV1: forced expiratory volume in one second
FVC: forced vital capacity
FeNO: fractional exhaled nitric oxide levels

HEPA: high-efficiency particulate air
NO_2: nitrogen dioxide
PEF: peak expiratory flow
REC: Research Ethics Committee
PM: particulate matter
VOC: volatile organic compound

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Protocol

Improving Physical Activity Levels in Prevocational Students by Student Participation: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: A consistent finding in the literature is the decline in physical activity during adolescence, resulting in activity levels below the recommended guidelines. Therefore, promotion of physical activity is recommended specifically for prevocational students.

Objective: This protocol paper describes the background and design of a physical activity promotion intervention study in which prevocational students are invited to participate in the design and implementation of an intervention mix. The intervention is expected to prevent a decline in physical activity in the target group.

Methods: The effectiveness of the intervention was evaluated in a two-group cluster randomized controlled trial with assessments at baseline and 2-year follow-up. A simple randomization was applied, allocating 11 schools to the intervention group and 11 schools to the control group, which followed the regular school curriculum. The research population consisted of 3003 prevocational students, aged 13-15 years. The primary outcome measures were self-reported physical activity levels (screen time, active commuting, and physical activity). As a secondary outcome, direct assessment of physical fitness (leg strength, arm strength, hip flexibility, hand speed, abdominal muscle strength, BMI, and body composition) was included. An intervention-control group comparison was presented for the baseline results. The 2-year interventions began by mapping the assets of the prevocational adolescents of each intervention school using motivational interviewing in the structured interview matrix and the photovoice method. In addition, during focus group sessions, students, school employees, and researchers cocreated and implemented an intervention plan that optimally met the students' assets and opportunities in the school context. The degree of student participation was evaluated through interviews and questionnaires.

Results: Data collection of the SALVO (stimulating an active lifestyle in prevocational students) study began in October 2015 and was completed in December 2017. Data analyses will be completed in 2021. Baseline comparisons between the intervention and control groups were not significant for age (P=.12), screen time behavior (P=.53), nonschool active commuting (P=.26), total time spent on sports activities (P=.32), total physical activities (P=.11), hip flexibility (P=.22), maximum handgrip (P=.47), BMI (P=.44), and sum of skinfolds (P=.29). Significant differences between the intervention and control groups were found in ethnicity, gender, active commuting to school (P=.03), standing broad jump (P=.02), bent arm hang (P=.01), 10× 5-m sprint (P=.01), plate tapping (P=.01), sit-ups (P=.01), and 20-m shuttle run (P=.01).

Conclusions: The SALVO study assesses the effects of a participatory intervention on physical activity and fitness levels in prevocational students. The results of this study may lead to a new understanding of the effectiveness of school-based physical activity interventions when students are invited to participate and cocreate an intervention. This process would provide structured health promotion for future public health.

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KEYWORDS

physical activity; participatory; adolescents; protocol; assets; school-based; students; participation; school-age children; teenagers; exercise

Introduction

Background

The decline in physical activity levels among young people is an increasing problem. Adolescents in particular show a relapse in sport and exercise participation below the minimum recommended guidelines for physical activity [1-5]. Consequently, the risk of health problems later in life has increased [6,7]. Physical inactivity is a risk factor for chronic diseases, such as cardiovascular disease, cancer, and osteoporosis [8,9]. Therefore, the development and evaluation of interventions with the aim of encouraging adolescents to stay physically active is therefore urgent. Guidelines for adolescents recommend a minimum of 1 hour of moderate-intensity physical activity a day, muscle and bone strengthening exercises three times a week, and avoiding excessive sitting [10].

The school context is potentially an important environment that encourages adolescents to become physically more active [11]. Dutch databases for available school-based interventions contain some *well-described* and *theoretically substantiated* interventions, but little is known about their effectiveness in promoting physical activity [12,13]. Many of these are single risk factor interventions, but the effectiveness of interventions is context dependent, meaning that interventions that might work for senior, general secondary education students cannot immediately be translated to prevocational students [12,14]. Bernaards et al [15] demonstrated that deploying multirisk factor interventions is more effective for prevocational students in terms of increasing physical activity levels [15]. A review of school-based physical activity promotion interventions for prevocational adolescents also indicates that effectiveness increases with an optimal mix of intervention characteristics considering organizational (intracurriculum interventions of short-to-medium duration), personal (tailoring the intervention and empowering students to participate), social (empowering school staff), and content (inclusion of physical activities) determinants [16].

Studies in which students were invited to participate by cocreating an intervention appeared to be potentially more effective [17-19]. Actively involving students using dialog about their perspectives on lifestyle seems to lead to more acceptable and effective interventions [20,21]. It is important to focus on what they enjoy doing and taking into account the possibilities of their local context and characteristics [22]. Therefore, schools aiming to promote healthy lifestyles need to find strategies to involve students to discover their perspectives and empower them for action. This study encourages the full participation of students in the health development process and embraces a *salutogenic* notion of health creation [23,24]. A salutogenic approach seeks the origins of health and focuses on factors that support human health and well-being, rather than factors that cause disease (pathogenesis). People are seen as active and participating subjects, shaping their lives through their action competences [25]. Therefore, it focuses on resources and assets for health and health-promoting processes rather than deficits, risk factors, and disease. As such, a *health asset* can be described as any factor (or resource), which enhances the ability of prevocational students and their social and physical (school) context to maintain and sustain health and well-being and to help reduce health inequities [24]. Resources in a school context are not only a playground, greenery, provision of equipment, and peers of professional school staff but also the capacities and talents of students themselves.

To promote an active lifestyle in prevocational students, it is therefore a challenge to put together an intervention mix that matches specific behavioral determinants (assets) of the students and their environments that support the adoption of a more active lifestyle. This school-based physical activity promotion intervention study, SALVO (stimulating an active lifestyle in prevocational students), aims to evaluate the effectiveness of a physical promotion intervention in prevocational students. This protocol describes the background, design, and baseline results. The results that will be presented include details of the interventions that were developed and baseline characteristics.

Objectives

The SALVO study is developed to evaluate the effectiveness of a school-based physical activity intervention in improving physical activity behavior in prevocational students. An additional goal of the study is to determine if an intervention is more effective when students participated in the development and implementation process of the intervention. In this paper, we describe the study design and protocol details of the SALVO study.

Methods

Objectives and Design

The SALVO study aimed to evaluate the effectiveness of a physical promotion intervention. The intervention was evaluated by a two-group cluster randomized controlled trial (N=3003; 11 intervention schools and 11 control schools) with assessments at baseline (2015) and 2-year follow-up (2016 and 2017). The primary outcome measure was self-reported physical activity as a marker of an active lifestyle. With regard to a secondary outcome, this study examined the effects of interventions on

physical fitness measures. The hypotheses tested were as follows:

1. Over 2 years of follow-up, the intervention group had a higher degree of physical activity compared with the control group.
2. Over 2 years of follow-up, the intervention group had a higher physical fitness level compared with the control group.
3. Over 2 years of follow-up, the intervention group with a higher degree of student participation showed a greater intervention effect on the outcome measures compared with the intervention group with a lower degree of student participation.

Pilot Study

A pilot study aimed to pretest the test battery, and the cocreation and implementation process of the intervention was conducted in students of two prevocational pilot schools aged 12-14 years. The feasibility of the battery measurement during school lessons was evaluated. Furthermore, the usability, comprehension, and acceptability of the interactive methods to involve students in the design and implementation of the intervention were examined.

A valid physical activity questionnaire was filled digitally during mentor hours [26]. A mentor hour is the class time used to acquire skills, such as study skills and social skills. The surveys were conducted in a computer room. Organizing such a room requires preparation in a timetable. The questionnaire was completed under supervision and took 10 to 15 minutes. Together with the instruction, guiding, and use of log-in codes, it was possible to conduct the survey in 20 minutes of class time. The preparation, guidance, and duration required to complete the questionnaire ensured adequate usability, comprehension, and acceptability. Physical performance was tested using the Eurofit test battery during the physical education (PE) lessons [27]. Minor adaptations (class management and use of research assistants) to improve the efficiency of the physical fitness measurement procedures were made.

The pilot study was also used to optimize two action research methods that were deployed to actively engage prevocational students in the SALVO study. Assets were assessed efficiently rather than needs. For this purpose, the structured interview matrix (SIM) and photovoice (PV) were adapted and optimized to fit the interaction with prevocational students in classroom settings. The protocols developed were applied in the pilot schools and adapted iteratively based on the evaluations by critically reflecting on the experiences [28]. The combination of SIM and PV, labeled as triple I, was evaluated as a playful visual method (PV) with an interactive, reflective verbal method (SIM) that was found to work well with the target group of prevocational students.

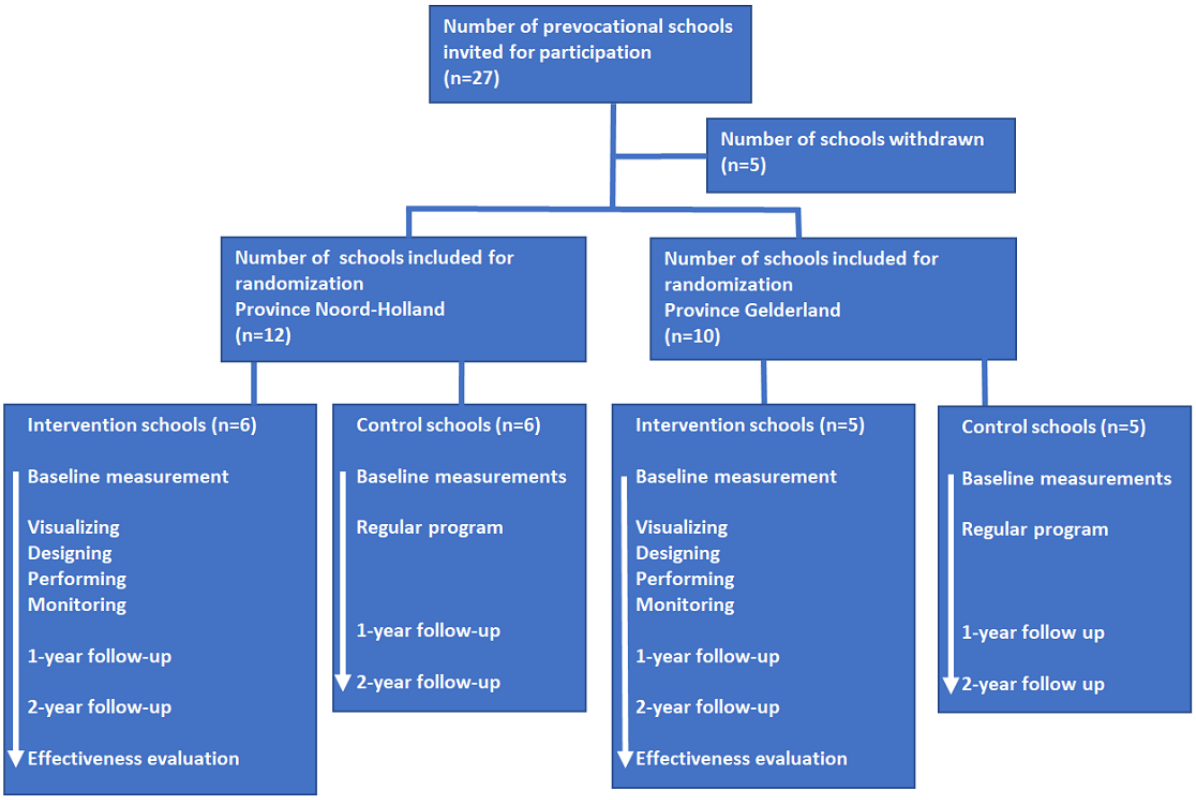
SALVO Study: Recruitment of Schools and Students

In accordance with the location of the two Dutch universities collaborating in the SALVO study, 27 prevocational schools located in the provinces of Noord-Holland and Gelderland were invited to participate. If there was a positive response, further information was provided about the design and content during a school visit. Of the 27 schools, five schools indicated that they would not participate because of contented and organizational reasons and wishes. All parents of the students in the second school year received a letter explaining the goals and content of the study and the data collection that went with it. The researchers asked parents a passive form of consent for their child's participation. Parents and children were given clear instructions on the option to drop out of the study whenever they wanted, without having to give a reason. A total of 6 students of parents who objected were not tested. The study was approved by the ethics committee of the HAN University of Applied Sciences (number ACPO 34.05/16) and retrospectively registered as ISRCTN35992636 in the ISRCTN registry on February 12, 2020 [29].

Randomization Procedure

A stratified randomization process assigned the 22 participating schools to either the intervention or control group. Schools were stratified according to their location (the district Noord-Holland or Gelderland), with Noord-Holland schools in one stratum and Gelderland schools in the other. A simple randomization was applied, allocating 11 schools to the intervention group and 11 schools to the control group (Figure 1).

Figure 1. Flowchart of the recruitment and randomization of schools. Timeline for the intervention implementation and evaluation.



Measurements

The primary outcome measures were physical activity behavior determined using a validated questionnaire and taken digitally during a mentor hour [26]. Textbox 1 presents an overview and description of the variables derived from the questionnaire: screen time, active commuting to school, free time active commuting, time spent in sports, and total physical activity. The physical fitness data were collected using a Eurofit test battery [27]. In two regular PE lessons, the tests were conducted by trained test leaders in accordance with the Eurofit test protocol. Students and test leaders were not blinded, as it is difficult to realize in this kind of research. Prevocational students were instructed on arrival and completed the following components in circuit form (Textbox 1): standing broad jump, bent arm hang, 10× 5-m sprint, sit and reach (sit and reach box), plate tapping, sit-up, and handgrip (Takei hand dynamometer TKK 5401). The next PE class, the 20-m shuttle run, was performed. Anthropometric measures were collected during one of the two classes according to the preferences of the PE teacher. Body weight (Seca robusta 813), body height (Seca 213), and the sum of four skinfolds (Slimguide) were assessed in separate rooms for boys and girls. All measures were taken at baseline and at follow-up after 1 and 2 years.

Textbox 1. Overview and description of the outcome measures included in the study.

Physical Activity

- Screen time (hours/week): hours a week of screen time
- Active commuting school (hours/week): hours a week of walking or cycling to school
- Active commuting other (hours/week): hours a week of walking or cycling to other destinations
- Total time of sport (hours/week): hours a week of sports activities in a club or free time
- Total physical activity (hours/week): hours a week of physical activity in school, club, and free time

Physical Performance

- Standing broad jump (cm): explosive leg power
- Bent arm hang (seconds): endurance arm strength
- 10× 5-m sprint (seconds): running speed and agility
- Sit and reach (cm): hip flexibility
- Plate tapping (seconds): arm speed
- Sit-up (numbers/30 seconds): trunk endurance strength
- Handgrip (kg): static arm strength
- 20-m shuttle run: cardiorespiratory endurance

Anthropometry

- Sum of skinfolds (mm): sum of four skinfolds
- BMI: body weight/(body height)^2

The Intervention

Intervention Objectives and Behavioral Goals

The objective of the intervention was to stimulate prevocational adolescents aged 13-15 years to become physically more active and physically more fit. In addition, the objective was to tailor the intervention to the needs and interests of the students themselves by actively involving the students in the cocreation of the intervention. The interventions that resulted from this process were implemented along the possibilities and context of the school. For this reason, tailor-made interventions could differ across schools. The control group went through a regular school curriculum without the development and implementation phases of the intervention. Table 1 presents an overview of the intervention characteristics for each school. A description of one of the interventions is included as an example in Textbox 2.

Table 1. Estimation of intervention characteristics in the intervention schools.

Intervention school	1	2	3	4	5	6	7	8	9	10	11
Physical activities	✓[a]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Curriculum											
Intra				✓	✓	✓			✓		
Extra	✓	✓	✓	✓		✓	✓	✓		✓	✓
School staff participation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
School management participation									✓		✓
Tailored intervention		✓	✓	✓	✓		✓				
Student participation											
Low	✓					✓	✓				✓
Moderate		✓	✓		✓			✓	✓	✓	
High				✓							

[a]The intervention of the school includes the intervention characteristic.

Textbox 2. Example of an intervention cocreated by students and teachers.

School A offers prevocational courses aimed at the agricultural sector. It recently has moved into a new building. From the assets determination, students indicated that the new schoolyard is empty and boring. The students' wish is to use the school playground during breaks to play and exercise. After focus group sessions, the plan is to make small sports equipment available from the gym during school breaks. Students coordinate the distribution and cleaning up of the equipment. The regional Sports Service Centre supports by providing larger equipment that is borrowed and replaced on a monthly basis (soccer goals and basketball installation). One of the handicraft teachers decides to build the soccer goals during the lesson by the students themselves so that they can be used permanently. The schoolyard has transformed into a daily useful playground for the students. The success of the solution did lead to some nuisance complaints from teaching teachers about the sound produced by the playing students.

Theoretical Background and Determinants Addressed

Within the salutogenic framework, health was seen as a process in which people are always in some regard healthy and independent of existing distress and diseases [30]. It focuses on resources and assets for health and health-promoting processes, rather than deficits, risk factors, and disease. The values and principles of the asset model emphasize the need to strengthen local communities [24]. Morgan [24] defined health assets as any factor or resource that enhances the ability of individuals, groups, communities, populations, social systems, and institutions to maintain health and well-being and help to reduce health inequities. These assets could work at the level of the individual, group, or population as protective or promoting factors to buffer against life's stresses. The SALVO study embraced the model through asset mapping to promote community empowerment. It created supportive (healthy) environments by helping to identify the key assets that generate living and working conditions that are safe, stimulating, satisfying, and enjoyable.

General Intervention Framework

In line with the salutogenic framework, the SALVO study focused on the strengths and resources that strengthen the ability of prevocational students to become physically more active. Therefore, the process of intervention development and implementation was conducted in the intervention schools and followed several phases to respond to students' personal motives (Table 2). During the start-up phase (visualizing), the behavioral determinants of students were assessed based on asset mapping. The positive aspects of students are listed and ranked on the basis of SIM, PV, and focus group sessions. The Morgan study [24] showed that asset mapping ensures more involvement and health control for participants. Co-designing the intervention with students ensured a better connection with the experienced world (context) of prevocational students, so that a more active lifestyle could be developed on the basis of intrinsic motivation [24]. Asset mapping was performed with a subsample of prevocational adolescents (one class) in each intervention school. Motivational interviewing in the SIM and PV methods was used, taking into account the application of relevant quality procedures [31]. The SIM examined what students thought of an active lifestyle and how they knew how to follow up on this lifestyle [32]. In the PV method, students used photos to present opportunities for an active lifestyle in the school environment and their own neighborhood. These photos were then presented to each other with an oral explanation [33,34]. All conversations were supervised by trained research assistants and were voice recorded. Both students and school teachers actively participated in this process of asset mapping. The goal of asset mapping was to identify which resources may contribute to the more active lifestyle of students. All SIM and PV recordings were analyzed using the standards for qualitative research [35]. The assets were mapped on the basis of four factors that influence the physical activity behavior of prevocational students: social environment, physical environment, personal skills, and passions and interests. The results were interpreted by researchers and, in the next phase, the students were checked to what extent this interpretation matched their conception. During the design phase in each intervention school, two focus group sessions were held with a subsample of 4-6 students, researchers, members of the teaching staff, and school board. The goal was to create an intervention plan. In the triangulation process, the drivers of behavior (assets) were matched with an inventory of databases containing the existing well-described and substantiated interventions for this target group and the opportunities for implementation of an intervention provided by the school. During the focus group sessions, students were encouraged to advise and co-decide on the development of the intervention [32]. Extra focus group sessions were held if external stakeholders, such as providers of sports activities, played a role in conducting the intervention. In the implementation phase (performing), the students and teachers jointly implemented the intervention mix. The researchers monitored the implementation process through regular conversations with all the stakeholders. The final phase—the evaluation phase (monitoring)—was intended to evaluate the intervention mix. In this phase, the intervention was evaluated based on the degree of alignment with the wishes and needs of the students. The findings arising from this process evaluation were used to initiate a new process of cocreation. Students and employees actively participated in this process.

Table 2. Summary of the goals, methods used, and results of the intervention design and implementation phases of the SALVO (stimulating an active lifestyle in prevocational students) study.

Phase and goal	Method	Result
Visualizing		
Students' asset mapping	• Structured interview matrix • Photovoice • Qualitative analysis	• Social environment • Physical environment • Motor skills • Passions and interests
Designing		
Cocreation intervention	• Focus group sessions	• Intervention plan
Performing		
Intervention implementation	• N/A[a]	• Intervention activities
Monitoring		
Evaluation of intervention mix	• Focus group sessions	• Intervention adjustments

[a]N/A: not applicable.

Sample Size

The sample size was based on a power analysis using the results of a previous Dutch study, in which an increase from 41% to 55% of norm actives was reported in 17,891 prevocational students [15]. Assuming a similar effect with a power of 0.90 and an α of .05, a required number of 536 students were divided into two groups. Taking into account the cluster effect, the sample size was calculated for 901 students with an intracluster correlation of 10%.

Procedure of the Process Evaluation

During the implementation phase of the intervention, consultation moments between the researchers and teachers were planned on a regular basis. The purpose of these consultations was to monitor the implementation and, if necessary, adjustment of this process. After the intervention period, interviews were conducted with the students and teachers for each intervention school. Surveys determined the degree of student participation during the design and implementation phases. The degree of participation was expressed ordinally from weak (to inform) to moderate (to think along) and strong (to co-decide) [36].

Statistical Analysis

The effectiveness of the SALVO intervention was analyzed using a multivariable analysis. Therefore, generalized estimating equations (GEEs) were used to evaluate the intervention that explains the variability between the intervention and control groups on the outcome variables of physical activity and physical fitness. GEEs are chosen to account for the possible intragroup correlation, and an exchangeable correlation structure was assumed for these analyses. The coefficient of interest in this analysis is the regression coefficient of the interaction between the group (intervention or control) and time [37]. One model considers the explanatory variables over time, including baseline values of the outcome variable, gender and ethnicity, the group (intervention or control), time, and the interaction between group and time. The second model presents a sensitivity analysis that includes intervention schools with moderate to strong levels of participation of students or intervention schools with the lowest level of student participation. The results of GEE analyses are expressed as the β coefficient of the interaction between group and time, with corresponding 95% CI and associated *P* values. In this design and protocol paper, the results of the baseline comparison between the intervention and control groups for physical activity and physical fitness data are presented. In addition, the distributions of gender, ethnicity, and age are presented. A two-tailed independent *t* test and chi-square test were performed for continuous and nominal variables, respectively. *A priori*, the criterion for statistical significance, was set at $P<.05$. All analyses were performed using the SPSS software (version 26; IBM Corp).

Results

Demographics

The total study population of 3003 students consists of 1457 girls (48.52%) and 1546 boys (51.48%) aged 13.8 years (SD 0.5). The students mainly had a Dutch background (1754/2640, 66.44%). The reported countries of origin of the parents of children with a migration background were Morocco, Turkey, Suriname, the Netherlands Antilles, Poland, Iraq, and Somalia. A total of 42.16% (1266/3003) students lived in the province of Gelderland. A total of 57.84% (1737/3003) students lived in the province of Noord-Holland.

Table 3 provides the baseline results for the distribution of gender and ethnicity in the intervention and control groups. Boys were overrepresented in the control group ($P<.001$), whereas students with a migration background were overrepresented in the intervention group ($P<.001$). The mean age of the population in the control and intervention groups was similar ($P=.12$; Table 4).

Table 3. Baseline demographic and gender comparisons between the intervention and control groups.

Characteristic	Control group, n/N (%)	Intervention group, n/N (%)	*P* value
Gender			<.001
Girls	725/1611 (45)	732/1392 (52.58)	
Boys	886/1611 (54.99)	660/1392 (47.41)	
Ethnicity (n=2640)			<.001
Domestic	1042/1455 (71.62)	712/1185 (60.08)	
Immigrant	413/1455 (28.38)	473/1185 (39.92)	

Table 4. Baseline physical activity and physical fitness comparison between the intervention and control groups.

Baseline characteristic	Girls (N=725)		Boys (N=886)	
	Students, n (%)	Values, mean (SD)	Students, n (%)	Values, mean (SD)
Control				
Age (years)	725 (100)	13.8 (0.5)	886 (100)	13.8 (0.5)
Screen time (hours/week)	493 (68)	52.1 (0.5)	566 (63.8)	55.1 (17.3)
Active commuting school (hours/week)	487 (67.2)	1.2 (0.5)	561 (63.3)	1.31 (1.0)
Active commuting other (hours/week)	248 (34.2)	0.5 (0.5)	229 (25.9)	0.5 (0.5)
Total time of sport (hours/week)	385 (53.1)	4.3 (0.5)	456 (51.5)	5.1 (2.4)
Total physical activity (hours/week)	479 (66.1)	5.0 (0.5)	559 (63.1)	5.6 (3.1)
Standing broad jump (cm)	643 (88.7)	139.5 (22.7)	785 (88.6)	158.0 (25.8)
Bent arm hang (Ln[a])	642 (88.6)	1.3 (1.5)	787 (88.8)	2.3 (1.3)
10× 5-m sprint (seconds)	634 (87.5)	21.5 (1.9)	773 (87.3)	19.8 (1.7)
Sit and reach (cm)	651 (89.8)	27.1 (8.3)	788 (88.9)	20.5 (7.3)
Plate tapping (seconds)	653 (90.0)	12.6 (1.8)	790 (89.1)	12.5 (1.7)
Sit-up (numbers/30 seconds)	644 (88.9)	18 (4)	784 (88.5)	22 (4)
Handgrip (kg)	656 (90.5)	29.4 (5.4)	790 (89.2)	32.6 (7.5)
20-m shuttle run (score)	511 (70.5)	5.9 (2.0)	649 (73.3)	7.8 (2.2)
Sum of skinfolds (Ln)	635 (87.6)	3.0 (0.2)	783 (88.4)	3.0 (0.2)
BMI (Ln)	634 (87.4)	4.0 (0.4)	779 (87.9)	3.5 (0.5)
Intervention				
Age (years)	732 (100)	13.8 (0.5)	660 (100)	13.8 (0.5)
Screen time (hours/week)	515 (70.4)	52.1 (18.2)	464 (70.3)	56.6 (18.6)
Active commuting school (hours/week)	514 (70.2)	1.4 (1.0)	461 (69.9)	1.3 (1.0)
Active commuting other (hours/week)	225 (30.7)	0.4 (0.5)	210 (31.8)	0.6 (0.6)
Total time of sport (hours/week)	359 (49.0)	4.1 (2.4)	364 (55.2)	5,1 (2.5)
Total physical activity (hours/week)	482 (65.9)	4.8 (3.1)	453 (68.6)	5.7 (3.3)
Standing broad jump (cm)	624 (85.2)	139.7 (21.9)	597 (90.5)	155.6 (24.1)
Bent arm hang (Ln)	612 (83.6)	1.1 (1.5)	575 (87.1)	2.0 (1.5)
10× 5-m sprint (seconds)	620 (84.7)	21.9 (2.2)	590 (89.4)	20.5 (2.0)
Sit and reach (cm)	630 (86.1)	26.0 (8.5)	603 (91.4)	20.0 (7.5)
Plate tapping (seconds)	630 (86.1)	13.0 (2.0)	604 (91.5)	12.8 (1.9)
Sit-up (numbers/30 seconds)	626 (85.5)	17 (4)	603 (91.4)	21 (4)
Handgrip (kg)	633 (86.5)	29.4 (5.6)	606 (91.8)	32.5 (8.2)
20-m shuttle run (score)	387 (52.9)	5.3 (2.3)	401 (60.8)	7.3 (2.7)
Sum of skinfolds (Ln)	613 (84.7)	3.0 (0.2)	596 (90.3)	3.0 (0.2)
BMI (Ln)	620 (84.7)	3.9 (0.4)	596 (90.3)	3.5 (0.5)

[a]Ln: log-linear transformed data.

Physical Activity

From the total student population (N=3003), 2286 (76.12%) students participated in the baseline measurements (Table 4). During the week, 28.39% (560/1972) of the total population reported being physically active for at least seven hours. The mean total physical activity level of 1983 students was 5.3 hours a week (SD 3.2). Sports activities contribute the most, with 4.7 hours a week (SD 2.5). The students spend approximately 1.5 hours a week walking or cycling to school. Screen time use among 2038 students is 53.9 hours a week (SD 18.5). A comparison between 1054 intervention students and 1232 controls did not show significant differences in screen time behavior (P=.53), active commuting other than going to school

(*P*=.26), total time spent on sports activities (*P*=.32), and total time spent on physical activity (*P*=.11). Intervention students spent more time on active commuting to school than did the controls (*P*=.03).

Physical Performance and Anthropometry

Physical fitness was assessed in 2566 students (1168 intervention vs 1398 controls). Table 4 presents the baseline gender-specific results of the outcome measures in the intervention and control groups. The variables that were not normally distributed were log-linear transformed (bent arm hang, BMI, and sum skinfolds). The mean hip flexibility (*P*=.22) and maximum hand grip strength (*P*=.47) were comparable between the intervention and control groups. Other physical performance parameters were found to be significantly better for students in the control group. Baseline outcome values for body composition (*P*=.29) and body mass (*P*=.44) were similar between the intervention and control groups.

Discussion

Principal Findings

The aim of the SALVO study is to promote an active lifestyle in prevocational students by allowing students to participate in intervention development and implementation. To this end, students have been invited to participate in dialog with peers and school staff. It is expected that the alignment of students' assets and interventions will lead to a meaningful basis for a sustainable active lifestyle of students.

Most of the prevocational students in this study did not meet the minimum guidelines for healthy exercise and showed a high degree of screen use. The physical fitness of boys exceeds that of girls, except for hip flexibility.

Normative values for physical fitness were published in a recent review of 2,779,165 adolescents from 30 European countries [38]. Compared with the normative centile scores of their peers, the students aged 14 years in this study achieved relatively low scores on standing broad jump (P10-30), plate tapping (P30-40), and sit-ups (30-40). In addition, students who can barely hang from bent arms are overrepresented. In contrast, hip flexibility (P60) and the shuttle run test scores (P60-80) were relatively better developed in boys and girls. Hand grip scores of girls (P70) were comparatively better than those of boys (P40). The 10× 5-m shuttle run agility test scores were normative (P50-60). Finally, students with high BMI and sum or skinfold values are overrepresented.

The mean total physical activity level found in this study of 5.3 hours (SD 3.2) a week is less than the 18 hours a week reported by the Dutch National Institute for Public Health and the Environment [5]. A possible reason for this is the difference in the questionnaires used. In addition, the study population in this study is specifically aimed at prevocational secondary education students instead of all young people between the ages of 12 and 19 years. Physical activity such as sports activities and cycling are the main physical activities that contribute to the total physical activity of this population. This is in line with data reported by the Dutch National Institute for Public Health and the Environment [5]. The prevalence of students that meet the physical activity guidelines for Dutch adolescents found in this study is 28.39% (560/1972), which corresponds to the levels of 28% reported by the Dutch Health Council [10]. The prevalence of insufficient physical activity of 71.6% (1412/1972) is approximately 7% less than the internationally reported percentage of 78.2% for high-income Western countries [39].

The participatory approach is sparsely used in research when evaluating active lifestyle interventions among prevocational secondary education students [31,40-44]. This is surprising, since the involvement of students in developing an intervention is considered an effective intervention characteristic [16]. This research will provide insight into the effects of such a participatory approach on physical activity and fitness among prevocational students.

Strengths and Limitations

The strength of this study is that the design process of the intervention is based on students' assets, existing and theoretically well-described interventions for this target group, and the opportunities and possibilities offered by the school context. This triangulation process unfolds in focus group sessions between different stakeholders, such as school management, researchers, and staff. It provides valuable practical experiences for every school that would like to support students in developing an active lifestyle. Another strength of the research is the size of the number of participants and the experimental design. Evidence-based practice and practice-based evidence meet in this study.

Considering that there are few studies that have rigorously investigated the participation of students in intervention development, the SALVO study will provide needed insight into the promotion of physical activity in a school context. The results of this study could help in creating more refined and successful school-based physical activity interventions in the future.

Acknowledgments

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Authors' Contributions

HK and HT contributed to the development and implementation of the SALVO study intervention. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

GEE: generalized estimating equation
PE: physical education
PV: photovoice
SALVO: stimulating an active lifestyle in prevocational students

SIM: structured interview matrix

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Protocol

Implementation and Effects of an Information Technology–Based Intervention to Support Speech and Language Therapy Among Stroke Patients With Aphasia: Protocol for a Virtual Randomized Controlled Trial

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Abstract

Background: Mobile app–based therapies are increasingly being employed by speech-language pathologists in the rehabilitation of people with aphasia as adjuncts or substitutes for traditional in-person therapy approaches. These apps can increase the intensity of treatment and have resulted in meaningful outcomes across several domains.

Objective: VoiceAdapt is a mobile therapy app designed with user and stakeholder feedback within a user-centered design framework. VoiceAdapt uses two evidence-based lexical retrieval treatments to help people with aphasia in improving their naming abilities through interactions with the app. The purpose of the randomized controlled trial (RCT) proposed here is to examine the feasibility and clinical efficacy of training with VoiceAdapt on the language and communication outcomes of people with aphasia.

Methods: A multicenter RCT is being conducted at two locations within Canada. A total of 80 people with aphasia will be recruited to participate in a two-arm, waitlist-controlled, crossover group RCT. After baseline assessment, participants will be randomized into an intervention group or a waitlist control group. The intervention group participants will engage in 5 weeks of training with the app, followed by posttreatment and follow-up assessments after an additional 5 weeks. Those in the waitlist control group will have no training for 5 weeks; this is followed by pretreatment assessment, training for 5 weeks, and posttreatment assessment. All trial procedures are being conducted remotely given the COVID-19 pandemic.

Results: Recruitment of participants started in September 2020, and the study is expected to be completed by March 2022. Publication of results is expected within 6 months of study completion.

Conclusions: The results of the RCT will provide information on evidence-based practice using technology-based solutions to treat aphasia. If positive results are obtained from this RCT, the VoiceAdapt app can be recommended as an efficacious means of improving lexical retrieval and communicative functioning in people with aphasia in an easily accessible and a cost-effective

manner. Moreover, the implementation of this RCT through remote assessment and delivery can provide information to therapists on telerehabilitation practices and monitoring of app-based home therapy programs.

Trial Registration: ClinicalTrials.gov NCT04108364; https://clinicaltrials.gov/ct2/show/NCT04108364

International Registered Report Identifier (IRRID): DERR1-10.2196/30621

(JMIR Res Protoc 2021;10(7):e30621) doi:10.2196/30621

KEYWORDS

aphasia; rehabilitation; speech-language pathology; app-based therapy; user-centered design; mHealth; adaptive software

Introduction

Background

Aphasia is an acquired language disorder, most commonly caused by stroke. It can impact linguistic expression and comprehension in written and oral modalities. As such, this condition can have devastating consequences on the social, emotional, and occupational functioning of people with aphasia [1]. Although aphasia affects nearly one-third of all individuals who experience a stroke [2,3] and has been associated with poorer outcomes in the acute and chronic periods following stroke [4], the condition itself remains relatively unknown among the general public [5].

Rehabilitation for people with aphasia provided by speech-language pathologists (SLPs) has shown improved outcomes [6,7]. However, several factors, including constraints on health care resources, often prevent people with aphasia from receiving services, particularly in the chronic stages. The recent proliferation of mobile app–based therapies (apps) has provided a cost-effective means by which people with aphasia can receive prolonged rehabilitation. SLPs have been increasingly employing such apps as adjuncts or substitutes for traditional (in-person) therapy approaches, with meaningful outcomes observed across several domains [8,9]. Such apps have the potential to increase the intensity of rehabilitation, a factor that is associated with greater long-term recovery [10-12]. Moreover, recent evidence has shown that people with aphasia can self-deliver this type of intervention and attain positive language and communication outcomes [13-15]. Technology also enables measuring multiple parameters of user interactions with touch-based devices, and algorithms can be deployed to adapt content based on the user/patient state.

Large-scale randomized controlled trials (RCTs) investigating the clinical utility of tablet-based speech-language therapy apps for aphasia have not been conducted. Nevertheless, preliminary evidence on the utility of app-based therapy for adults with acquired aphasia is emerging. Mallet and colleagues [16] demonstrated that mobile tablet–based rehabilitation is feasible for delivering speech-language therapy in an acute care setting. In this study, patients with communication deficits following acute stroke interacted with tablets containing commercially available speech-language therapy apps. The participants in this study expressed a desire to be more active in their rehabilitation, and they even exceeded the minimum time (one hour per day) recommended for engaging with the mobile tablet. In a more recent RCT conducted on 32 people with aphasia, Braley and colleagues [13] reported that people with aphasia in the treatment group who practiced a variety of speech, language, and cognition exercises using a tablet-based therapy app (ie, Constant Therapy) demonstrated greater language outcomes than a group who completed worksheet exercises. Importantly, this RCT was conducted virtually with participants self-managing their participation through periodic monitoring by the researchers. Additional evidence derived from case series and small group studies also proves the utility of app-based therapy for adults with aphasia in the chronic stages. Participants in these studies have shown improvements across a variety of outcome measures, including naming of trained and untrained items, standardized language and cognitive assessment batteries, and spoken discourse [15,17-19].

Despite the increasing availability of therapy apps designed for aphasia [20], very few have been designed with inputs from relevant stakeholders following the principles of user-centered design (UCD). UCD is a systematic approach to meet usability and user experience goals through integrating the needs and abilities of users during the design process of an artifact. This ensures that the product/service design and development align with all the relevant stakeholders' needs (ISO 9241-220). Essential UCD activities include planning and managing the process, defining the context of use for each user group, gathering user and stakeholder requirements, designing an ergonomic solution based on the requirements, and evaluating the design within a user-centered approach [21].

In a recent review, only three apps were identified where developers engaged people with aphasia in the design process [22]. All these apps engaged patients to varying extents during therapy evaluation or prototype testing. There was no evidence of patients being involved in either of the two initial phases of app development (ie, theory-based conception, software implementation). Based on the above review, the authors present a broad, four-phase model of the app development process encompassing the following: (1) theoretical considerations, (2) software development, (3) pilot testing, and (4) long-term evaluation. The authors conclude that people with aphasia should be involved in all phases during the development and evaluation of therapy apps, as their involvement could "enhance the product quality, functionality and acceptability, and increase patients' motivation to use these digital therapies" [22].

VoiceAdapt

Recently, the VoiceAdapt Consortium (VC), an international team of researchers from the fields of computer science, usability design, and speech-language pathology, has produced an app for treating naming impairments in people with aphasia. Using evidence-based lexical retrieval protocols, the VoiceAdapt

app instantiates Phonological Components Analysis (PCA) [23] and Semantic Feature Analysis (SFA) [24] into an adaptive, voice-responsive therapy app that people with aphasia can use to improve their naming skills.

The VoiceAdapt project has so far involved 75 end users (people with aphasia, clinicians, and caregivers) in the UCD process to identify the main barriers and obstacles to app-based training and rehabilitation; ensure independent usage and sustained motivation; and optimize the end-user experience and training impact. This was achieved by eliciting user requirements (conducting guideline-based structured interviews), designing solutions (mock-ups, prototypes), and evaluating the designs against the requirements (focusing on user experience in terms of multimodal speech interaction and adaptivity) over three iterative cycles. The result is a mobile speech-language training app for people with aphasia that can run on iOS and Android platforms. The app supports regular training sessions, adaptivity (individual performance thresholds for training material selection), personalization (training content is selected based on individual interests), and coordination between therapists and patients; it also addresses multimodal language goals (reading, understanding, and production).

Study Purpose

The purpose of this study is to examine the impact of the VoiceAdapt adaptive speech-language treatment app, created using the principles of UCD, on the naming abilities of people with aphasia within an RCT. Secondary outcomes focusing on overall language improvement, communication, and quality of life will also be examined. Herein, we present the protocol of the VoiceAdapt study (ClinicalTrials.gov NCT04108364).

Methods

Selection of Communities for the Study, Participants, and Procedures

Participants will be recruited from two geographic regions in Canada through the Language Sciences Lab (Department of Speech-Language Pathology, University of Toronto) and Aphasia Research Lab (Department of Communication Sciences and Disorders, University of Alberta), based in Toronto, Ontario and Edmonton, Alberta, respectively. Participants with aphasia will be recruited from community-based aphasia centers and programs, clinics, and research databases. Initial contacts will be made with aphasia centers and programs providing information about the study, followed by recruitment presentations and meetings with interested participants.

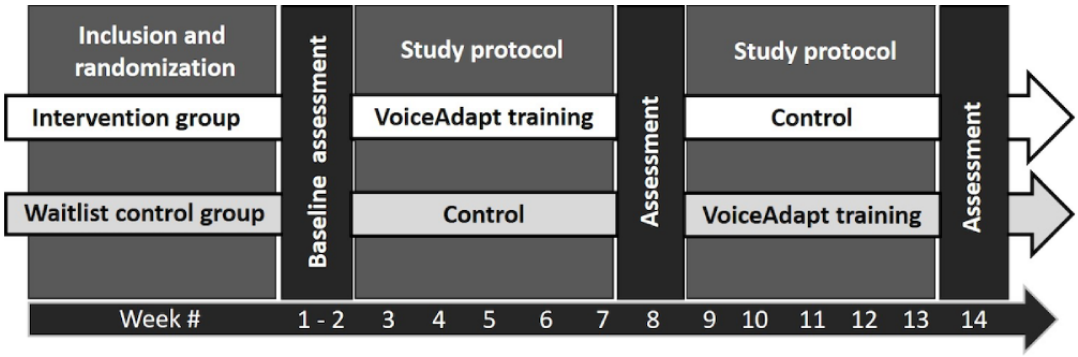
Inclusion and Exclusion Criteria

The participants enrolling in the study will meet the following inclusion criteria: be at least 6 months post the onset of a stroke in the left hemisphere; have mild-to-moderate aphasia (Aphasia Quotient ≥30 on the Western Aphasia Battery-Revised [WAB-R]) [25]; score below 75% correct on the Boston Naming Test (BNT) [26] during initial assessment; exhibit prominent verbal expression impairment; pass screenings for vision, hearing, and basic cognitive functioning; speak English as a primary language; and be willing to commit to participation for the entire study duration. Despite meeting all these inclusion criteria, participants will be excluded if they are currently engaged in individual (one-on-one) speech-language therapy or are using speech-language therapy apps.

Study Design

The RCT will have a two-arm, randomized, waitlist-controlled, crossover group design. In Phase 1, people with aphasia randomized to the intervention group will train with VoiceAdapt. The control group will be a waitlist treatment-deferred group. In Phase 2, the control group will train with VoiceAdapt (see Figure 1). Participants will be randomized to groups according to a computer-generated randomization list.

Figure 1. Schematic of the study design.



Intervention

The app intervention comprises naming exercises based on evidence-based anomia treatments, SFA and PCA, delivered on a mobile tablet. The exercises involve the presentation of a colored picture and a series of prompts designed to engage the people with aphasia in providing semantic features (eg, "What is it used for?" [action]; "What does it look like?" [properties]); or phonological components (eg, "What sound does it start with?" [first sound]; "What is a rhyming word?" [rhyme]). Figures 2 and 3 display summary screens reviewing the generated semantic and phonologic features of the target items, respectively (Additional screenshots of the app are displayed in Multimedia Appendix 1). A help screen also reminds users

of the various features (Figure 4). The patient's voice is recorded and used as the input for the app. The app is designed to maximize user engagement through UCD principles. People with aphasia randomized to the VoiceAdapt treatment group will be instructed to practice using the app during weekdays for one hour per day for 5 weeks. The people with aphasia will have the option of downloading the app on their own tablets from a link provided by the researchers, or the researchers will provide them with tablets with the app loaded. Research staff will check in and monitor progress through email or telephone/video calls on a weekly basis.

Figure 2. Screenshot from the VoiceAdapt app displaying the summary screen of the Semantic Feature Analysis protocol.

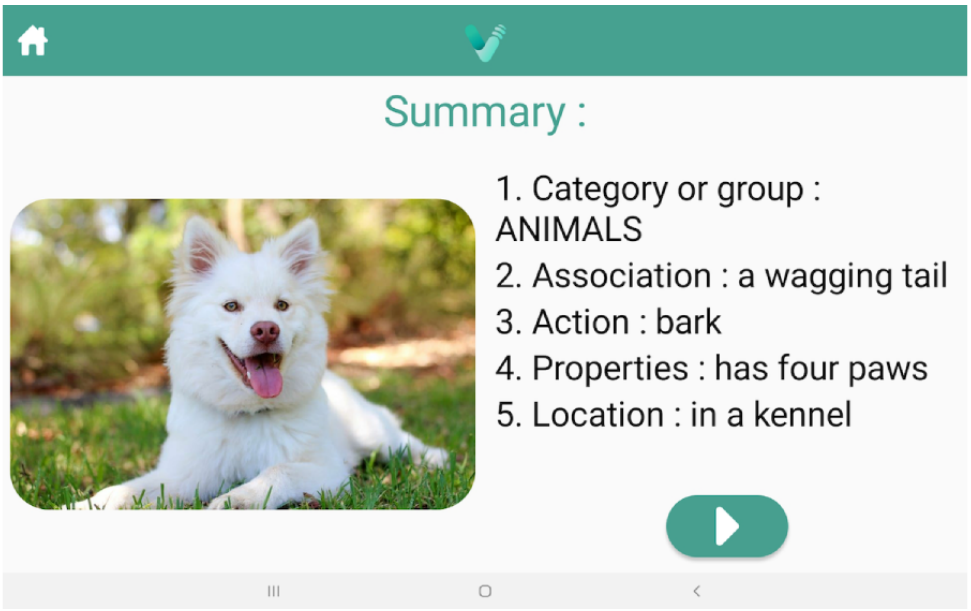


Figure 3. Screenshot from the VoiceAdapt app displaying the summary screen of the Phonological Components Analysis protocol.

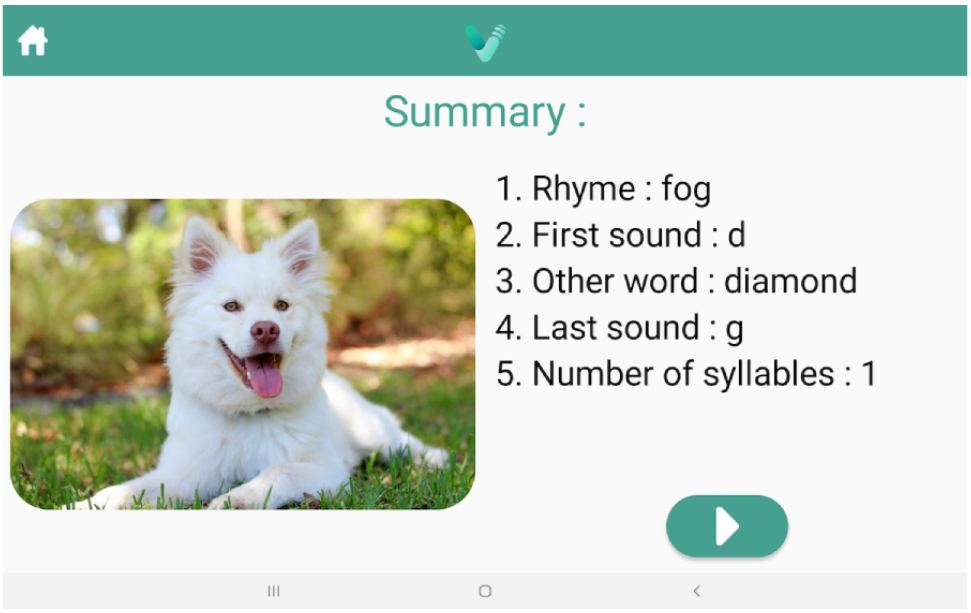
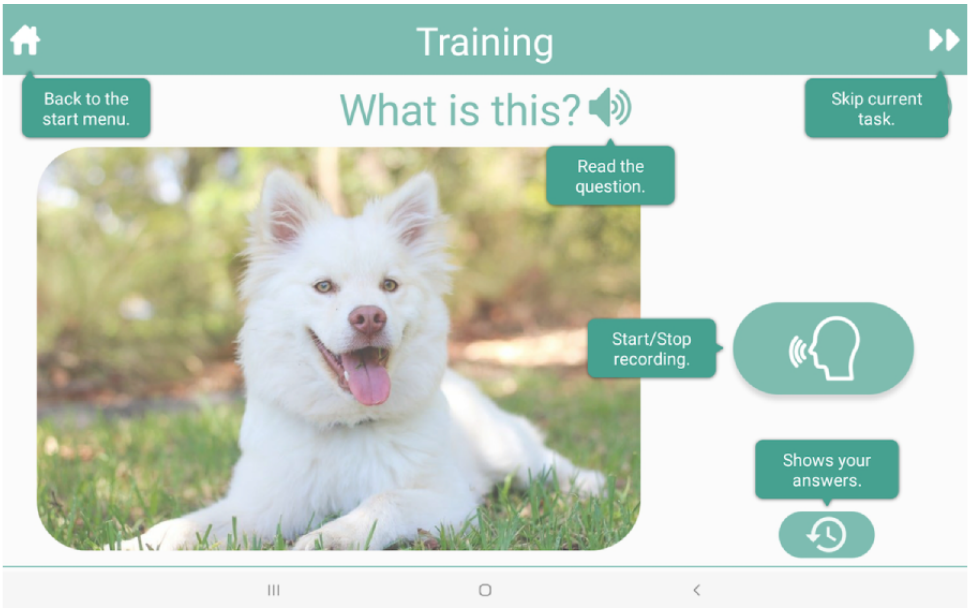


Figure 4. Screenshot from the VoiceAdapt app displaying the user help screen.



Duration

The participants will take part in the study for approximately 13 weeks once enrolled. Pretreatment assessment will take place in Week 1, followed by 5 weeks of engagement in Phase 1 (treatment or control). Midpoint assessments will take place in Week 7, followed by 5 weeks of engagement in Phase 2 (crossover into control or treatment). Final assessments will take place in Week 13 following study enrollment.

Measures

Efficacy will be monitored by the scores on primary and secondary outcome measures. The primary outcome measure will be the BNT [25] to measure naming; secondary outcome measures will be the WAB-R [26]; Stroke and Aphasia Quality of Life Scale-39 (SAQOL-39) [27] to measure quality of life; and Communication Effectiveness Index (CETI) [28] to measure the communication capabilities of the participants with aphasia and their partners' perception of the participants' communication. In addition to the primary and secondary outcome measures, the System Usability Scale (SUS) [29], Situational Motivation Scale (SIMS) [30], and a posttreatment questionnaire specific to app usage will be administered to all participants. In addition, the in-app parameters evaluating aspects such as the amount of time spent on training per session, total amount of time spent on training over the study duration, etc will also be measured for future analysis.

Sample Size Determination

The planned enrollment for the study is 80 (ie, 40 at each of the two sites in Canada). The sample size calculation is based on the medium effect sizes estimated in our study according to previous results. Accounting for a dropout rate of approximately 10%, we need to include 79 people with aphasia; thus, we plan to enroll 80 people with aphasia. We will conduct an intention to treat analysis and include all the randomized participants in our analyses.

Analytic Strategy

Mixed-effects regression will be used to analyze the 2 × 2 crossover trial with one baseline [31]. The analysis will include covariate adjustments for variables such as the recruitment site and participant characteristics (eg, sex, age, hours of training, assessors, and caregiver characteristics). Adjustment can increase the precision of the treatment effect estimates and confirm whether training was equally efficacious across covariates (ie, using covariates by treatment interaction) and whether the retention of improvement was equal across covariates (ie, covariates by carryover interaction). Mixed-effects regression can also account for hierarchical sampling, which is important if participants within sites are more similar than if they were randomly chosen. If carryover is detected, we will also estimate the treatment effects after excluding the Period 2 assessments affected by carryover.

The Mauchly test will be used to evaluate whether the sphericity assumption is tenable. If the variances are unequal, we will disaggregate the analysis and use paired and two-group *t* tests as appropriate to estimate the treatment, carryover, and period effects; if covariate adjustment is required, these contrasts will be evaluated using mixed-effects regression while also accounting for hierarchical sampling.

Interim analyses will be conducted when quarterly enrollment targets are met (ie, 20, 40, and 60 participants).

Ethics Statement and Consent

This study will be conducted according to Canadian and international standards of Good Clinical Practice for all studies. Applicable government regulations and the University of Toronto and University of Alberta research policies and procedures will also be followed.

This protocol and any amendments to the same will be submitted to the University of Toronto Human Research Ethics Unit (HREU) and University of Alberta Health Research Ethics Board (HREB) for formal approval to conduct the study.

All participants selected for this study will be provided a consent form describing the study and providing sufficient information for them to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the HREU and HREB. The formal consent of a participant, using the HREU- and HREB-approved consent form, will be verbally obtained and recorded before that participant is subjected to any study procedure per HREU- and HREB-approved procedures.

Adaptations for Data Collection During the COVID-19 Pandemic

With in-person research activities limited due to the COVID-19 pandemic, all data collection activities will be conducted virtually using HREU- and HREB-approved video conferencing software. Recruitment presentations, initial informational/screening interviews, and all assessment sessions will take place remotely. All assessment instruments have been adapted for remote delivery and will be administered by the assessors through sharing their screen and eliciting verbal responses or pointing to responses using annotation functions within the software. All adaptations to the research protocol for remote delivery have been approved by the Research Ethics Boards of the University of Toronto and University of Alberta.

Results

The project was funded in 2018 and enrolment for the RCT is ongoing. A primary completion date is expected in March 2022, and publication of results is expected within 6 months of work completion.

Discussion

This RCT is designed to assess the efficacy of the VoiceAdapt app, a new, tablet-based therapy program for people with aphasia. This app was designed using the principles of UCD, incorporating inputs from the end users (people with aphasia, their caregivers, and SLPs) through an iterative process. The end result is a mobile speech-language training app instantiating evidence-based treatment principles into an adaptive and a personalizable app that addresses multimodal language stimulation. The RCT will examine the effect after 5 weeks (25 hours) of training with the app on language production (ie, naming) in people with aphasia in the chronic stage of recovery. The impact on secondary outcomes, including communication effectiveness and quality of life, will also be assessed.

Technology-based solutions, including apps to reach speech-language therapy and communication goals can be a means to increase home practice and therapy intensity in a cost-effective manner. Particularly for people with aphasia who are in the chronic stages of recovery (ie, more than a year post the onset of aphasia), there can be limited rehabilitation options. It is recommended that technology-based rehabilitation approaches engage participants in a personalized manner [8,13]. Although an increasing number of therapy apps are entering the market, they do not engage people with aphasia in the development and testing stages [22]. The VoiceAdapt app differs from other apps currently available on the market in that it incorporates evidence-based treatment approaches within a framework that was identified by the end users through a UCD process in the conceptualization, development, and implementation stages of the app.

If positive results are obtained from this RCT, the VoiceAdapt app can be recommended as an efficacious means of improving lexical retrieval and communicative functioning in people with aphasia in an easily accessible and a cost-effective manner. Moreover, the implementation of this RCT through remote assessment and delivery can provide information to therapists on telerehabilitation practices and monitoring of app-based home therapy programs.

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Authors' Contributions

ESK and ER designed the study with assistance from LL, J-N V-A, SM, R Schatz, SS, TB, and R Spang. All authors designed the VoiceAdapt app. PM developed the VoiceAdapt app and backend programs. EK, ER, LL, and CW recruited the participants and managed the RCT. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Screenshots of VoiceAdapt app.

[PDF File (Adobe PDF File), 7078 KB - resprot_v10i7e30621_app1.pdf]

Multimedia Appendix 2
Peer-review report by the funding committee of the JTC 2017 launched by the Joint Programming Initiative “More Years Better Lives” (JPI MYBL).
[PDF File (Adobe PDF File), 316 KB - resprot_v10i7e30621_app2.pdf]

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Abbreviations

BNT: Boston Naming Test
CETI: Communicative Effectiveness Index
HREB: Health Research Ethics Board
HREU: Human Research Ethics Unit
RCT: randomized controlled trial
PCA: Phonological Components Analysis
SAQOL-39: Stroke and Aphasia Quality of Life Scale - 39
SFA: Semantic Features Analysis
SLP: speech-language pathologist
SIMS: Situational Motivation Scale
SUS: System Usability Scale
UCD: user-centered design
WAB-R: Western Aphasia Battery-Revised

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Protocol

Developing and Implementing a Web-Based Psychotherapy Program to Address Mental Health Challenges Among Patients Receiving Oncologic and Palliative Care: Protocol for an Open-Label Randomized Controlled Trial

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Abstract

Background: The demand for mental health care, particularly for depression and anxiety, is 3-fold greater among patients receiving oncologic and palliative care than for the general population. This population faces unique barriers, making them more susceptible to mental health challenges. Various forms of psychotherapy have been deemed effective in addressing mental health challenges in this population, including supportive psychotherapy, cognitive behavioral therapy, problem-based therapy, and mindfulness; however, their access to traditional face-to-face psychotherapy resources is limited owing to their immunocompromised status, making frequent hospital visits dangerous. Additionally, patients can face hospital fatigue from numerous appointments and investigations or may live in remote areas, which makes commutes both physically and financially challenging. Web-based psychotherapy is a promising solution to address these accessibility barriers. Moreover, web-based psychotherapy has been proven effective in addressing depression and anxiety in other populations and may be implementable among patients receiving oncologic and palliative care.

Objective: The study will investigate the feasibility and effectiveness of web-based psychotherapy among patients receiving oncologic and palliative care, who have comorbid depression or anxiety. We hypothesized that this program will be a viable and efficacious treatment modality compared to current treatment modalities in addressing depression and anxiety symptoms in this population.

Methods: Participants (n=60) with depression or anxiety will be recruited from oncology and palliative care settings in Kingston (Ontario, Canada). Participants will be randomly allocated to receive either 8 weeks of web-based psychotherapy plus treatment as usual (treatment arm) or treatment as usual exclusively (control arm). The web-based psychotherapy program will incorporate cognitive behavioral therapy, mindfulness, and problem-solving skills, and homework assignments with personalized feedback

from a therapist. All web-based programs will be delivered through a secure platform specifically designed for web-based psychotherapy delivery. To evaluate treatment efficacy, all participants will complete standardized symptomology questionnaires at baseline, midpoint (week 4), and posttreatment.

Results: The study received ethics approval in February 2021 and began recruiting participants in April 2021. Participant recruitment has been conducted through social media advertisements, physical advertisements, and physician referrals. To date, 11 participants (treatment, n=5; control, n=4; dropout, n=2) have been recruited. Data collection and analysis are expected to conclude by December 2021 and January 2022, respectively. Linear regression (for continuous outcomes) will be conducted with interpretive qualitative methods.

Conclusions: Our findings can be incorporated into clinical policy and help develop more accessible mental health treatment options for patients receiving oncologic and palliative care. Asynchronous and web-based psychotherapy delivery is a more accessible, scalable, and financially feasible treatment that could have major implications on the health care system.

Trial Registration: ClinicalTrials.gov NCT04664270; https://clinicaltrials.gov/ct2/show/NCT04664270

International Registered Report Identifier (IRRID): DERR1-10.2196/30735

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KEYWORDS

anxiety; cognitive behavioral therapy; depression; eHealth; electronic care; internet; mental health treatment; oncology; palliative care; psychotherapy

Introduction

Background and Rationale

Common psychiatric disorders are highly prevalent among patients receiving oncologic and palliative care, with approximately 40% of these patients showing symptoms of depression and anxiety [1]. This alarming prevalence is 3-fold that in the general population, with mood and anxiety disorders being the most common psychiatric challenges among these patients [1,2]. Additionally, the prevalence of this psychiatric morbidity is further elevated in those with more advanced and incurable diseases [3]. Despite this high comorbidity of mood and anxiety disorders in patients with cancer, these disorders are massively underdiagnosed and often remain untreated [4]. In addition to the increased burden these mental health challenges have on individual patients, the cost of care for their underlying medical problem is almost twice as high in the presence of mental health comorbidities [5]. Therefore, addressing these mental health challenges must be of top priority to help patients, and is necessary to limit the costs of these diseases on public health.

Both medication and psychotherapy are effective in treating mood and anxiety disorders in patients receiving oncologic and palliative care. However, considering the complex pharmacological management of cancers and the possibility of medication interactions, psychotherapy may be a better choice for managing mental health disorders in these patient groups [6]. Different studies have shown the efficacy of psychotherapy in patients with cancer to control mental health comorbidities, and it has been shown that in addition to mental health symptoms, supplementation of psychotherapy to the normal course of treatment can improve medical outcomes as well [7,8]. However, while highly effective, the traditional face-to-face method of delivering psychotherapy has significant limitations that are magnified among patients receiving oncologic care. The duration of treatment, access to treatment, access to qualified personnel, and specific evidence-based tools are barriers that can limit patients receiving oncologic and palliative care from accessing the care they need and deserve. To address these challenges, 1 potential solution is to offer web-based, asynchronous therapy instead of or in addition to traditional live, in-person treatment.

In recent years, web-based psychotherapy has emerged as a promising solution to address the inaccessibility and inefficiency issues of in-person treatment. More specifically, web-based delivery of cognitive behavioral therapy (e-CBT) has been shown to decrease depressive symptoms and sustain beneficial effects [9-12]. Being available anywhere, at any time, and in any language, e-CBT can make mental health care more accessible geographically, temporally, and culturally. Furthermore, by delivering psychotherapy on the internet, clinicians can sustain a cost-effective and time-efficient practice. This method of delivery can also increase treatment flexibility and improve treatment adherence among patients.

Addressing the psychological needs of patients receiving oncologic and palliative care can significantly decrease the burden of disease and their overall suffering. Considering previous reports of the successful outcomes of e-CBT for various mental health challenges [9,13,14], we believe that e-CBT can be successfully implemented in an oncology and palliative care setting as well.

Objectives

This study aims to establish a web-based psychotherapy clinic at an academic center for the management of depression and anxiety in patients receiving oncologic and palliative care, specifically to meet the needs of this underserved specialized population. If successful, this approach could increase the capacity and quality of mental health among patients with cancer who receive palliative care and could also, directly and indirectly, minimize the financial burden of these diseases on the public health system. We hypothesized that this e-CBT program can effectively address depressive and anxiety

symptoms in patients receiving oncologic and palliative care. This study will aim to address the following research questions:

1. Is this e-CBT and mindfulness program a suitable therapeutic modality to address the psychological needs of patients receiving oncologic and palliative care?
2. Is the web-based delivery of this psychotherapy program through a secure platform an effective solution to meet the increased demands of patients receiving oncologic and palliative care?

Methods

Study Design

This study will employ an open-label randomized controlled trial design to investigate the efficacy of a web-based psychotherapy program in treating anxiety and depressive symptoms in patients receiving oncologic and palliative care. Participants will be randomly allocated to receive either the web-based psychotherapy program or treatment as usual (TAU) for 8 weeks. This study has been registered on ClinicalTrials.gov (protocol# NCT04666974).

Participants

Patients (n=60) diagnosed with depressive or anxiety disorders due to another medical condition in the context of oncologic or palliative care will be recruited through referrals from the Kingston Health Sciences Centre (including the cancer center), Providence Care Hospital, family physicians, other health care providers, and self-referrals in Kingston (Ontario, Canada). After consenting to take part in the study, a complete assessment will be performed by one of the psychiatrists on the team to confirm the diagnosis. Inclusion criteria are an age of 18-55 years at the start of the study; a diagnosis of depression or anxiety secondary to a general medical condition (in the context of oncologic or palliative care conditions), using the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, by one of the psychiatrists on the team; competence to consent and participate in the study; ability to speak and read in English; and consistent and reliable access to the internet. Exclusion criteria are having acute hypomanic or manic episodes, acute psychosis, severe alcohol or substance use disorder, active suicidal or homicidal ideation, or currently receiving or having received CBT in the past year. Participants will then be randomly assigned to two groups: TAU control group (ie, medication, psychiatric consultation, referrals to in-person activities or groups, etc) or the e-CBT (e-CBT + mindfulness + problem solving + TAU) treatment group. Participant allocation will be equally stratified (e-CBT, n=30; TAU, n=30).

Procedures

Patients in the e-CBT group will receive an 8-week web-based program that includes CBT in combination with mindfulness and problem-based therapy in addition to TAU. The content of this program will be customized to reflect challenges that patients receiving oncologic and palliative care face through the course of their treatment, and developed to contain interactive and engaging therapy modules. All web-based sessions and interactions will occur through the Online Psychotherapy Tool (OPTT), a secure internet-based platform. Through this platform, the predesigned therapy modules will be assigned to the patients, which will be accessible to them at any time throughout the week. Each module will consist of approximately 30 slides, which take an average of 50 minutes to complete. Each weekly module will highlight a different topic and includes general information, an overview of skills, and homework to be completed within that week. This homework can be directly submitted through the OPTT to the clinician who will then provide personalized feedback to the patient. The average time spent per week by a clinician with a particular patient is approximately 15 minutes. Patients in the control group will receive TAU for the first 8 weeks; if still significantly symptomatic (<50% response to treatment from baseline), they will then be offered the 8-week e-CBT program.

Therapist Training

All therapists have experience in psychotherapy delivery and are trained by a psychiatrist in our group. Additionally, all therapists learn the specifics of the modules covered in treatment, along with the standard care pathway. The therapists in our group include a combination of medical graduates and residents, graduate students, and trained research assistants. Before working with any patients, therapists will provide practice feedback on simulated sessions, which will be analyzed by the psychiatrists in our group to ensure that the quality of care is adequate. All therapists will be supervised by the principal investigator, who is an expert in delivering web-based psychotherapy. Moreover, feedback on homework will only be sent to patients after it is read, edited, and approved by the supervisor. Any issues regarding OPTT will be handled through OPTT technical support, which can be accessed at any time.

Ethics and Data Privacy

All procedures have been approved by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (file# 6031471). For privacy purposes, participants will only be identifiable by an identification number on the OPTT, and hard copies of the consent forms with participants' identities will be stored securely on site and destroyed 5 years after study completion. Participant data are only accessible by the care providers who are directly assigned to that participant, and only anonymized data are provided to the analysis team. Participants have the option to withdraw from the study at any point and request for their data to be removed from the analysis. However, since the collected data are considered a medical record, they will not be permanently deleted for 10 years after treatment.

The web-based platform used in this study (OPTT) complies with the Health Insurance Portability and Accountability Act, Personal Information Protection and Electronic Documents Act, and Service Organization Control-2 policy. Additionally, all servers and databases are hosted in the Amazon Web Service Canada cloud infrastructure, which is managed by Medstack, to ensure that all provincial and federal privacy and security regulations are met. The OPTT does not collect any identifiable personal information or IP addresses for privacy purposes. The OPTT only collects anonymized metadata to improve its service quality and provide advanced analytics to the clinician team. The OPTT encrypts all data, and no employee has direct access

to the participant data. All encrypted backups are maintained in the S3 storage, which is dedicated to Queen's University, Kingston.

Outcome Evaluation

The primary outcome measure will be the progression or regression of our participants' mental health symptoms. Outcome measures will include the scores of the following standardized questionnaires: Functional Assessment of Cancer Therapy-General, 9-item Patient Health Questionnaire, 7-item Generalized Anxiety Disorder, 14-item Resilience Scale, and the Quality of Life and Satisfaction Questionnaire. Assessments will be completed upon study entry and after weeks 4 and 8 of the program. Other behavioral data regarding patients' interaction and engagement with their therapy (ie, number of logins per day and amount of time spent on each session) will be collected directly through the OPTT to obtain further insight. We hypothesized that the level of patient engagement may have predictive power in therapy outcomes.

The anticipated quantitative outcomes include a progression of questionnaire scores, high frequency of logins, and high frequency of logins during nonbusiness hours. The anticipated qualitative outcome is positive feedback from participants receiving e-CBT and health care providers.

Data Analysis

Initially, all data will be examined for missing, nonsensical, and outlying variables. Missing data will be treated as missing and not imputed (ie, will be analyzed on a per-protocol basis). Given the likelihood of participant dropout or withdrawal, participants have been purposely oversampled to obtain meaningful and statistically significant results at the end of the study. Based on previous experience with CBT and e-CBT in similar patient populations, the anticipated dropout is up to 30% by the end of the phases. However, the remaining individuals will be able to provide significant information regarding changes in their symptoms. Given that several outcomes will be considered, it is difficult to calculate a single sample size or provide a specific power calculation. However, using the 9-item Patient Health Questionnaire as an example, as it is common to all participants, a 30% change is considered clinically significant. Therefore, a sample size of 20 participants in each arm of the study would be sufficient for obtaining significant results with P=.05 and a power of 0.95.

Baseline and demographic data from individuals who drop out will be compared to those who finish identifying any fundamental differences between completers and noncompleters. Linear regression models will be used to compare treatment and control outcomes while controlling for demographic variables such as age and gender.

Results

This study received funding in August 2020 and ethics approval from the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (file# 6031471) in February 2021. Participant recruitment has been conducted through social media advertisements, physical advertisements, and physician referrals. To date, 11 participants (e-CBT, n=5; TAU, n=4; dropout, n=2) have been recruited. Data collection is expected to conclude by December 2021, and data analysis is expected to be completed by January 2022. Linear regression (for continuous outcomes) will be conducted with interpretive qualitative methods. All protocols and results have been, and will be, reported using the GUIDED and TIDieR Report Checklists and Guidelines (Multimedia Appendices 1 and 2).

Discussion

Previous studies have reported the efficacy of e-CBT in managing mood and anxiety disorder in the general population [13-15]. Based on these previous and promising results, showing efficacies comparable to face-to-face psychotherapy, web-based delivery of psychotherapy to patients receiving oncologic and palliative care who have comorbid anxiety or depression could be an effective treatment option. Using the predesigned therapy modules, an experienced care provider can deliver asynchronous care to 3-4 patients simultaneously for 1 synchronous session. This effectively implies that more service could be provided at a lower cost, effectively increasing the capacity and performance of the health care system by 4 folds. This would result in drastic shortening of wait times and increased coverage, leading to significant financial and societal cost savings. Our findings have the potential to be encoded into clinical policy and could potentially be used by family medicine clinics, specialists, and insurance companies as a new resource. To our knowledge, there have been no similar studies in this field. If successful, this innovation has the potential to propagate significant positive change.

Acknowledgments

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Conflicts of Interest

NA has cofounded the care delivery platform in use (ie, OPTT) and has ownership stakes in OPTT Inc. MO is the CEO and has ownership stakes in OPTT Inc.

Multimedia Appendix 1
GUIDED Report Checklist and Guidelines.
[PDF File (Adobe PDF File), 72 KB - resprot_v10i7e30735_app1.pdf]

Multimedia Appendix 2
TIDieR Report Checklist and Guidelines.
[PDF File (Adobe PDF File), 97 KB - resprot_v10i7e30735_app2.pdf]

Multimedia Appendix 3
Peer-review report by Queen's University Department of Psychiatry Internal Grant Competition 2020.
[PDF File (Adobe PDF File), 108 KB - resprot_v10i7e30735_app3.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
e-CBT: electronically delivered cognitive behavioral therapy
OPTT: Online Psychotherapy Tool
TAU: treatment as usual

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Protocol

Delivering an Online Cognitive Behavioral Therapy Program to Address Mental Health Challenges Faced by Correctional Workers and Other Public Safety Personnel: Protocol for a Mixed Methods Study

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Abstract

Background: Public safety personnel have regular and often intense exposure to potentially traumatic events at work, especially workplace violence in the case of correctional workers. Subsequently, correctional workers are at higher risk of developing mental health problems such as posttraumatic stress disorder. Public safety personnel are up to 4 times more likely to experience suicidal ideation, suicidal attempts, and death by suicide compared to the general population. Despite this high prevalence, help-seeking behaviors from public safety personnel are low due to stigma and irregular work hours limiting access to care. Innovative treatments are needed to address these challenges.

Objective: This study will investigate the efficacy of an electronically delivered cognitive behavioral therapy (e-CBT) program tailored to correctional workers' mental health problems.

Methods: This study is composed of 4 phases. In phase 1, we will interview correctional workers individually and in focus groups to identify personal, social, and cultural factors affecting their mental health and barriers to care. Phase 2 will use the information gathered from the interviews to develop gender- and diagnosis-specific e-CBT modules. These will be presented to a new group of participants who will provide further feedback on their usability and accessibility. In phase 3, we will randomly assign participants to either an e-CBT or treatment as usual arm. The program will be evaluated with validated symptomatology questionnaires and interviews. Phase 4 will use this additional information to fine-tune the e-CBT modules for a larger-scale randomized controlled trial design comparing the e-CBT program to in-person CBT. All e-CBT modules will be delivered through a secure online platform.

Results: The study received ethics approval in December 2020, and participant recruitment began in March 2021. Participant recruitment has been conducted through targeted advertisements and physician referrals. To date, there have been 15 participants recruited for Phase 1, and it is expected to conclude in July 2021, with phase 2 beginning in September 2021. Complete data collection and analysis from all phases are expected to conclude by July 2023. Linear and binomial regression (for continuous and categorical outcomes, respectively) will be conducted along with interpretive qualitative methods.

Conclusions: If proven efficacious and feasible, this e-CBT program can provide a high-quality and clinically validated resource to address the mental health problems of correctional workers. Additionally, findings can contribute to the development of innovative treatments for other public safety professions.

Trial Registration: ClinicalTrials.gov NCT04666974; https://www.clinicaltrials.gov/ct2/show/NCT04666974

International Registered Report Identifier (IRRID): DERR1-10.2196/30845

(JMIR Res Protoc 2021;10(7):e30845) doi:10.2196/30845

KEYWORDS

mental health; correctional workers; public safety personnel; depression; anxiety; psychotherapy; cognitive behavioral therapy; online; internet; treatment

Introduction

Background

Public safety personnel (PSP) have regular and often intense exposure to traumatic events and are at higher risk for developing mental health disorders including posttraumatic stress disorder (PTSD), major depressive disorder (MDD), generalized anxiety disorder (GAD), and drug and alcohol use disorders [1]. PSPs are up to 4 times more likely to experience suicidal ideation, suicidal attempts, and death by suicide compared to the general population [2]. Correctional workers (CWs) are at a particularly elevated risk of developing mental health disorders, as they work in a hostile environment with an increased prevalence of violence [3]. A survey found that over 98% of CWs have had at least one encounter with job-related traumatic events, frequently involving exposure to serious injury or death; casualties; unusual sights, sounds, and circumstances; first-hand knowledge of the victim(s); and threats to their safety and security [4]. It was also found that CWs, on average, will experience approximately 28 traumatic events during their career [4]. Many CWs feel there are not enough organizational policies to debrief following the occurrence of such difficult situations, along with a lack of after-hour counselling, leaving them concerned with the limited support available through their employee assistance programs [5]. The absence of sufficient organizational policies exacerbates the effects of violent incidents on CWs, leading to PTSD being 3 times more prevalent in CWs compared to the general population [6-8]. Therefore, the need to address this mental health crisis in CWs must be a top priority.

Psychotherapy, and more specifically, cognitive behavioral therapy (CBT), is the first-line treatment for various anxiety disorders, including PTSD [9-17]. Psychotherapy can be more cost-effective, decrease relapse prevalence, outperform many pharmacotherapies, and be the intervention of preference for many patients when treating anxiety disorders [18-23]. CBT is one of the most widely investigated and practiced forms of psychotherapy and is effective in reducing the deleterious symptoms of mood and anxiety disorders [24].

While CBT has a well-established efficacy in improving various mental health disorder symptoms, many patients do not receive treatment [25]. This is due to the multitude of barriers to receiving treatment, which include psychological, social, geographical, financial, and systemic factors [26]. Despite the high rate of mental health disorders in PSPs, their willingness to seek treatment is low because of the stigma attached to mental health in their profession [27,28]. Many PSPs feel discredited by seeking treatment for their mental health and feel an expectation from their job to tolerate their symptoms [28,29]. Among those who do seek help, they face unique barriers including irregular work hours, limiting their access to resources otherwise available to the public. In many cases, the publicly available options, such as group CBT, add to the stigma of receiving care, especially in smaller cities.

A promising solution to address these barriers is the asynchronous, text-based, module-driven, diagnosis-specific, electronic delivery of CBT (e-CBT). In recent years, there has been an increased interest in researching the efficacy of e-CBT, due to its ability to address many barriers associated with in-person CBT [30-32]. Delivering e-CBT asynchronously allows for therapy to be accessed at a convenient time for the patient from the comfort of their own home. e-CBT content can be adapted to a multitude of languages and cultures, meeting the needs of more patients. Moreover, the private nature of

e-CBT can reduce the stigma of receiving care [28,33]. e-CBT has been shown to effectively treat a variety of mental health disorders, supported by several meta-analyses [34-37]. Regarding depression and anxiety disorders, e-CBT can be efficacious as a singular or adjunctive treatment [38-40]. Additionally, e-CBT has also been shown to effectively address PTSD symptoms [41-45]. These findings are promising as e-CBT techniques are cost-effective, are geographically and temporally accessible, have shorter waiting times for treatment, reduce stigma, increase help-seeking among patients, and can increase treatment adherence [46,47]. More importantly, the treatment outcomes of e-CBT are suggested to be comparable to in-person psychotherapy for individuals with GAD [38]. Regarding scalability, e-CBT can offer up to 70%-80% time savings for therapists [47].

There are many forms of e-CBT, including unguided self-help, guided self-help (standardized program with support from a mental health professional), and individualized therapy (tailors therapy modules to patient needs based on an entry interview) [48-50]. The length and mode of delivery vary between programs; however, they all utilize the same strategies as in-person CBT. While all programs have some form of efficacy, their impact can vary greatly. It has been found that the major factor affecting program efficacy is the level of care provider engagement [51]. While many studies suggest even self-guided content can be beneficial, more therapist engagement is related to higher treatment efficacy [51,52]. Therapy outcomes (ie, symptom reduction, remission) are up to 3 times higher in supervised e-CBT compared to self-guided methods [53]. Therefore, a supervised e-CBT approach is needed to effectively address the mental health needs of this PSP population.

Objectives

Each phase has a respective objective. In phase 1, the aim is to understand CWs' mental health challenges and barriers to receiving care. In phase 2, we will create e-CBT modules to address the CW-specific mental health problems found in phase 1. In phase 3, the aim is to evaluate the e-CBT program efficacy compared to treatment as usual (TAU). In phase 4, we will evaluate the e-CBT program efficacy compared to in-person CBT.

Methods

Design

This study is split into 4 phases with the first 2 using a qualitative approach to uncover mental health challenges and barriers to care faced by CWs, along with the usability of the e-CBT modules developed. These phases will use qualitative interviews and focus groups to collect data. Phase 3 will use a randomized controlled trial (RCT) design, with participants being allocated to either an e-CBT or TAU arm. In phase 4, an RCT design will be employed again, comparing the efficacy of the e-CBT arm to an in-person CBT arm. This study has been registered with ClinicalTrials.gov (NCT04666974).

Recruitment

In phase 1, a group of experienced CWs (n=5) will be initially recruited. These CWs will have in-depth knowledge of CW problems and will be chosen in consultation with CW union members. Moreover, members of this research team have extensive experience working with Correction Services Canada and will use their expertise to select suitable participants. Following this, a larger group of CWs (n=40; 20 men, 20 women) will be recruited for individual and focus group interviews. Recruitment will be conducted using flyers (distributed in the workplace), advertisements in specialized journals, union representatives, and word of mouth.

In phase 2, CWs (n=20; 10 men, 10 women) will be recruited using the same methods as in phase 1.

In phase 3, CWs (n=100; 50 men, 50 women) will be recruited using the same materials as in the previous phases; however, participants will also be accepted based on physician referrals.

In phase 4, CWs (n=100; 50 men, 50 women) will be recruited using the same methods as in phase 3. However, an additional step will be taken to ensure eligibility by conducting a comprehensive interview by a psychiatrist, further validated by a structured interview performed by a trained research assistant.

Inclusion/Exclusion Criteria

Participants will undergo a comprehensive initial mental health assessment by a psychiatrist on the research team. These assessments will occur either in person or through video calls. Diagnoses will be identified using the structured Mini-International Neuropsychiatric Interview (MINI) performed by a trained research assistant and a psychiatric assessment conducted by a psychiatrist on the research team. Inclusion criteria include 18-55 years of age at the start of the study; diagnosis of MDD, GAD, or PTSD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5); competence to consent and participate; ability to speak and read English; and consistent and reliable access to the internet [54]. Exclusion criteria include diagnosis of hypomanic/manic episodes, psychosis, severe alcohol or substance use disorder, and active suicidal/homicidal ideation.

Phase 1

An expert end-user group of CWs (n=5) will help the research team across all phases of this project. These experts will have in-depth knowledge of CW problems and will be chosen in consultation with CW union members. A new set of CWs (n=40; 20 men, 20 women) will be recruited to participate in individual interviews and then in virtual focus groups through Microsoft Teams as this platform is approved for security reasons by the Queen's University Health Science and Affiliated Teaching Hospitals Research Ethics Board (HSREB). These interviews will be used to identify the main mental health challenges and the best methods to address them in the context of different groups of CWs (eg, administrative staff, operational workers, direct vs indirect contact with prisoners, working in a prison vs working in probation offices) and investigate the barriers specific to each group. Each individual will be independently interviewed by a trained research assistant hired for the project (60-90–minute duration). Interviews will occur remotely via a secure video conference with Microsoft Teams. Questions will include topics of the level of interaction with prisoners, types and frequency of violence at work, sexual assault, work

condition (staffing, shift length, relationship with superiors and co-workers, workload, over-crowdedness), socioeconomic factors (race, gender, language, sexuality, religious discrimination), mental challenges, resources (training, peer support, and professional help) and frequency they use them, reasons for refraining to use resources, preferred method of support (onsite vs offsite, individual vs group), and attitude towards online care (willing to do so and what content they want to be covered). Information gathered through individual interviews will form the basis for further focus group discussions via Microsoft Teams.

Following individual interviews, 5 half-day focus groups (8 participants per group, 2 exclusively female, 2 exclusively male, 1 sex balanced) will be conducted to gather more information regarding issues uncovered in individual interviews. These focus groups will occur remotely via video conference with Microsoft Teams. A list of challenges to be addressed in phases 2-4 will be formed from these interviews. The principal investigator, 1 psychiatrist, 1 psychologist, 1 research assistant, and at least 2 members of the end-user expert group will attend each group meeting to form a better understanding of the problems faced by each group. All interviews and focus group discussions will be recorded and transcribed verbatim for further discussion at the investigative team meetings.

Phase 2

Following the first round of content development, e-CBT modules will be presented to the end-user expert group and a smaller number of interview/focus group participants (n=20; 10 men, 10 women) for feedback. Each participant will be asked to provide feedback on 1 of the 6 therapeutic modules regarding content, form, presentation, examples, and helpfulness, based on the challenges it tries to address. All feedback will be summarized and compiled by research assistants and discussed in 6 separate focus group discussions attended by the principal investigator, 1 psychiatrist, 1 psychologist, 1 research assistant, and at least 2 members of the end-user expert group. Each participant is requested to attend 2 virtual focus group discussions on the module they have not seen yet or commented on. This is done to ensure each participant can provide feedback on all gender-specific therapy contents. A list of recommended changes to each module will be developed through these discussions. Recommendations will be reviewed by the principal investigator, co-applicants, and the knowledge users for clinical validation. The final changes, compiled by clinicians, will be applied to the e-CBT module.

Phase 3

CWs (n=100; 50 men, 50 women) meeting the inclusion/exclusion criteria will complete a set of socioeconomic, demographic, and the following clinical questionnaires (primary diagnosis dependent) at baseline: Depression and Anxiety Stress Scale - 42 Item (DASS-42), Quality of Life Satisfaction and Enjoyment Questionnaire (Q-LES-Q), Quick Inventory of Depressive Symptoms Self Report - 16 Item (QIDS-SR16), Patient Health Questionnaire - 9 Item (PHQ-9), Generalized Anxiety Disorder - 7 Item (GAD-7), and PTSD Checklist for the DSM-5 (PCL-5) [55-60]. Questionnaires and e-CBT modules will be completed through the Online Psychotherapy Tool (OPTT; OPTT Inc.), a secure, cloud-based, mental health care delivery, online platform. OPTT can be accessed from various devices (ie, computer, cellphone, tablet) and internet browsers. Following the initial assessment, participants will be randomly allocated to the e-CBT + TAU (n=50; 25 men, 25 women) or TAU (n=50; 25 men, 25 women) arm.

Participants in the e-CBT group will be assigned to 1 of the 6 therapy modules based on their gender and diagnosis (ie, female/male; GAD/MDD/PTSD). All e-CBT sessions will be completed through OPTT. Sessions will be designed to mirror in-person CBT content and consist of approximately 30 slides and interactive therapist videos (40-60–minute completion time), with 12 sessions in total (1 module per week). The modules will focus on standard aspects of CBT (the connection between thoughts, behaviors, emotions, physical reactions, and environment) and incorporate different skills into each session (eg, mindfulness, goal setting, activity scheduling). Each participant will be assigned a specific therapist who will be their care liaison through the program. Each week, the clinician will send the new e-CBT session to the participant through OPTT on a predetermined day of the week. Each of these sessions will include a homework assignment that the participant must send back to their clinician by a predetermined date to gain access to the next session. Upon receiving the homework submission, the clinician will review the participant's work and provide individualized feedback on their performance. This feedback will be sent back to the participant with their new e-CBT module the following week. Clinician feedback will follow a structured format and take approximately 15 minutes per patient, allowing for increased scalability.

Participants in both arms will complete the symptomology questionnaires every 2 weeks along with 6-month and 12-month follow-ups. Additionally, participants in the e-CBT arm will complete a qualitative questionnaire regarding their experience using OPTT. These questions will relate to the aesthetic appeal of OPTT, the intuitiveness of OPTT, technical support experience, OPTT navigation and simplicity, and the kinds of devices used to access therapy. Information from this qualitative questionnaire will be used to fine-tune the e-CBT modules for phase 4.

Phase 4

At baseline, participants (n=100; 50 men, 50 women) will complete the same socioeconomic, demographic, and clinical questionnaires as in phase 3 through OPTT. Following the initial assessment, participants will be randomly allocated to either the e-CBT + TAU (n=50; 25 men, 25 women) or in-person CBT + TAU (n=50; 25 men, 25 women) arm. Participants in the TAU arm will continue with current lifestyle choices (ie, physical activity, diet, socialization) and current treatments (ie, pharmacotherapy, meditation) for the duration of the program.

Participants in the e-CBT arm will receive a specific program based on their primary diagnosis and gender (male/female; GAD/MDD/PTSD). Participants will be assigned a specific therapist who will be their care liaison throughout the program. Participants in the in-person CBT arm will receive similar content, homework, and feedback compared to the e-CBT arm.

All in-person CBT sessions (60-75–minute completion times) will be delivered by a trained professional.

Participants in both arms will complete the symptomology questionnaires biweekly (same as in phase 3) along with 6-month and 12-month follow-ups. Following week 12 (posttreatment), participants will also complete an additional MINI. Additionally, participants in the e-CBT arm will complete the same qualitative questionnaire relating to their experience using OPTT. These responses will be discussed with the end-user expert group to form recommendations for improving the e-CBT modules through OPTT.

Training

Therapists will be trained in psychotherapy delivery and supervised by a psychiatrist on the research team who has extensive experience in e-CBT. To ensure consistency of care, therapists will learn a standardized pathway of care and undergo sample training sessions before interacting with patients. Feedback templates will vary between e-CBT modules with therapists providing personalization directly related to their participants' work. Before submission, all feedback will be reviewed and approved by a psychiatrist on the research team.

Outcomes

Phases 1 and 2 will be completed using qualitative individual interviews along with focus groups. Phases 3 and 4 will be completed using the quantitative methodology and will be based on the findings from phases 1 and 2.

Phase 1 aims to evaluate mental health challenges and barriers to receiving care faced by CWs. This information will be used to create the e-CBT modules that will be presented to participants in phase 2, where the usability of these modules will be investigated.

In phases 3 and 4, the primary outcome will be comparing changes in symptom severity from baseline to posttreatment between e-CBT and TAU/in-person CBT arms, respectively. This will be evaluated using the DASS-42, Q-LES-Q, QIDS-SR16, PHQ-9, GAD-7, and PCL-5. These questionnaires will be completed biweekly starting at baseline until posttreatment (week 12), followed by 6-month and 12-month follow-ups.

The secondary outcomes of phases 3 and 4 will be evaluating how personal, social, and demographic factors can impact treatment experience. This will be investigated using the data from the qualitative questionnaires.

Analysis

Qualitative analysis of interview and focus group data (phases 1 and 2) will be performed using an iterative analysis process where investigators will review interview transcripts and search for key phrases, ideas, and themes directly pertaining to the research questions. Similarly, the qualitative comments and feedback obtained from questionnaires in phases 3 and 4 will also be transcribed and analyzed for themes. The information collected in phases 1 and 2 will be used to develop the e-CBT modules, with the information collected through phases 3 and 4 being used to finalize the format of the e-CBT (if necessary).

In phases 3 and 4, the relationship between socioeconomic status, demographic factors, and mental health challenges faced by CWs will be investigated. Questionnaire data will initially be examined for missing, nonsensical, and outlying variables and corrected where possible. Missing data will be treated as missing and not imputed (ie, will be analyzed on a per-protocol basis).

Following this, the symptomatology questionnaires (DASS-42, Q-LES-Q, QIDS-SR16, PHQ-9, GAD-7, and PCL-5) will be analyzed based on score change from baseline to posttreatment, 6-month follow-up, and 12-month follow-up. Questionnaire scores will be calculated for each time point, and then the changes between the times will be assessed using multivariate repeated measures analysis of variance (MANOVA). Comparisons will then be made between the e-CBT and control arms using linear regression models while controlling for demographic variables (eg, age, gender).

Factoring in anticipated dropouts, recruitment numbers have been purposely oversampled. From previous research in similar patient populations, dropouts can be expected to be up to 25% [61]. Given that there are 6 specialized versions of the e-CBT modules with different symptom questionnaires, it is difficult to calculate a single sample size or provide specific power calculations. However, using the PCL-5 as an example as it will be common to all participants, a 10-point change is considered clinically significant [62]. Therefore, a sample size of 30 participants in each arm will be sufficient for detecting significant results with P=.05 and a power of 0.8.

Ethics and Data Privacy

Only the care providers directly involved in participant interaction will be able to access their information. Participant identity will be kept anonymous through randomized participant ID numbers on OPTT. OPTT is compliant with the Health Insurance Portability and Accountability Act, the Personal Information Protection and Electronic Documents Act, and the Service Organization Control - 2. Additionally, all servers and databases are hosted in Amazon Web Service Canada cloud infrastructure, which is managed by Medstack to assure all provincial and federal privacy and security regulations are met. OPTT will not collect any identifiable personal information or internet protocol addresses for privacy purposes. OPTT will only collect anonymized metadata to improve its service quality and provide advanced analytics to the clinician team. All encrypted backups will be kept on secure Queen's University servers.

Results

The study received notice of funding acceptance in March 2020. Ethics approval from the Queen's University HSREB (File Number: 6029966) was obtained in December 2020. Participant recruitment began in March 2021 using targeted advertisement and physician referrals (see the Recruitment section). To date, there have been 15 participants recruited for Phase 1, and it is expected to conclude in June 2021 with phase 2 beginning in September 2021. Complete data collection and analysis from all phases are expected to conclude by July 2023. Focus group

analysis described earlier will be conducted after phases 1 and 2, and regression analysis (continuous and categorical outcomes) will be conducted after phases 3 and 4. All procedures and outcomes have been and will be reported using the GUIDED (Multimedia Appendix 1) and TIDieR Report Guidelines (Multimedia Appendix 2).

Discussion

CWs are at a significantly elevated risk of developing a mental health disorder. Due to stigma, geographic isolation, cost, and irregular work hours, CWs are less likely to seek treatment for their mental health struggles. To address this, innovative treatments are needed. CBT is an effective treatment; however, it is not readily available to CWs due to long wait times. The delivery of CBT through the internet is a promising solution. The outcomes of this study can both improve our understanding of CW mental health challenges and provide an innovative approach to address them. Focus group discussions will explore specific challenges each group of CWs face so therapy modules can be designed and targeted accordingly. The comprehensive mental health evaluations will also provide an invaluable survey of the mental health status of CWs.

If proven effective, e-CBT could be an accessible option for CWs to receive care whenever, wherever, and in any language they need without worrying about the stigma of receiving care. If shown to be comparable to in-person CBT, this method of care delivery could massively expand the therapy capacity in the public sector without sacrificing the quality of care.

This project has the potential to influence clinical care and health care policy by addressing barriers currently preventing CWs from receiving the care they need. This approach would offer monetary savings to the health care system and provide a more equitable and accessible method of delivery. Asynchronous e-CBT takes less time for the clinician to deliver, while still providing comprehensive benefits of therapy with added accessibility and efficiency. This increased efficiency can allow clinicians to be more productive within their clinical time and workload.

Acknowledgments

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Conflicts of Interest

NA and MO cofounded the care delivery platform in use (ie, OPTT) and have ownership stakes in OPTT Inc.

Multimedia Appendix 1
GUIDED Report Checklist.
[PDF File (Adobe PDF File), 72 KB - resprot_v10i7e30845_app1.pdf]

Multimedia Appendix 2
TIDieR Report Checklist.
[PDF File (Adobe PDF File), 97 KB - resprot_v10i7e30845_app2.pdf]

Multimedia Appendix 3
Funding acceptance letter and reviewer comments from the Canadian Institutes of Health Research.
[PDF File (Adobe PDF File), 226 KB - resprot_v10i7e30845_app3.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
CW: correctional worker
DASS-42: Depression and Anxiety Stress Scale - 42 Item
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
e-CBT: electronically delivered cognitive behavioral therapy
GAD-7: Generalized Anxiety Disorder - 7 Item
HSREB: Health Science and Affiliated Teaching Hospital Research Ethics Board
MANOVA: multivariate repeated measures analysis of variance
MDD: major depressive disorder
MINI: Mini-International Neuropsychiatric Interview
OPTT: Online Psychotherapy Tool
PCL-5: PTSD Checklist for the DSM-5
PHQ-9: Patient Health Questionnaire - 9 Item
PSP: public safety personnel
PTSD: posttraumatic stress disorder
QIDS-SR16: Quick Inventory of Depressive Symptoms Self Report - 16 Item
Q-LES-Q: Quality of Life Satisfaction and Enjoyment Questionnaire
RCT: randomized controlled trial
TAU: treatment as usual

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Protocol

Presence of Urinary Exosomes for Liquid Biopsy of Clear Cell Renal Cell Carcinoma: Protocol for a Pilot Feasibility Study

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Abstract

Background: Approximately 70%-80% of kidney cancers are clear cell renal cell carcinomas (CCRCCs). Patient management is based on imaging (abdominal ultrasound and computerized tomography), surgical excision of the tumor, and pathological analysis. A tissue biopsy is therefore necessary to confirm the diagnosis and avoid unnecessary nephrectomy. For metastatic cancers, a tissue biopsy is essential for establishing the targeted therapy. This biopsy of tumor material is invasive and painful. Other techniques such as liquid biopsy would help reduce the need for tissue biopsy. The development of a simple biological test for diagnosis is essential. CA9 is a powerful marker for the diagnosis of CCRCC. Exosomes have become a major source of liquid biopsy because they carry tumor proteins, RNA, and lipids. Urine is the most convenient biological liquid for exosome sampling.

Objective: The aim of this study (PEP-C study) is mainly to determine whether it is possible to detect urinary exosomal CA9 for the molecular diagnosis of CCRCC.

Methods: This study will include 60 patients with CCRCC and 40 noncancer patients. Exosomes will be isolated from urine samples and exosomal CA9 will be detected by transmission electron microscopy, flow cytometry, and reverse transcription-quantitative polymerase chain reaction.

Results: This study is currently underway with funding support from the CHU Saint-Etienne of France.

Conclusions: We expect to demonstrate that urinary tumor exosomes could be a novel liquid biopsy to diagnose CCRCC and to guide clinicians in treatment decision-making.

Trial Registration: ClinicalTrials.gov NCT04053855; https://clinicaltrials.gov/ct2/show/NCT04053855

International Registered Report Identifier (IRRID): DERR1-10.2196/24423

(JMIR Res Protoc 2021;10(7):e24423) doi:10.2196/24423

KEYWORDS

liquid biopsy; urine exosome; CA9; clear cell renal cell carcinoma; kidney cancer

Introduction

Renal cell carcinomas are serious and common cancers [1]. Approximately 70%-80% of kidney cancers are clear cell renal cell carcinomas (CCRCCs). Patient management is based on imaging (abdominal ultrasound and scanner), surgical excision of the tumor, and pathological analysis. Approximately one-third of patients with CCRCC have a locally advanced or metastatic tumor at the time of diagnosis and nearly 30% of treated patients will develop secondary metastases [1]. Recent advances in imaging techniques have increased the detection of kidney tumors; however, not all tumors are cancerous, with 10%-15% of all kidney tumors being benign and 20%-30% of tumors smaller than 4 cm being benign [2]. A tissue biopsy is therefore necessary to confirm the diagnosis and avoid unnecessary nephrectomy. For metastatic cancers, tissue biopsy is also essential for establishing the targeted therapy. This biopsy of tumor material is invasive and painful. Alternative techniques such as liquid biopsy would help reduce the rate of tissue biopsy. Therefore, development of a simple biological test for diagnosis is essential.

The notion of liquid biopsy has been mentioned in recent publications [3]. Liquid biopsies are based on the detection of cancerous biomarkers in body fluids, mostly in the blood, but can also include the urine, saliva, or other fluid. Liquid biopsies are preferable to tissue biopsies because they are less invasive.

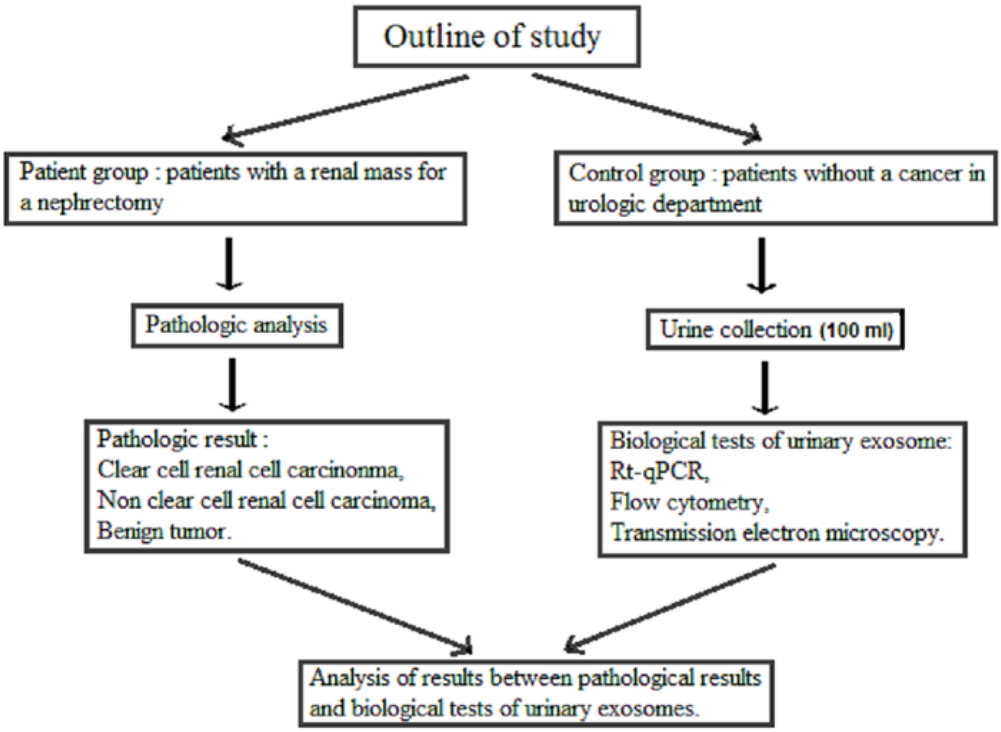
Exosomes are small nanoparticles that are secreted into the extracellular medium by different cell types [4,5]. We propose detecting urinary exosomes from patients with CCRCC. A urine sample would be preferable to a blood sample because of the anatomical proximity of the urine to the kidney tumor. Moreover, urine is the simplest biofluid that can be obtained. We and others have found that urine is an important target for the exploration of markers for renal diseases [6]. The tumor exosomes from CCRCC in the urine are particularly abundant because of the location of the tumor directly in contact with the urine. Our hypothesis is that tumor exosomes present in the urine of patients with CCRCC could be detected. Our aim is to develop a reliable technique for the detection of tumor exosomes in the urine of patients with CCRCC to explore their usefulness as a liquid biopsy of CCRCC.

Methods

Study Design

This is a descriptive study (PEP-C study). The investigators will provide eligible patients with an informative notice on the PEP-C study. Upon a patient providing written consent, 100 ml of urine will be collected in a sterile tube for each exosomal analysis. The study design is outlined in Figure 1.

Figure 1. Outline of study. RT-qPCR: reverse transcription-quantitative polymerase chain reaction



Study Population

There is no available publication in the literature to calculate the number of subjects required for this type of study. Thirty patients receive surgery for removal of CCRCC in our department per year. Therefore, we propose to study 60 patients over 2 years. In addition, 20 control patients without cancer in our department are expected per year. Therefore, we propose

studying 40 controls over 2 years. Eligibility criteria for cancer patients and controls are listed in Textbox 1. The age of the control group will be determined in agreement with the average age of occurrence of the CCRCC patients included in the study.

Textbox 1. Inclusion and exclusion criteria of participants.

Inclusion criteria for patients

- Adult patient >18 years old
- All patients with a renal mass and scheduled for surgery (partial or total nephrectomy)
- Patients having accepted and signed the consent form
- Patients benefitting from social security

Inclusion criteria for controls

- Adult patient >18 years old
- Patients hospitalized in the urology department without a known cancer
- Patient having accepted and signed the consent form
- Patients benefitting from social security

Exclusion criteria

- Insufficient volume of urine sample
- Patients with a urinary catheter
- Patients under court-ordered guardianship or curatorship

Study Objectives and Endpoints

Since CD63, CD9, and CD81 are the common markers for exosomes, we will test these three markers for detecting urinary exosomes. CA9 and vascular endothelial growth factor receptor 2 (VEGFR2) are two markers for CCRCC, which are used as markers for tumor exosomes.

The primary objective of this study is to detect urinary exosomes from CCRCC using an exosome marker (CD63) and CCRCC marker (CA9).

The secondary objectives are to assess (1) agreement between identification of CD63+/CA9+ tumor exosomes and patient status (clear cell kidney cancer), (2) agreement between the identification of CD9+/CD63+/CD81+/CA9+ tumor exosomes and patient status (clear cell kidney cancer), and (3) agreement between the identification of CD63+/VEGFR2+ tumor exosomes and patient status (clear cell kidney cancer).

The primary endpoint of the study is to characterize patients for whom CD63+ and CA9+ exosomes are detected. The secondary endpoints are as follows: (1) percentage of CD63+/CA9+ exosomes in patients with CCRCC compared with that of controls, (2) percentage of CD9+/CD63+/CD81+/CA9+ exosomes in patients with CCRCC compared with that of controls, and (3) percentage of CD63+/VGEFR2+ exosomes in patients with CCRCC compared with that of controls.

Sample Analysis

Exosomes will be isolated using a well-established commercial kit and will be characterized using exosome markers. The tumor markers will be analyzed by transmission electronic microscopy, reverse transcription-quantitative polymerase chain reaction (RT-qPCR), and flow cytometry. Transmission electronic microscopy is typically used to characterize exosomal markers. RT-qPCR is a well-established tool for detecting gene expression and is frequently used in exosome analysis. However, conventional flow cytometry may be inconvenient for exosome analysis given the small size of exosomes. Therefore, we will use aldehyde/sulfate latex beads to capture the exosome. This technique was recently proposed to advance conventional flow cytometry as a suitable tool for analyzing exosomal markers [7].

Data Collection

Data collected during the study will be recorded on a case report form for patients and control subjects. On the initial visit, age, sex, and medical history will be noted. For patients, date of disease diagnosis, surgical procedures, and pathological results will be noted.

Sample Size and Statistical Analysis

A selected group of 60 patients with renal cancer and 40 control subjects will be included in the study (Figure 1). The aim of this project is to evaluate the feasibility of detecting tumor exosomes as a liquid biopsy for CCRCC. We assume a 90% assay feasibility rate, 5% unilateral α, 90% power, and 10% patient withdrawal before the initial assay. According to the one-step Fleming design, 60 patients are required. The assays of the 60 patients will be compared with those of controls to evaluate if the tumor exosomes could be cancer markers.

The diagnostic performance of tumor exosomes will be evaluated by receiver operating characteristic curves. The area under the curve will be determined with its 95% CI. Analyses will be performed using SAS 9.4.

Patient and Public Involvement

The ethics committee examined the information notice that will be given to participants of this project. This consultation helped to improve the patient information notice on the design and aim of the study so that the participants will clearly understand and decide whether to participate in this study, in agreement with the principle of informed consent.

Results

This study is currently underway with funding support from the CHU Saint-Etienne of France. Recruitment of all patients will be completed in 2 years. The results of the study will then be communicated via presentations and publications.

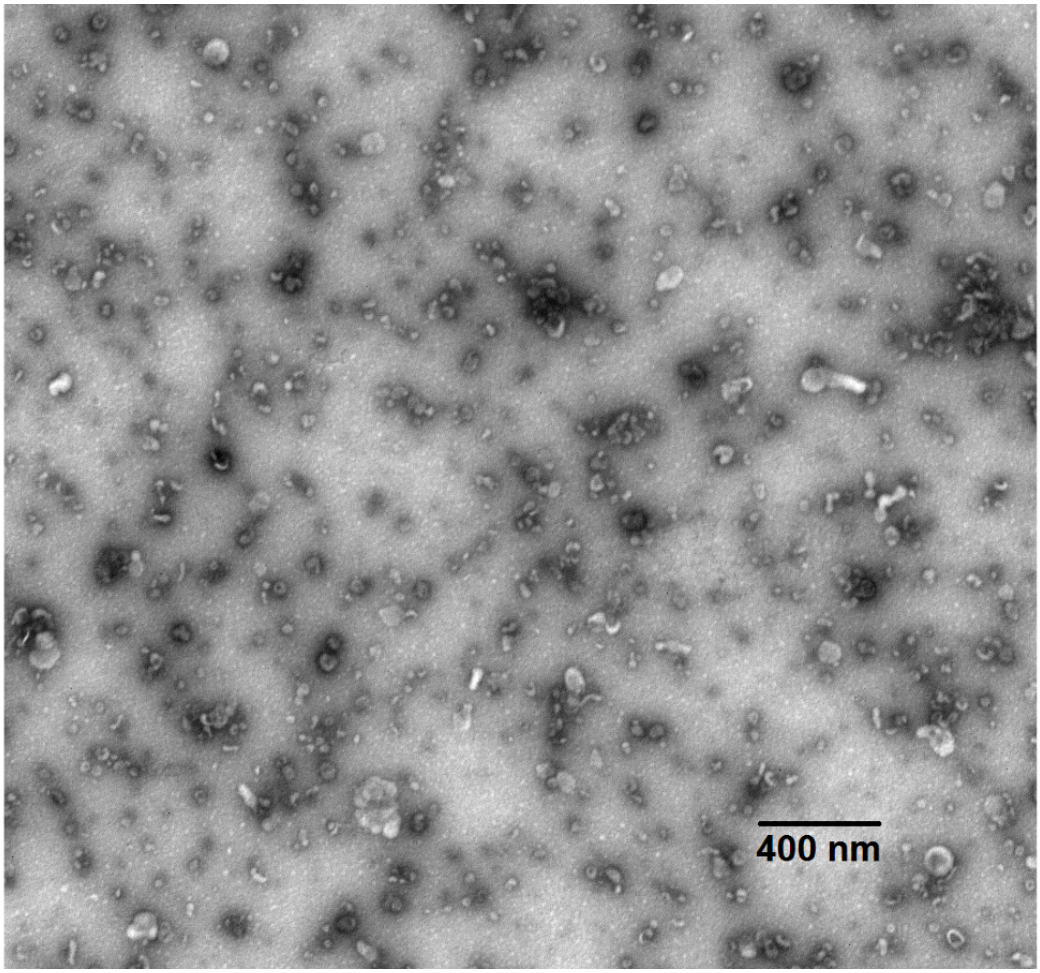
Discussion

Research on liquid biopsy has become a hot topic. Liquid biopsy allows for the detection of tumor markers in bodily fluids for the management of cancer patients. Compared with tissue biopsy, liquid biopsy is noninvasive. Liquid biopsy usually utilizes circulating tumor cells, cell-free DNA, and exosomes. Compared with circulating tumor cells and cell-free DNA, the use of exosomes is relatively more recent, but has shown rapid development. Exosomes carry tumor markers such as nucleic acids, proteins, and lipids, including mRNAs, microRNAs, and signaling molecules that reflect the physiological and pathological condition of the cells of origin [4]. The bilayer lipid membrane of the exosome considerably improves the stability of the internal components; exosomes are therefore a rich source of biomarkers. Exosomes have recently been the subject of research into biomarkers, which hold great promise for cancers [7]. Significant advances in exosome research have been made in body fluids such as saliva, serum, urine, and amniotic fluid [5]. Blood is particularly interesting as a source of liquid biopsy since it contains cancer-specific markers in extracellular vesicles. Currently, most of the research in this field focuses on blood exosomes. Urinary exosomes are also an excellent resource for biomarkers and a promising noninvasive diagnostic instrument for kidney disease [8-11]. Moreover, urine is the easiest available bodily fluid.

Our previous study demonstrated that CA9 is a powerful marker for the diagnosis of CCRCC [12]. Exosomes from the renal tumor could be discharged into the urine since urine is in close contact with the tumor. Thus, we suggest that urinary exosomal CA9 could be used as a biomarker in the diagnosis of CCRCCs. For this purpose, we have designed a pilot study, named PEP-C, to demonstrate whether it is possible to detect exosomal CA9 in the urine of patients with CCRCC. We expect that exosomal CA9 will be detectable in the urine of patients suffering from CCRCCs when compared with that of control subjects. A cutoff corresponding to cancer detection will be determined. Moreover, we will test urinary exosomal VEGFR2 expression since VEGFR2 was found to be highly expressed in CCRCCs [13]. The exosome markers CD9, CD63, and CD81 will also be analyzed as references. These markers will be assessed using transmission electron microscopy, flow cytometry, and RT-qPCR techniques [14,15]. Our aim is to develop a liquid biopsy assay for the diagnosis of CCRCC. In the future, we hope to demonstrate that urinary exosomes could be a powerful tool to diagnose cancer and to guide clinicians in therapeutic decision-making.

Several techniques for the isolation of urinary exosomes have been proposed, which can be classified according to the biochemical principle of purification: ultracentrifugation, filtration, immunocapture, or precipitation [16,17]. Ultracentrifugation isolation is the standard technique for obtaining exosomes. However, ultracentrifuges are not routinely available in clinical laboratories and this method requires a relatively long preparation time. Manufacturers have developed reagents for isolating exosomes from large volumes of urine, such as ExoQuick-TC (System Biosciences). This type of process makes clinical application possible. In preliminary tests for this project, we observed the urinary exosomes by transmission electron microscopy (Figure 2). Typical cup-shaped exosomes were observed. The size and the morphology are two important indicators for defining the urinary exosomes. Our preliminary results showed that urinary exosomes were abundant from cancer patients. Research on liquid biopsies using urine for CCRCC is very new. To our knowledge, there is almost no publication in this area. In contrast, prostate cancer–specific genes have been detected in urinary exosomes, constituting a new liquid biopsy tool to diagnose high-risk prostate cancer [18,19]. This technique of urine liquid biopsy was developed exclusively for prostate cancer and no such diagnostic method is available for CCRCC at present.

Figure 2. Transmission electron microscopy observation of urinary exosomes.



In conclusion, this will be the first study to evaluate the technical feasibility of detecting urinary exosomal CA9 in CCRCC patients. The results of this study might highlight the strong potential of liquid biopsy through urinary exosomes in the diagnosis of CCRCC. Therefore, if this pilot study is successful, a multicenter study will be envisaged.

Acknowledgments

This research is supported by CHU Saint-Etienne, France.

Conflicts of Interest

None declared.

Multimedia Appendix 1
External peer report A from CHU St-Etienne.
[PDF File (Adobe PDF File), 66 KB - resprot_v10i7e24423_app1.pdf]

Multimedia Appendix 2
External peer report B from CHU St-Etienne.
[PDF File (Adobe PDF File), 65 KB - resprot_v10i7e24423_app2.pdf]

Multimedia Appendix 3
External peer report C from CHU St-Etienne.
[PDF File (Adobe PDF File), 96 KB - resprot_v10i7e24423_app3.pdf]

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Abbreviations

CCRCC: clear cell renal cell carcinoma
RT-qPCR: reverse transcription-quantitative polymerase chain reaction
VEGFR2: vascular endothelial growth factor receptor 2

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Protocol

Combining Ketamine and Internet-Based Cognitive Behavioral Therapy for the Treatment of Posttraumatic Stress Disorder: Protocol for a Randomized Controlled Trial

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Abstract

Background: Over one third of patients with posttraumatic stress disorder (PTSD) do not respond to current interventions. Ketamine presents a potential treatment option; however, its effects are temporary. Administering ketamine alongside psychotherapy is one potential means of prolonging its effects; however, only a few studies have investigated this treatment method to date, and none have tested ketamine with internet-based or electronically delivered cognitive behavioral therapy (e-CBT).

Objective: This open-label randomized controlled trial aims to assess the efficacy of a combined treatment method of subanesthetic intravenous ketamine and e-CBT for treating patients with PTSD.

Methods: In total, 20 patients with refractory PTSD recruited from a community clinic will be randomly assigned to either an experimental group (n=10), receiving a combination of ketamine and therapist-administered e-CBT over 14 weeks, or a waitlist control group (n=10), receiving the experimental treatment after 14 weeks. Both groups will be assessed for the symptoms of PTSD and comorbid disorders before treatment, at two midway points, and at the end of the experiment.

Results: PTSD symptoms of participants in the experimental group are expected to improve significantly more than those of participants in the waitlist control group (P=.05) with a large effect size (η^2=0.14).

Conclusions: This is the first study to assess the relationship between e-CBT and ketamine and their combined ability to treat refractory PTSD. If successful, this study will open web-based, asynchronous therapeutic options for patients with PTSD and will provide new insights into the functional role of glutamate in trauma-related disorders as well as in learning, memory, and fear extinction.

Trial Registration: ClinicalTrials.gov NCT04771767; https://clinicaltrials.gov/ct2/show/NCT04771767.

International Registered Report Identifier (IRRID): PRR1-10.2196/30334

(JMIR Res Protoc 2021;10(7):e30334) doi:10.2196/30334

KEYWORDS

mental health; PTSD; psychotherapy; cognitive behavioral therapy; online; internet; electronic; virtual; mental health care; ketamine

Introduction

Challenges in Treating Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is a chronic and debilitating mental illness that affects 3.5% of North American adults, or approximately 28 million people, with a lifetime prevalence of 8% [1]. PTSD develops after direct or indirect exposure to a psychologically traumatic incident, thereby leading to a host of cognitive, emotional, and behavioral symptoms [1]. Although most patients recover after a psychological trauma, a considerable minority of individuals remain chronically symptomatic or experience a delayed onset of PTSD [2]. PTSD is a particularly refractory disorder that persists for years, with many patients still displaying symptoms 20 years after a trauma, with prevalence often increasing over time after a trauma [3,4]. PTSD is also associated with high comorbidity rates with depression, anxiety, and substance abuse disorders [5,6]. Furthermore, patients with PTSD are 4 times more likely to attempt suicide than trauma survivors without PTSD [7]. Taken together, these features highlight the urgent need of effective treatments for this disorder.

A number of empirically supported psychotherapeutic treatments are available for PTSD, with trauma-focused cognitive behavioral therapy (TF-CBT) and eye movement desensitization and reprocessing therapy being the most effective [8,9]. However, psychotherapeutic treatments have a considerable nonresponse rate [10,11]. A number of pharmacotherapies have also become available for treating PTSD, with selective serotonin reuptake inhibitors such as paroxetine and sertraline showing the greatest success [12]. Unfortunately, pharmacotherapies have a larger nonresponse rate than psychotherapeutic treatments [12]. As a result, a sizeable proportion of patients with PTSD remain resistant to treatment. The objective of this study is to provide a greater reduction in symptoms with a combination treatment of ketamine and electronically delivered cognitive behavioral therapy (e-CBT) as compared with currently available therapeutic options for treatment-resistant patients.

Ketamine and PTSD

Ketamine offers a promising research avenue for treating refractory PTSD. It is primarily a glutamate antagonist at the N-methyl-D-aspartate (NMDA) receptor and has achieved considerable success in rapidly reducing symptoms of mood disorders [13]. Ketamine is believed to function by disengaging an established pattern of thought [14,15], which in the case of PTSD would involve counteracting the impaired fear extinction seen in PTSD as ketamine increases neuroplasticity toward fear learning [16,17]. It is important to note that the exact mechanism of action in the treatment of emotional disorders is only partly understood. In terms of the development of PTSD, recent advances have generally implicated the NMDA receptor, where rodents subjected to chronic stress have elevated gene expression for producing NMDA receptors in the ventral hippocampus in comparison with control subjects [18]. Moreover, in humans, the prefrontal cortex and amygdala are connected by glutamatergic projections, suggesting that glutamate mediates a fear response [19]. Ketamine, in turn, has achieved considerable success in treating refractory PTSD, where it reduces symptoms significantly more than an active placebo for treatment-resistant patients [20].

Although ketamine opens treatment options to a new patient cohort, a purely pharmacological approach would be an oversimplification given the nature of PTSD, as the disorder develops in the wake of a trauma and cannot develop from pathological neurochemistry or neuroanatomy alone. Moreover, ketamine's effects wear off in less than a week [20,21] and repeated infusions can induce potentially negative long-term outcomes on cognitive and physical health [22]. One potential way to prolong its effects is to capitalize on ketamine's role in facilitating fear extinction by combining it with psychotherapy. This is partly attributed to psychotherapeutic interventions having greater longevity than pharmacological techniques for reducing PTSD symptoms [23]. Currently, there have been very few studies combining ketamine and psychotherapy to treat PTSD. As of May 2021, there were 4 studies listed on the ClinicalTrials.gov database that investigated ketamine used in combination with psychotherapy for treating PTSD (NCT02727998, NCT02766192, NCT04560660, and NCT03960658). These studies have shown promising results, where patients who were administered a combination of ketamine and prolonged exposure therapy or mindfulness-based extinction and reconsolidation therapy had a greatly prolonged therapeutic response as compared with ketamine alone [24,25]. The proposed study would therefore attempt to build on these findings by examining other types of psychotherapy in conjunction with ketamine for treating PTSD.

This Study

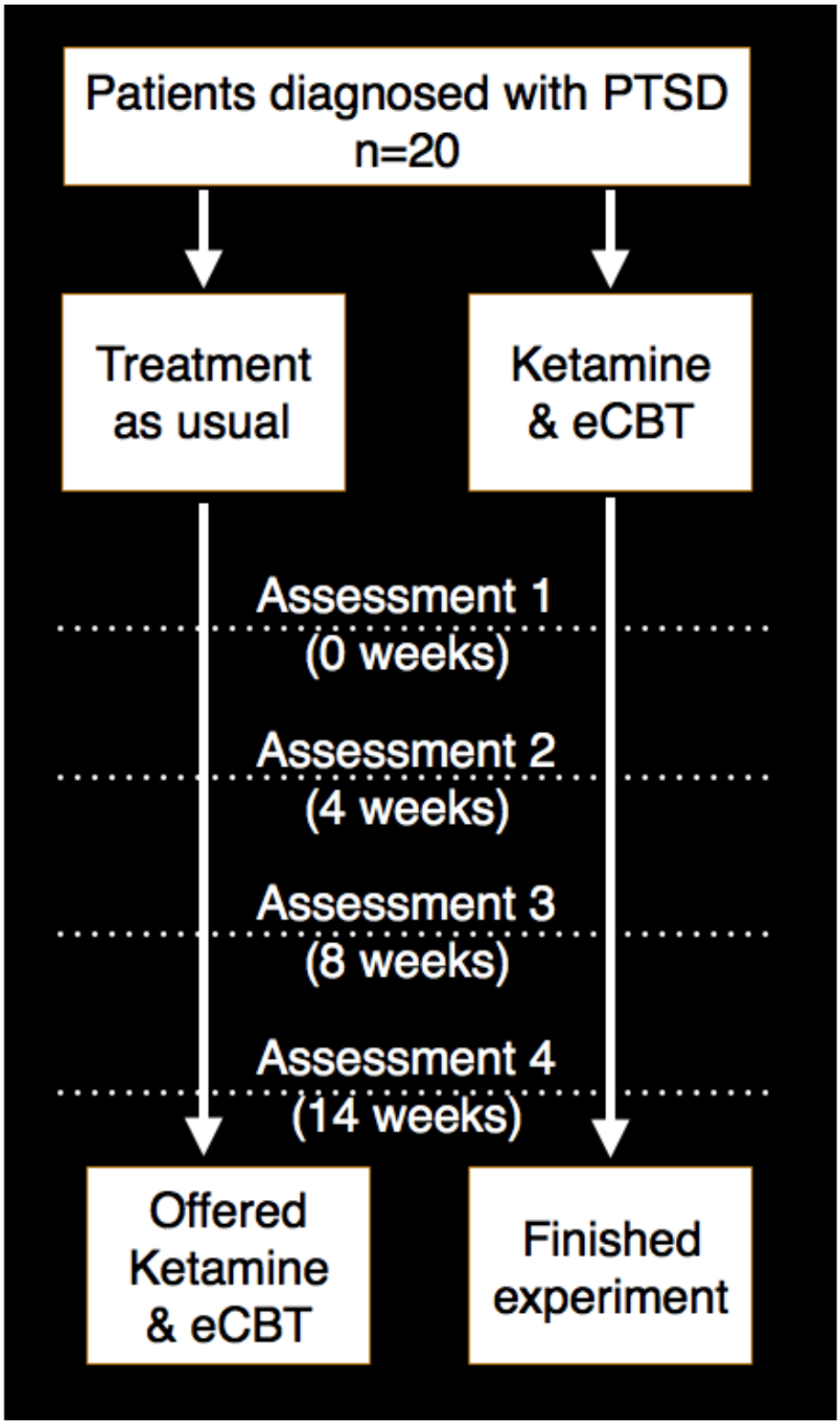
In this study, we will focus on TF-CBT. As mentioned earlier, TF-CBT is a well-established form of psychotherapy and is considered among the most effective forms of psychotherapy for PTSD immediately after treatment and at follow-up [8,26,27]. However, as mentioned earlier, a considerable proportion of patients with PTSD still do not respond to TF-CBT. One challenge associated with cognitive behavioral therapy (CBT) is to optimize inhibitory learning, which is inherently challenging for patients with PTSD [28,29]. Ketamine treatment may address this challenge because it acts to boost neuroplasticity. Another challenge with CBT is its resource-intensive nature, with large associated costs and waiting times [30,31]. One variant of CBT that addresses this second challenge is e-CBT, which has equivalent efficacy as face-to-face CBT for treating PTSD as observed in several meta-analyses [32,33]. However, no studies have yet examined the interaction of ketamine treatment with e-CBT or CBT in general. Therefore, this study assessed whether ketamine combined with e-CBT significantly reduces the symptoms of PTSD in treatment-resistant patients. We hypothesize that ketamine treatment alongside e-CBT will reduce symptoms of treatment-resistant PTSD more significantly than a waitlist control, thereby providing preliminary evidence that these two treatments can be successfully combined.

Methods

Study Design Overview

This study had a randomized, open-label, parallel design. Participants in the intervention group will be offered a combined treatment involving a 14-week trauma-focused e-CBT program alongside 6 doses of intravenous (IV) ketamine. Participants in the control group will be placed on a 14-week waitlist receiving treatment as usual. Quantitative analyses will be conducted using standard measures of PTSD symptom severity and symptom severity of comorbid disorders. The Queen's University Health Sciences and the Affiliated Teaching Hospitals Research Ethics Board approved this protocol. Figure 1 presents a summary of the experimental design.

Figure 1. Summary of the experimental design and time course. This study will follow a 25- to 39-week period, including an 8-week period of stable treatment before recruitment, 3 weeks of screening, 14 weeks of experimental treatment or waitlist treatment, and 14 weeks of postexperiment treatment for patients in the waitlist condition. eCBT: electronically delivered cognitive behavioral therapy; PTSD: posttraumatic stress disorder.



Participants

Participants (n=20) aged 18-65 years were enrolled in the study based on referrals from outpatient psychiatry at Hotel Dieu Hospital in Kingston, Ontario, Canada. A power analysis based on the most conservative effect size found in previous works [24,25] demonstrates that at least 5 participants will be required from each treatment group for a power of at least 0.9 (Cohen *d*=1.21; *P*=.05). In addition, although there has been a very strong effect observed in previous work, this study will take a conservative approach to the sample size, recruiting 10 participants per treatment group.

Recruitment

The referring physicians will first be given flyers containing a brief description of the study with inclusion and exclusion criteria and contact information. They will then provide incoming patients that match the basic criteria with a copy of the flyer, informing them of this study. Patients who are interested in participating will contact the study coordinator, who will call the patient to conduct a prescreening interview and ask basic questions to determine if the patient may be eligible. If the patient passes the interview, the patient will proceed to the screening phase.

Screening

The participant will participate in three separate screening appointments as follows:

First Screening Visit

At this 1-hour virtual meeting, participants will meet with one of the psychiatrists on the research team who will conduct an interview using the Clinician-Administered PTSD Scale (CAPS-5) [34], which is a detailed psychiatric interview that will be used to confirm the diagnosis of PTSD using the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (*DSM-5*) and to determine the exact severity of each participant's case. Participants will also be screened for study-specific inclusion and exclusion criteria. Patients who qualify for this study will satisfy all inclusion and exclusion criteria and will have a score of at least 50 on the CAPS-5 with the required distribution of symptoms across subcategories as outlined in the *DSM-5* to qualify at least as moderate presentation. Participants will also provide basic demographic data, including age and sex.

The inclusion criteria are as follows:

1. Provide oral consent.
2. Patients age 18-65 years at the start of the study.
3. Patients will be diagnosed with PTSD by a psychiatrist on the team as outlined in the *DSM-5* to qualify at least as a moderate presentation on the CAPS-5 with a score of at least 50.
4. Patients will be resistant to treatment, having previously received at least two different types of treatment, including any combination of selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors or TF-CBT, and all previous treatments will have produced less than a 50% reduction in the participant's symptoms.
5. Patients will be on stable treatment for at least eight weeks before screening, with no alterations to the treatment regimen.
6. If a participant is female and of childbearing potential, then an effective method of contraception must be used as ketamine can be harmful to the neural development of an embryo or fetus.
7. Participants must be able to speak and read in English and have consistent and reliable access to the internet to complete the e-CBT course.
8. Participants must agree to adhere to the study protocol.

The exclusion criteria are as follows:

1. Previous hypersensitivity or allergy to ketamine
2. Hypomanic or manic episodes, bipolar disorder, acute psychosis, or schizophrenia
3. Opioid use disorder, current use of opioids, or treatment with naltrexone
4. Currently pregnant, postpartum, or breastfeeding
5. Untreated or inadequately controlled hypertension or cardiovascular disease
6. Elevated intracranial pressure
7. Renal or hepatic disease
8. Antisocial personality disorder or active homicidal ideation

Second Screening Visit

At this virtual meeting, participants will meet with a research assistant who will interview them using the Mini-International Neuropsychiatric Interview [35], designed to assess symptoms across a wide array of psychiatric conditions.

Third Screening Visit

At this screening session, an anesthesiologist will consult the patient. Here, they will have a complete assessment with several exams and tests including vital signs (blood pressure, heart rate, and pulse oximetry), electrocardiography, and routine bloodwork, including a complete blood count with electrolytes, creatinine, blood urea nitrogen, and liver function tests. This visit will assess the patient's cardiovascular, hepatic, and renal health. Patients will not be able to participate if they have untreated hypertension, cardiovascular disease, renal disease, or hepatic disease.

Procedures

Patients will first attend the screening sessions listed above, after which, if they are eligible and have provided consent, they will be assigned to one of two treatments: the combination therapy group receiving e-CBT and IV ketamine or the control group receiving no treatment for the 14 weeks during which study measures will be administered. The study coordinator will then enter participants into the study through computer-generated block randomization and will recruit them in pairs so that 10 patients will receive the experimental condition and 10 will be in the control group.

Electronically Delivered Cognitive Behavioral Therapy

Overview

Participants from the combination therapy group will begin an e-CBT program, which will involve a 14-week course of

TF-CBT. The content of the therapy course will mirror the in-person TF-CBT and cognitive processing therapy intervention for PTSD [36]. The format for the content of the modules and the overall structure of the therapy course and delivery platform is based on previous work by Alavi et al [37-39]. All web-based sessions will be conducted through the Online Psychotherapy Tool (OPTT), which is a secure, cloud-based web service for hosting asynchronous psychotherapy. Patients will first be introduced to their therapist, who will then email the patient a link to their weekly module that will be presented to them in the form of approximately 30 presentation slides. Each week's module will highlight a particular topic and will include general information, an overview of skills, and homework to be completed at any time within the week. OPTT will save a patient's progress so that they may work at their own pace, resuming when it is convenient for them. This homework will take approximately 40 minutes to complete and will be submitted within 1 week via OPTT to the therapist, who will provide personalized feedback across the same platform.

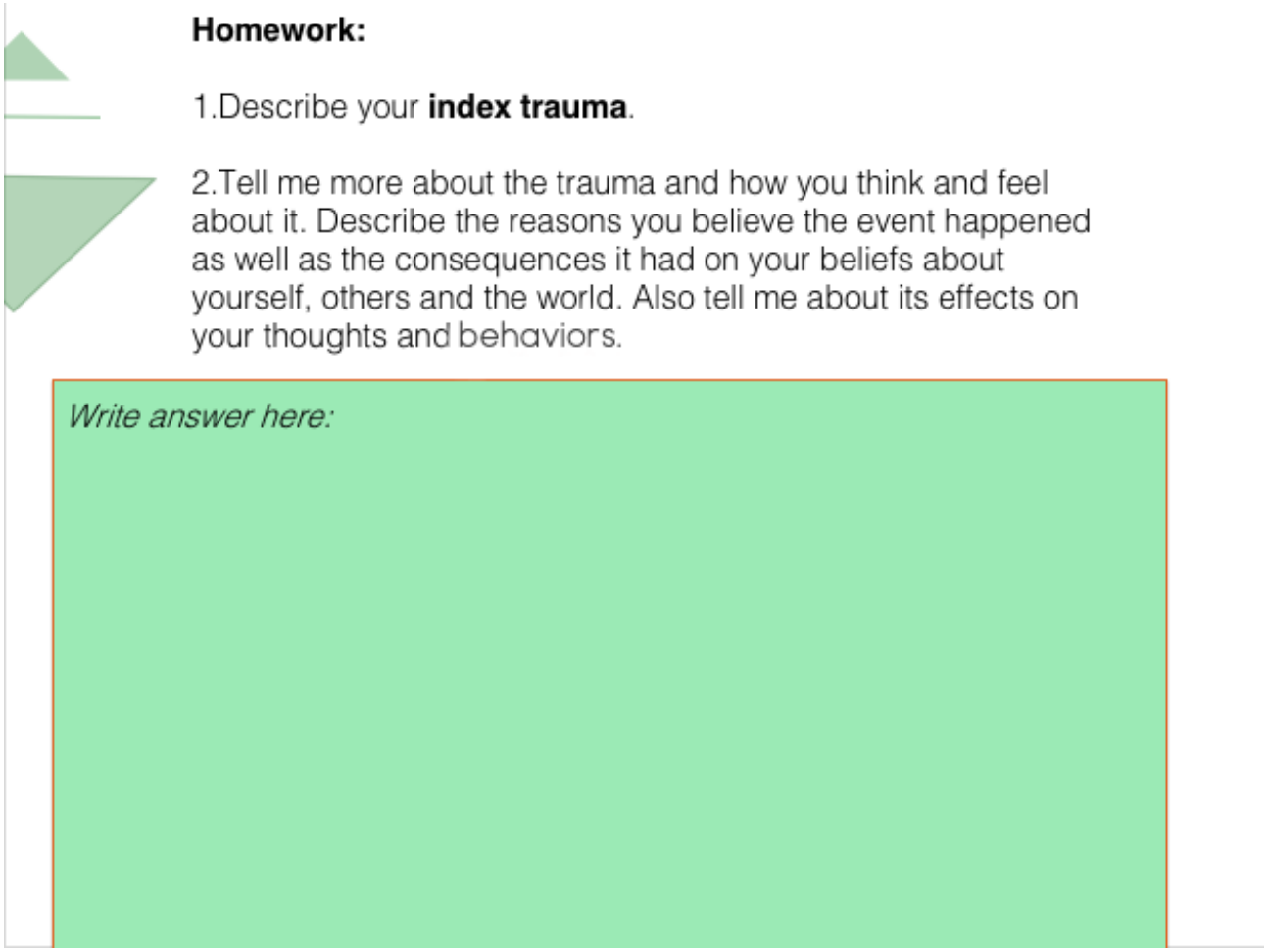
Therapist feedback will involve content that seeks to build rapport, review skills, review the content of the patient's homework, and provide constructive feedback. A detailed explanation of this structure can be found in *Online Cognitive Behavioral Therapy: An e-Mental Health Approach to Depression and Anxiety*, a book by Alavi and Omrani [40].

Although homework and clinician feedback are considered as the main modes of communication between therapists and participants, participants can also communicate with their therapist via a secure chat function that is found directly within the OPTT. This is mainly used to let participants ask further questions about their care if anything is unclear. The OPTT technical support team will handle any technical issues and provide continuous access to the participants during the program. The patient care team (ie, the therapist and the psychiatrist) will also be able to securely communicate through the OPTT to make decisions regarding each patient's care path. Finally, if a patient does not complete their homework for the week, they will receive 3 weekly emails, after which they will be removed from the study.

Web-Based Module Content

The TF-CBT is focused on strategies that would be helpful in handling stress and mood problems related to the trauma experienced by patients. The program helps patients independently manage their emotions, thoughts, and behaviors. The course is specifically designed to address the need for healing from traumatic events and to facilitate recovery through trauma-informed care. Topics include stuck points, identifying events, index events, problematic thinking, challenging beliefs, safety, and trust (see Figure 2 for an example of the module content).

Figure 2. Web-based intervention example material.



Training

All therapists are research assistants hired by the coprincipal investigator leading the web-based psychotherapy portion of the research. They will undergo training in psychotherapy and additional training from a psychiatrist on the research team before any interaction with the participants. During this training, therapists will complete feedback on practice homework, which will be reviewed by a psychiatrist on the research team to ensure an adequate quality of work. The lead psychiatrist, who is an expert in electronically delivered psychotherapy, will supervise all the therapists [40], and will review feedback before it is sent to the participants.

Ketamine

Patients in the combination therapy group will also receive ketamine infusions at the Providence Care Hospital Ketamine Clinic. An indwelling catheter will be first placed in the antecubital vein of the nondominant arm. Patients will then be administered with an IV subanesthetic dose of ketamine hydrochloride (0.5 mg/kg) over 40 minutes. Nasal cannula oxygen may be administered, if needed, with sidestream capnometry monitoring. Pulse, blood pressure, pulse oximetry, and electrocardiography will be assessed before the start of each infusion and will be monitored throughout the infusion for adverse effects, such as an increase in blood pressure and dissociative state, which will terminate an infusion if identified. Physiological monitoring data will be recorded on a standard anesthesia record beginning 5 minutes before infusion. Participants will complete a total of 6 infusions over a 14-week period. Participants will receive 1 dose per week for the first 4 weeks, followed by 1 dose every other week for the next 4 weeks, followed by 0 doses per week for the remaining 6 weeks of the study. Side effects will be recorded before each infusion, at the end of each infusion, and 30 minutes after the end of each infusion. To reduce the chances of adverse psychological reactions, patients will be kept in a room with reduced tactile, visual, and auditory stimulations throughout the infusion and recovery period. Patients will be instructed not to operate a vehicle or heavy machinery on the day following ketamine infusion and will require a responsible adult to accompany them to their appointments. Patients and chaperones will be compensated for public transit or parking fares. Finally, patients will undergo monthly assessments with a clinician where they may report any adverse physical or psychological symptoms that arise over the course of treatment. All adverse events will be recorded, tabulated, and reported in the final publication. Table 1 summarizes the ketamine administration protocols.

Table 1. Summary of the ketamine administration protocol.

Characteristic	Specification
Generic product name	Ketamine
Dose (mg/kg)	0.5
Route of administration	Intravenous
Dosing schedule	Weekly×4, then biweekly×2
Ketamine treatment period	8 weeks

Control

Overview

Patients in the control condition will be put on a 14-week waitlist during which they will receive regular psychiatric care, including continuing any previous treatment regimens and receiving monthly check-ups. These patients will also be assessed at the same 4 time points as patients in the experimental condition. At the end of the 14-week experimental period, patients in the control group will receive the experimental treatment.

Stopping Guidelines

The following conditions, if met, will necessitate a participant's removal from the study:

1. If a participant failed to submit their e-CBT homework within 21 days of receiving their module for a given week and after receiving 3 reminders, or if a participant missed a ketamine appointment as well as their makeup appointment.
2. If a participant were to develop adverse effects from participation so that the principal investigator deems it unsafe for them to continue, such as physical or psychological adverse side effects from the ketamine (eg, allergy), or if participants develop psychologically adverse symptoms resulting from the assessments or e-CBT.
3. If a participant were to meet an exclusion criterion during the study duration.
4. If a participant withdraws consent for any reason.

Multimedia Appendix 1 provides more information on stopping guidelines and general safety procedures.

Outcome Evaluation

Overview

Patient outcomes will be measured through clinical interviews and questionnaires completed at the start (baseline measurement) and end of treatment. The primary measure, covered in detail in the following section titled *Primary Outcome Measure*, will also have midway assessments at 4 and 8 weeks through treatment. All questionnaire data will be administered electronically to the patients through OPTT alongside their e-CBT sessions that week. Interviews and observational data will be collected either in person or through virtual (video) appointments.

Primary Outcome Measure

The primary outcome measure is the CAPS-5 interview [34]. The treatment response is defined as a 50% reduction in the participants' scores at the end of the 14-week period as compared with their scores at baseline. Nonresponse is defined as less than a 50% reduction in scores. Remission is defined as a 75% reduction in scores, whereas relapse is defined as a temporary treatment response or remission at one or both of the halfway points with a return to nonresponse at the final assessment.

Secondary Outcome Measures

Secondary outcome measures will include the following:

1. The Montgomery-Asberg Depression Rating Scale to measure depression symptoms [41].
2. Columbia-Suicide Severity Rating Scale, risk assessment version to measure suicidality [42].
3. The Clinical Global Impression scale to measure a patient's overall clinical presentation from a clinician's perspective and to provide interrater reliability [43].
4. Sheehan Disabilities Scale to provide insight into a patient's social and occupational functioning [44].
5. The Global Assessment of Functioning Scale provides additional insights into social and occupational function [45].

Ethics and Data Privacy

All procedures were approved by and comply with the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board. Multimedia Appendix 2 [1,2,4,7-15,18-24,28-33,46-54] shows the full protocol approved by the research ethics board. Each participant will be given an anonymous, unique code, with all screening and study outcome measures, including interviews, questionnaires, and observations, which will be associated with the patient's code alone. All data will be stored as encrypted files on a secure Queen's University server for 5 years after the study completion date.

The research team will protect the identity and confidentiality of participants to the extent permitted by the applicable laws and duty to report. Child abuse and neglect, elder abuse, and immediate physical risk to the self or others are grounds for breaching confidentiality. The identity of participants will remain completely anonymous in all future plans for knowledge dissemination, including but not limited to peer-reviewed publications, scientific presentations, grant proposals, and reports. Hard copies of consent forms and participant identities will be securely stored on-site and destroyed 5 years after study completion.

To ensure data privacy and security, OPTT was developed to comply with the Health Insurance Portability and Accountability Act, Personal Information Protection and Electronic Documents Act, and Service Organization Control-2. All servers and databases are hosted in the Amazon Web Service Canada cloud infrastructure, which is managed by Medstack (Medstack Inc) [46] to ensure that all Canadian provincial and federal privacy and security regulations are met. For privacy purposes, the OPTT will not collect any identifiable personal information or internet protocol addresses from the participants. The OPTT will only collect anonymized metadata to improve its service quality and provide advanced analytics data to the clinical team. The OPTT will encrypt all data, and no employee will have direct access to the participant data. All encrypted backups are to be kept in Amazon S3 storage, which is dedicated to Queen's University, Kingston, Ontario, Canada.

Data Analysis

Data will first be entered into a spreadsheet and then imported into the R data analysis software program (R Core Team) [55]. Descriptive statistics including mean, median, SD, maximum, and minimum scores for primary and secondary outcome measures, as well as demographic data, including age and sex of the participants, will be computed and reported. Box plots for descriptive statistics will also be prepared for each outcome measure, demonstrating the mean and SD across time points and experimental conditions.

The data will be tested for statistical assumptions, including normality using the Shapiro-Wilk test, skew using Pearson coefficient of skewness, kurtosis using Pearson measure of kurtosis, homogeneity of variance using Levene test, and homogeneity of covariance using Box's M. The results of these tests will be reported later. Outliers were not extracted because of the small sample size.

If the assumptions are met, then a 2×4 mixed effects analysis of variance (P=.05) will be conducted to determine the main effects of the two factors, namely *time* and *condition*, as well as the interaction effect between time and condition on PTSD symptom outcome for CAPS-5 symptom severity. *Time* comprises 4 levels, including before treatment, 4 weeks through treatment, 8 weeks through treatment, and end of treatment. However, *condition* includes 2 levels, including the experimental condition and waitlist control condition. Simple main effects will be tested for time and condition, and a Bonferroni P value adjustment will be made for the *time* factor. Post hoc tests will be conducted on the *time* variable with a Tukey range test.

The secondary outcome measures are exploratory in nature and will be conducted with a 2×2 mixed effects analysis of variance (P=.05), where *time* has only 2 levels and no post hoc tests will be conducted.

This analysis will also measure the effect size, where the interaction is expected to have a large effect size (η^2=0.14). Finally, all adverse events will be recorded and reported, grouped by the type of adverse event, and reported by frequency. No interim analysis was planned for this study, and participants in the control condition will only be assessed while on the waiting list and will not be assessed for any separate analyses.

Results

The study was approved for funding in September 2020 and received ethics approval from Health Canada and the Queen's University Health Science and Affiliated Teaching Hospitals Research Ethics Board in May 2021. The recruitment of participants was set to begin in July 2021, based on clinician

referrals from outpatient psychiatry at Hotel Dieu Hospital. Recruitment will be conducted with approximately 3 participants added each month until January 2022. The study outcomes will be shared with the National Institute of Health ClinicalTrials.gov database in the summer of 2022.

Discussion

Principal Findings

The main anticipated findings of this study will evaluate the efficacy of a novel intervention in a previously treatment-resistant patient population. Although ketamine has been used to treat other affective disorders, very few trials have been conducted on its use for treating PTSD. In addition, ketamine and CBT have been successfully combined in the past to treat other psychiatric disorders [47], but they have never been amalgamated to treat PTSD, nor have they ever been combined with a web-based component. This study will also increase access to care and help hospitals and clinics provide patients with accessible and affordable treatment. The ketamine component of this study will improve access due to its rapid symptom relief [48] and the resulting increased patient volume. Similarly, e-CBT will improve access to treatment for patients without the time or ability to travel to an in-person clinic weekly while benefiting economically disadvantaged patients and those living in rural areas with low access to specialized care. e-CBT also provides a safe alternative to in-person therapy during the COVID-19 pandemic. Such an approach to treatment can help address lengthy wait times and the cost of mental illness in health care systems [30,31]. Finally, this study aims to contribute toward the discussion on glutamate and its role in fear extinction. An effective combined treatment would suggest that the glutamatergic system may help in facilitating fear extinction.

Limitations and Future Directions

As this is a proof-of-concept study, the goal is to determine whether the treatment model works to reduce PTSD symptoms. Nevertheless, because of the preliminary aims of this study, there are a number of limitations. First, if the treatment successfully reduces symptoms, this protocol offers no way to determine the source of the improvement. Symptom improvement could be attributed primarily to e-CBT, ketamine, or both. A second issue is that this study does not offer insights into the posttreatment timeline for relapse, as the last assessment is immediately following treatment. Another issue is the unblinded nature of the study potentially biasing the participants as a result.

In terms of future directions, a follow-up study is needed with 40 participants and a four-arm design, including a control group receiving an active ketamine placebo and sham-CBT, a group receiving true e-CBT and placebo ketamine, a group receiving true ketamine and sham-CBT, and a group receiving both ketamine and e-CBT. Furthermore, follow-up assessments should be performed at 3 months, 6 months, and 1 year after treatment. These research design elements would allow for an investigation of the compounding effects of the two treatments and the symptom time-course posttreatment.

Acknowledgments

The Queen's Faculty of Psychiatry Internal Faculty Grant provided Can $17,000 (US $12,750) of funding for this study. Multimedia Appendices 3 and 4 provide more information on the funding review process. The funding source had no role in the study design, study execution, data collection, data analysis, or data interpretation.

Conflicts of Interest

NA is Assistant Professor of Psychiatry at Queen's University and has cofounded OPTT, the care delivery platform in use, and has ownership stakes in OPTT Inc. RM has received consulting and speaking honoraria from AbbVie, Allergan, Eisai, Janssen, KYE, Lallemand, Lundbeck, Otsuka, and Sunovion, and research grants from CAN-BIND, the Canadian Institutes of Health Research, Janssen, Lallemand, Lundbeck, Nubiyota, the Ontario Brain Institute, and the Ontario Mental Health Foundation.

Multimedia Appendix 1
Safety parameters.
[PDF File (Adobe PDF File), 108 KB - resprot_v10i7e30334_app1.pdf]

Multimedia Appendix 2
Full protocol approved by the research ethics board.
[DOCX File , 103 KB - resprot_v10i7e30334_app2.docx]

Multimedia Appendix 3
Peer review document for funding.
[PDF File (Adobe PDF File), 121 KB - resprot_v10i7e30334_app3.pdf]

Multimedia Appendix 4
Funding approval letter.

[PDF File (Adobe PDF File), 195 KB - resprot_v10i7e30334_app4.pdf]

Multimedia Appendix 5
CONSORT-eHEALTH checklist (V 1.6.2).
[PDF File (Adobe PDF File), 108 KB - resprot_v10i7e30334_app5.pdf]

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Abbreviations

CAPS: Clinician-Administered PTSD Scale
CBT: cognitive behavioral therapy
***DSM-5*:** *Diagnostic and Statistical Manual of Mental Disorders, 5th edition*
e-CBT: electronically delivered cognitive behavioral therapy
IV: intravenous
NMDA: N-methyl-D-aspartate
OPTT: Online Psychotherapy Tool
PTSD: posttraumatic stress disorder
TF-CBT: trauma-focused cognitive behavioral therapy

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Protocol

A Randomized Controlled Trial Investigating the Feasibility of a Low-Intensity Psychological Intervention for Fear of Memory Loss and Quality of Life in Older Adults: Protocol for the Reducing Fear and Avoidance of Memory Loss (REFRAME) Study

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Abstract

Background: Dementia is the most feared disease associated with aging. Prolonged fears about memory loss and dementia can have harmful consequences even in the absence of cognitive decline. Fear of dementia is associated with poorer health outcomes and psychological well-being and increased memory failures in older adults.

Objective: We will conduct a randomized controlled trial to determine the feasibility of a tailored, web-based mindfulness program to reduce fear of memory loss and increase quality of life in older adults experiencing heightened fear.

Methods: Eighty participants will be recruited and divided into 2 groups (40 in each group). One group will receive psychoeducation plus mindfulness training. A second group will receive psychoeducation, mindfulness training, and additional modules targeting maladaptive behavioral avoidance (ie, social and cognitive withdrawal).

Results: Our recent etiological model posits that maladaptive behavioral avoidance strategies critically underlie psychosocial dysfunction associated with fear of memory loss. Thus, we predict better outcomes in the second group, including reduced fear of memory loss (primary outcome), Alzheimer disease, anxiety, and subjective memory failures, and increased quality of life (secondary outcomes). Outcome measures will be applied at 5 time points (before, baseline, interim, and after the intervention, and at 3-month follow-up). Data will be analyzed using mixed models and correlations.

Conclusions: Results from this study will contribute to the current literature on dementia-related fear and improve our understanding of how to effectively address and reduce these fears.

Trial Registration: ClinicalTrials.gov NCT04821960; https://clinicaltrials.gov/ct2/show/NCT04821960.

International Registered Report Identifier (IRRID): PRR1-10.2196/30514

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KEYWORDS

fear; memory loss; dementia; older adults; mindfulness; behavioral activation

Introduction

Background

Fear of dementia, also referred to as "dementia worry" [1] and "anticipatory dementia" [2], describes the fear that perceived changes in one's memory are indicative of dementia [3]. Many older adults worry about developing dementia, with evidence suggesting that dementia has become the most feared health condition among people over the age of 50, ranking higher than cancer and heart disease [4]. The number of people living with dementia worldwide is expected to triple from approximately 50 million to 152 million by 2050. Given this projected increase, the incidence of fear of dementia is also certain to increase [5]. The anticipated growth in dementia cases, coupled with improved societal awareness of the disease and the knowledge that as of yet there is no cure for dementia, has contributed to increased dementia-related fear in older adults [1,6].

Fear of dementia has been associated with poor health outcomes, lower levels of psychological well-being, memory failures, and lower quality of life in older adults [3,7]. Emerging evidence suggests that dementia-related fears perpetuate harmful cognitive–behavioral cycles [3,8,9]; for example, individuals who worry about developing dementia might fixate on what they perceive to be symptoms of neurodegeneration, such as when they forget someone's name. This excessive self-monitoring is fatiguing and can increase the frequency of cognitive failures, compounding the initial fear. In addition to self-monitoring, individuals can develop unnecessary and unproductive behavioral strategies to mitigate psychological distress and cognitive failures. These maladaptive strategies could include social withdrawal and avoidance of cognitive effort. In a recent study, Farina et al [3] showed that fear and avoidance of memory loss symptoms were associated with lower quality of life and greater self-reported memory failures in a community sample of older adults. Building on this, we posit that psychological distress and everyday cognitive failures may trigger maladaptive behavioral responses that undermine motivation and engagement in healthy activities, which could, in turn, accelerate cognitive decline.

Although many studies have investigated factors associated with dementia-related fear, only few have investigated ways to mitigate this fear. Interventions that disrupt the fear cycle have potential to reduce distress, while also accruing long-term benefits such as preventing the onset of cognitive decline [10]. One promising avenue is mindfulness-based training, which has been shown to improve health and well-being outcomes in other health-related difficulties, such as chronic pain and fatigue [11,12]. These outcomes may be driven by improvements in individuals' ability to acknowledge negative thoughts and feelings without fixating on them [13-15]. To our knowledge, no studies have investigated the efficacy of mindfulness-based interventions for dementia-related fear. Another promising avenue for tackling dementia-related fear is approach-oriented exercises, in which people practice behaviors that allow them to exercise their cognitive abilities even in the face of emotional distress. Although approach-oriented activities (eg, behavioral activation, exposure therapy) are widespread in behavior therapy, specific techniques for dementia-related fear warrant further exploration [16,17]. Further, a person with a clinically elevated level of dementia-related fear might be referred to clinical care (eg, working with a psychologist or social worker), but scalable interventions for subclinical fears are also needed.

This study will leverage web-based technology to deliver and compare 2 low-intensity, self-guided approaches to help older people manage dementia-related fears in daily life: (1) mindfulness and meditation exercises, and (2) mindfulness and meditation exercises combined with behavioral therapy exercises to facilitate approach, rather than avoidance. This research will contribute to existing knowledge of dementia-related fear and improve our understanding of how to effectively address and reduce these fears.

Purpose

The purpose of this study is to compare web-based programs to reduce fear of memory loss and increase quality of life in older adults experiencing dementia-related fear. This program (REFRAME) will focus on 3 components across 3 weeks. These include psychoeducation (Week 1), mindfulness-based exercises to identify and monitor dementia-related fears (Week 2), and behavioral activation to overcome unnecessary and maladaptive avoidance behaviors (Week 3). Further, we propose that maladaptive avoidance behaviors are a critical factor in maintaining dementia-related anxiety. Therefore, REFRAME will be tested against an active comparison group receiving psychoeducation and mindfulness only. The overarching goals of the project are to (1) determine the impact of REFRAME on dementia-related fear and maladaptive avoidance, (2) determine the feasibility of the low-cost web-based intervention program, and (3) investigate broad health-related secondary outcomes in older adults.

Hypotheses

1. We predict greater reductions in dementia-related fear and avoidance (23-item Fear and Avoidance of Memory Loss [FAM-23]) in the REFRAME program group relative to the comparison group.
2. We predict greater improvements in fear of Alzheimer disease, mental health (ie, anxiety), and psychosocial functioning (ie, quality of life, social functioning) in the REFRAME program group relative to comparison.
3. We predict a greater reduction in self-reported subjective memory failures in the REFRAME program relative to comparison.

Methods

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria for the study as presented in Textbox 1.

Textbox 1. Summary of inclusion and exclusion criteria.

Inclusion criteria

- Aged 55 or older
- Elevated dementia-related fear as measured by the 23-item Fear and Avoidance of Memory Loss (FAM-23) Scale (score of ≥61).
- Able and willing to provide informed consent.
- Able to read/write in English.
- Willingness to be randomized to the intervention group.
- Willingness to complete 3 weeks of self-guided intervention, questionnaires, and cognitive tests.
- Access to internet for completion of questionnaires and intervention materials.
- Resident in the larger Chicago (Illinois) area.

Exclusion criteria

- Diagnosis of mild cognitive impairment, Alzheimer disease, or dementia by a health care provider.
- Impaired cognitive or neurologic function as determined by the Montreal Cognitive Assessment for blind individuals (MoCA BLIND; score of <18 of 22).
- Unstable medical condition (hospitalization in the last 6 weeks or repeated emergency room visits).
- Severe depression (15-item Geriatric Depression Scale [GDS-15] cut-off score of ≥12).
- Undergoing psychotherapy treatment for anxiety or depression.
- Current participation in another psychotherapy.
- Inadequate vision or hearing to interact with study material.
- Current substance use disorder.

Sample Size

Eighty participants will be recruited (40 in each group). Power was estimated using a mixed ANOVA framework to detect a between-within interaction in G*Power with the following assumptions: medium effect size (*f*)=0.25, Type I error rate=0.05, sample size=80, groups=2, repeated measures=6 (Table 1), correlation among repeated measures=0.5, and nonsphericity correction epsilon=1.0 (ie, no correction) [18]. These assumptions yielded high power (99%). We anticipate losing some participants to follow-up and investigated a nonsphericity epsilon of 0.5; power remained at 92% even with the more conservative epsilon and with n=40. Although these power estimates are high, a goal of this study is to determine the effect sizes (within-subjects and across groups) for future randomized controlled trials.

Table 1. Timing of outcome measures and assessments.

Measures	2 weeks before the intervention	Intervention (3 sessions)			1 week after the intervention	Follow-up (4 weeks after the intervention)
		1	2	3		
Demographic (online)	✓[a]					
23-Item Fear and Avoidance of Memory Loss (FAM-23)	✓	✓	✓	✓	✓	✓
Fear of Alzheimer's Disease Scale (FADS)	✓	✓			✓	
Memory Failure Scale (MFS)		✓			✓	✓
Patient-Reported Outcomes Measurement Information System, 29-item (PROMIS-29)		✓			✓	✓
World Health Organization-Five Well-Being Index (WHO-5)		✓			✓	✓
Montreal Cognitive Assessment for blind individuals (MoCA BLIND)	✓					
15-Item Geriatric Depression Scale (GDS-15)	✓					
Patient Expectation Scale		✓				
1-item Patient Global Impression of Change (PGIC)						✓
Coronavirus Anxiety Scale (CAS)		✓			✓	✓
Qualitative questionnaire						✓

[a]✓ indicates the time points at which measures were taken.

Recruitment Methods

Participants will be recruited through community-based outreach methods, digital and print advertising (eg, flyers, postcards, email outreach, web postings, advertisements on transit lines, newspaper advertisements, radio advertisements), and official registries (eg, Research Match). One of the study PIs (JG) also has a list of participants from previous research studies that have agreed to be contacted for future projects. If a participant is interested, he/she can complete an online screening survey in REDCap to assess initial eligibility before a longer screening phone call. Potential participants can express their interest to take part by means of direct contact with the researchers via phone or email, after which they would be invited to complete the screening and consent process.

Consent Process

Because the study will be conducted remotely, we will obtain e-consent from participants via REDCap. Participants will be able to access the consent form as soon as they enter the study and they will only be redirected to the main study if they give their consent. Participants can review the consent form, sign their name, and provide other basic demographic information required if they agree to take part. They will also receive a read-only copy of the consent form, which they can review, download, or print. Participants will be explicitly informed that signing the electronic copy is equivalent to signing a physical document.

Study Design

The study design is a randomized controlled trial with a between-groups experimental comparison of 2 groups: REFRAME versus psychoeducation plus mindfulness only. The REFRAME program group will participate in psychoeducation, mindfulness, and behavioral activation activities. The comparison group will participate in psychoeducation and mindfulness, but not in behavioral activation activities. Thus, the study will allow us to determine the impact of psychoeducation and mindfulness (within-subjects in the comparison group) on fear reduction, in addition to approach-oriented exercises. The study will consist of 6 time points (2 baselines, 2 midtreatment, after treatment, and follow-up). At each time point, participants will complete outcome questionnaires.

Measures

Participants will be asked to complete questionnaires 2 weeks before commencing the intervention, at baseline, during the intervention (before Week 2 and Week 3), 1-week after the intervention, and at 4-week follow-up. All assessments will be completed using the REDCap platform with follow-up assessments carried out online via an email link [19]. The primary outcome measure will be the 23-item Fear and Avoidance of Memory Loss (FAM-23) Scale [3], which will assess fear and avoidance of memory loss. This will be administered 2 weeks before commencing the intervention. The Montreal Cognitive Assessment for blind individuals (MoCA BLIND) will also be administered at this time point to screen for cognitive impairment. Secondary outcome measures include the Fear of Alzheimer's Disease Scale (FADS [20]); World Health Organization-Five Well-Being Index (WHO-5); NIH Patient-Reported Outcomes Measurement Information System, 29-item (PROMIS-29 version 2.0); and Memory Failure Scale (MFS [21]). These assessments will be completed at baseline, after the intervention, and at follow-up. Depression will be measured using the 15-item Geriatric Depression Scale (GDS-15 [22]) 2 weeks after the intervention and at 1-week follow-up. Participants will also complete the 5-item Coronavirus Anxiety Scale (CAS [23]) at baseline, 1-week after the intervention, and

at 4-week follow-up. Finally, participants will complete the 1-item Patient Global Impression of Change (PGIC) and brief qualitative interviews at 4-week follow-up. Upon completion of the study, participants will receive a 1-page handout written in lay terms explaining ways to promote brain health, with information for mental health services provided if needed.

Intervention Overview

The intervention will be delivered over 3 weeks for both groups. The REFRAME group will receive a modular intervention, which is divided into psychoeducation, mindfulness, and behavioral activation. In the first week, participants will learn about concepts such as memory lapses, dementia, fear of memory loss, and causes of fear of memory loss through psychoeducation. Week 1 psychoeducation is divided into 4 modules and participants will be able to complete the modules by listening to the audio clips and completing short online workbook exercises. Week 2 is focused on mindfulness. Participants will learn introductory concepts about mindfulness, meditations (eg, the body scan), noticing thoughts, and grounding through audio and text-based exercises. The final week is focused on delivering behavioral techniques for overcoming avoidance; this involves exercises to increase awareness about avoidance and safety behaviors and identifying ways to challenge them. The comparison group will receive the same intervention during Weeks 1 and 2. For Week 3, they will receive a second week of mindfulness training, which includes additional novel exercises. Audio clips are provided in Multimedia Appendices 1-15.

Fidelity of the Intervention

Fidelity of the intervention will be checked by reviewing online activities. This will provide a proxy of intervention completion. Finally, postintervention interviews will be used to debrief participants about the intervention.

Study Team

The intervention was developed by postgraduate students enrolled in an Applied Psychology Master's Program (PO'L, PP, and JR) under the direct supervision of experienced clinicians (JG, a psychologist, and RS, a geriatrician and behavioral neurologist) and senior researchers in clinical psychology with expertise in mindfulness (MB) and older adult brain health (FF).

Results

This project received funding from the pilot grant from the Osher Center for Integrative Medicine awarded to FF, JG, and MB in August 2020 and was approved by the Institutional Review Board in Northwestern University Chicago in March 2021. Data collection has commenced as of May 2021 and will continue on a rolling basis until sufficient participants have been recruited.

Primary Outcomes and Analysis

We will specify a mixed model with a random intercept for each person, as well as fixed effects for treatment (1=REFRAME, 0=otherwise) and 5 dummy codes for the 6 time points. The mixed model will only include treatment–time interactions for the 4 time points after the baseline (for the 2 baselines, treatment should have no effect because the intervention has not yet begun). The primary effects of interest will be the interaction terms for post-treatment and follow-up, tested at α=.05. We will also compare the FAM-23 Scale with baseline using within-subjects *t* tests for all midtreatment, post-treatment, and follow-up time points.

Secondary Outcomes

The secondary analysis will evaluate if fear of Alzheimer disease, well-being, general anxiety, and memory failures are affected by either intervention. As such, mixed models, similar to above, will be used to analyze scores on the FADS, WHO-5, PROMIS-29, and MFS across time in both groups. In particular, the construct of fear of Alzheimer disease will be examined and compared with the construct of fear of memory loss. The relationship between scores on the FAM-23 Scale and the FADS will be examined through use of a Pearson correlation.

Further information on the data analysis plan is available on the ClinicalTrials registry (Trial Registration Number NCT04821960).

Participant Debriefing

Upon completion of the study, we will use an open-ended REDCap survey to explore participants' experiences. We will measure their experience of using the intervention materials, what they found most beneficial, if they plan on continuing to use the skills they have learned, and if they have any recommendations for how we can improve the intervention.

Missing Data

As per STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines, the total number of participants who take part in each stage of the study will be recorded [24]. Should a participant not take part in a certain wave, reasons will be reported for the absence, if available. Reasons for missing data will be discussed in terms of the intervention group that they were assigned to and the timepoint at which participation ceased. Furthermore, there may be important differences between participants who completed the intervention and those who dropped out. This will be investigated and reported along with the results.

The model does not require complete or imputed data to be estimated. Thus, we anticipate doing an intent-to-treat analysis in which all participants are included in the analysis.

Discussion

Limitations

The primary study limitation is the self-guided nature of the intervention. The intervention will be delivered through an online platform comprising weekly audio clips and written passages. This method of delivery could inflate the risk of attrition, as the researchers will not be present while participants engage with the materials. Remote delivery also makes it more difficult to determine if participants comprehended the materials as intended. To mitigate these potential effects, we will measure participants' engagement with the weekly exercises and

questionnaires throughout the study. We will also explicitly ask about accessibility of the materials in the debriefing interviews. A psychologist and geriatrician from the study team will also be available to troubleshoot any issues as they arise. A second limitation is recruitment of the small sample size from a single metropolitan area. Although the sample may limit generalization, the data collected here will help to guide future interventions with larger, more diverse cohorts.

Strengths and Future Directions

Fear of dementia is associated with a range of negative outcomes including poorer physical health, reduced well-being, and increased perceived memory failures. As such, it is vital that we establish evidence-based interventions to mitigate this fear. Similar to other health anxieties, excessive fear and avoidance of dementia are malleable psychological processes that can be reduced through low-cost interventions. By identifying and effectively treating maladaptive fear early, we may be able to reduce dementia risk, or prevent cases, in later life by fostering healthy lifestyle behaviors (eg, continued cognitive and social engagement). Reducing fear may also encourage people who may be experiencing changes with their memory to seek support from their doctor earlier, which could lead to improved assessment and treatment options.

Future scope of the research will include administering the intervention to a larger, more representative group. In line with the recent push toward early interventions, this research could also be expanded to include midlife (ie, 45+ years). Finally, future work should also aim to identify specific groups who are at a higher risk of experiencing maladaptive fear and avoidance behaviors and design tailored interventions for them; for example, people who are (or have been) a care partner for someone with dementia, or those with a family history of the disease.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Audio file for Week 1 Module 1 of the intervention.
[MP4 File (MP4 Video), 8009 KB - resprot_v10i7e30514_app1.mp4]

Multimedia Appendix 2
Audio file for Week 1 Module 2.
[MP4 File (MP4 Video), 4670 KB - resprot_v10i7e30514_app2.mp4]

Multimedia Appendix 3
Audio file for Week 1 Module 3.
[MP4 File (MP4 Video), 6470 KB - resprot_v10i7e30514_app3.mp4]

Multimedia Appendix 4
Audio file for Week 1 Module 4.
[MP4 File (MP4 Video), 5176 KB - resprot_v10i7e30514_app4.mp4]

Multimedia Appendix 5
Audio file for Week 2 Module 1.
[MP4 File (MP4 Video), 4662 KB - resprot_v10i7e30514_app5.mp4]

Multimedia Appendix 6
Audio file for Week 2 Module 2.
[MP4 File (MP4 Video), 5800 KB - resprot_v10i7e30514_app6.mp4]

Multimedia Appendix 7
Audio file for Week 2 Module 3.
[MP4 File (MP4 Video), 6019 KB - resprot_v10i7e30514_app7.mp4]

Multimedia Appendix 8
Audio file for Week 3 Module 1 Experimental.
[MP4 File (MP4 Video), 2279 KB - resprot_v10i7e30514_app9.mp4]

Multimedia Appendix 9

Audio file for Week 3 Module 1 Control.
[MP4 File (MP4 Video), 6131 KB - resprot_v10i7e30514_app10.mp4]

Multimedia Appendix 10
Audio file for Week 3 Module 2 Experimental.
[MP4 File (MP4 Video), 3761 KB - resprot_v10i7e30514_app11.mp4]

Multimedia Appendix 11
Audio file for Week 3 Module 2 Control.
[MP4 File (MP4 Video), 6227 KB - resprot_v10i7e30514_app12.mp4]

Multimedia Appendix 12
Audio file for Week 3 Module 3 Experimental.
[MP4 File (MP4 Video), 2909 KB - resprot_v10i7e30514_app13.mp4]

Multimedia Appendix 13
Audio file for Week 3 Module 3 Control.
[MP4 File (MP4 Video), 6029 KB - resprot_v10i7e30514_app14.mp4]

Multimedia Appendix 14
Audio file for Week 3 Module 4 Experimental.
[MP4 File (MP4 Video), 3327 KB - resprot_v10i7e30514_app15.mp4]

Multimedia Appendix 15
Audio file for Week 3 Module 5 Experimental.
[MP4 File (MP4 Video), 1695 KB - resprot_v10i7e30514_app16.mp4]

Multimedia Appendix 16
Peer-reviewed report submitted to the Osher Center for Integrative Medicine at Northwestern University for the Osher Pilot Research Awards 2020.
[PDF File (Adobe PDF File), 106 KB - resprot_v10i7e30514_app17.pdf]

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Abbreviations

CAS: Coronavirus Anxiety Scale
FADS: Fear of Alzheimer's Disease Scale
FAM-23: 23-item Fear and Avoidance of Memory Loss
GDS-15: 15-item Geriatric Depression Scale
MFS: Memory Failure Scale
MoCA BLIND: Montreal Cognitive Assessment for blind individuals
PGIC: 1-item Patient Global Impression of Change
PROMIS-29: Patient-Reported Outcomes Measurement Information System, 29-item
STROBE: STrengthening the Reporting of OBservational studies in Epidemiology
WHO-5: World Health Organization-Five Well-Being Index

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Protocol

The Effect of Periodontal Disease on Metabolic Control in Patients With Diabetes Mellitus in South Africa: Protocol for a Systematic Review

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Abstract

Background: The increase in the prevalence of type 2 diabetes mellitus (T2DM) and its associated complications is burdensome to the South African health system. Understanding the role of comorbid diseases, such as periodontal disease (PD), and their effect on metabolic control in patients with DM in South Africa will raise awareness about the importance of periodontal interventions among patients with DM in South Africa.

Objective: The review will aim to determine the effect of PD on the metabolic control of T2DM in a South African population.

Methods: A systematic review of the relationship between PD and metabolic control in patients with T2DM in a South African population will be conducted. Cohort, cross-sectional, and case-controlled studies will be considered in which the outcome of interest is diabetic control. A search will be done in the following sources: EBSCOhost (academic search complete; dentistry and oral sciences), PubMed, ScienceDirect, and the South African National ETD Portal for articles published in English. There will be no limit placed on the date of the publication. The reference list of articles will be reviewed for further inclusion of critical articles. Two independent reviewers (AJ and FK-D) will do study selection, data extraction, and quality analysis. All disputes will be resolved by discussion, and the entire team will verify final decisions.

Results: The systematic review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO). A preliminary search was conducted using the keywords ((perio*) AND (diabet*)) AND (“South Africa”). The review process should be completed by December 2021.

Conclusions: The review will determine the effect of PD on metabolic control in patients with T2DM in South Africa. The outcome would inform health policy to highlight the need to include periodontal care into treatment protocols in patients with T2DM. In this process, the feasibility for future research in this area of interest will also be defined.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42020221064; https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=221064

International Registered Report Identifier (IRRID): PRR1-10.2196/27471

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KEYWORDS

periodontal disease; periodontitis; bleeding on probing, type 2 diabetes mellitus; fasting glucose; HbA1C; South Africa

Introduction

Rationale

Acute and chronic inflammation of the attachment apparatus around teeth, the periodontium, due to dysbiosis in the oral microbiome, constitutes what is known as periodontal diseases (PDs) [1]. Inflammation limited to gingivae is known as gingivitis, whereas an extension of the inflammatory infiltrate can result in clinical attachment loss or periodontitis [2]. The progression to periodontitis depends on the host's susceptibility and the host's response to the dental biofilm [1].

Diabetes mellitus (DM) constitutes a group of diseases hallmarked by chronic hyperglycemia and is classified by etiology [3] into type 1 DM (T1DM), type 2 DM (T2DM), other specific types, and hyperglycemia first detected in pregnancy [3]. T1DM is caused by the autoimmune destruction of β cells of the pancreas. It constitutes 5%-10% of all diagnoses of DM, but has a higher prevalence in children diagnosed with DM (80%-90%) [4]. Insulin resistance is the hallmark of T2DM, and is also responsible for concurrent metabolic conditions that may occur simultaneously with T2DM [5]. T2DM represents 90%-95% of all diagnosed cases of DM [3]. A variety of conditions of mostly genetic origin, as well as related to drug therapy, have been included under other specific types of DM. Gestational DM is a potential precursor to the development of T2DM later in life and is classified under hyperglycemia first detected in pregnancy [6]. It is characterized by the inability to tolerate glucose during pregnancy, with no prior history of glucose intolerance. Adverse pregnancy outcomes may be associated with gestational DM [5].

South Africa has an increasing population of patients with T2DM [7], resulting in an increased health care burden. In 2000, it was reported that DM in South Africa accounted for approximately 14% of cases of ischemic heart disease, 12% of hypertensive disease, 12% of renal disease, and 10% of stroke [8]. Furthermore, the complications of T2DM are associated with a poor health-related quality of life [5]. These complications and their effects result from poor metabolic control that can be prevented or minimized by well-timed intervention strategies.

Currently, DM is the fourth highest combined cause of death and disability in South Africa [9]. Data from similarly classified income countries matched for socioeconomic demographics show that DM-related death and disability is significantly higher in South Africa [9]. In 2015, T2DM was the second largest cause of death in the South African population. It was also the leading cause of death in women in the same year [9]. Underdiagnosed DM and lifestyle risk factors such as obesity, urbanization, and limited access to health care have been cited as possible causes of the high diabetes-related mortality rate in the South African context [7].

Periodontitis and DM are established comorbid diseases [10]. A recent review reported poorer periodontal outcomes in patients with uncontrolled DM [11]. The study showed that patients with diabetes having concomitant periodontitis had increased glucose impairment and insulin resistance. Furthermore, the authors reported that patients with DM were 3 times more likely to develop periodontitis than those without. The investigation also showed that the incidence of DM and diabetic complications was higher in patients with periodontitis. Sanz et al [11] reported that the treatment of periodontitis improves serum HbA_{1C} levels in patients with DM [11]. The mechanistic links to the comorbid relationship between periodontitis and DM are primarily due to inflammation [12]. In vitro and in vivo studies have shown increased levels of proinflammatory cytokines in patients with poorly controlled diabetes and in those with diabetes and concimitant periodontitis [13]. These cytokines, tumor necrosis factor-α, other inflammatory markers such as C-reactive protein, and mediators of oxidative stress burden DM control, and have been shown to decrease after a periodontal intervention [13].

The South African context is unique due to the disparity between the socioeconomic groups, which is essentially a result of decades of laws that enforced racial segregation and disparate economic development in South Africa. These circumstances have resulted in socioeconomic segregation. Currently, South Africa has the highest income disparity according to the Gini Index (63.0) [14]. This disparity has caused unequal access to quality health care, as the public health system, with limited resources, services most of the population. In addition, South Africa has limited resources to manage the costs of diabetes, as the country is already overwhelmed with a quadruple burden of disease resulting from high infectious disease rates, noncommunicable disease, and maternal and child mortality [15]. Therefore, determining the influence of comorbid diseases such as PD on DM is important in the South African society so that protocols and standards of care can be influenced across the board to limit the unneccesary burden placed on the already overextended health care system.

Objectives

This review will determine the effect of PD on metabolic control in adults with T2DM in South Africa. Should PDs prove to have an adverse effect on metabolic control in T2DM in South Africa, this review will highlight the importance of PD intervention in this patient group. The latter will form the basis for policy development and augment holistic treatment strategies for T2DM in South Africa.

Methods

Overview

This systematic review will synthesize data to determine whether PDs affect metabolic control in patients with T2DM in South Africa. The proposed review will be conducted according to the requirements contained within the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist (Multimedia Appendix 1) for systematic review and meta-analysis protocol [16] and has been registered with PROSPERO (CRD42020221064).

Eligibility Criteria

Eligible studies that report on the metabolic control in South African patients with T2DM having PD will be reviewed. Metabolic control outcomes will be measured by HbA_{1C} and

fasting glucose levels. Only English publications will be included and there will be no date limitation for the eligible publications. Unpublished studies such as theses and dissertations will also be sourced. Reference lists of identified publications will be reviewed to find additional articles that may satisfy the eligibility criteria. The following study designs will be included in this review: cohort, cross-sectional, and case-controlled studies.

Information Sources

The following electronic databases will be searched for publications and unpublished studies that meet the eligibility criteria for this review: EBSCOhost (academic search complete; dentistry and oral sciences), PubMed, ScienceDirect, and the South African National ETD Portal. Authors will be contacted should any further data be required. All articles retrieved as of March 8, 2021, will be included for this review.

Search Strategy

An initial limited search of MEDLINE was undertaken to identify articles pertaining to the topic. The text words in the titles and abstracts and terms used to describe and index the relevant articles were used to develop a complete search strategy. An example of a search strategy outlined for PubMed can be found in Multimedia Appendix 2. The search strategy, including all identified keywords and index terms, will be adapted for each included database or information source. Studies will be limited to the English language and human patients only. The reference list of all included sources of evidence will be screened for additional studies. The results of the search will be recorded in a data capturing (Multimedia Appendix 3) sheet to include the source, the date of search, the number of hits, and a reference link to the articles.

Study Selection, Data Management, and Data Collection Process

The eligibility criteria will be used to guide 2 reviewers (AJ and FK-D), who will select studies for inclusion. Selections will be recorded in Rayyan [17], which will be used to manage records and resolve duplications.

Study selection will be blinded, and any disagreements will be resolved by discussion. A data extraction tool (Multimedia Appendix 4) will be used to guide reviewers on the data that would need to be extracted from the included articles.

Data Items

The extracted data will be recorded in duplicate by 2 independent reveiwers (AJ and FK-D) who will be blinded. An MS Excel spreadsheet will be used to capture extracted data that will include publication details, the setting of research study, age of the population, sex, PD clinical determinants, number of cases, total sample size, and diabetic control as measured by blood glucose or HbA_{1C} levels. PD clinical determinants will include bleeding index or bleeding on probing percentage, clinical attachment loss, and pocket depths.

Outcomes and Prioritization

The primary outcome is to determine the metabolic control of adults with T2DM in South Africa who have PD. HbA_{1C} and fasting glucose levels will be used as the primary measure of metabolic control in T2DM.

Risk of Bias in Individual Studies

To assess the risk of bias within included studies, the methodological quality of potential studies will be evaluated using the Joanna Briggs Institute (JBI) criteria for assessing the quality of nonrandomized studies (case-controlled, cross-sectional, or cohort) in meta-analyses. An 8-point item scale will be used to evaluate the risk of bias in a cross-sectional study using the JBI criteria. A cutoff point of 5 will indicate a low risk of bias. A 10- and 11-point item scale will be used to evaluate a case-controlled and cohort study, respectively. A minimum cutoff of 6 and 7 for case-controlled and cohot studies, respectively, will indicate a low risk of bias. Two separate reviewers (AJ and FK-D) will undertake the assessments and a third reviewer (TR) will be used as an arbiter to resolve any disagreements. Reveiwers will be blinded throughout the process.

Data Synthesis

Studies with homogenous designs will be subjected to a meta-analysis. The choice of the model (fixed or random) and the method for meta-analysis will be based on the guidance by Tufanaru et al [18] and Moola et al [19].

Continuous outcomes will be analyzed using weighted mean differences (with 95% CI) or standardized mean differences (95% CI) if different measurement scales are used. Skewed data and nonquantitative data will be presented descriptively.

When there are missing data, an attempt will be made to contact the author(s) of the original study to obtain the relevant missing information. If missing data cannot be obtained, an imputation method will be used. Important numerical data will be evaluated with care.

Assessment of Heterogeneity

Clinical heterogeneity will be tested by considering the variability in participant factors among trials (eg, age) and trial factors (randomization concealment, blinding of outcome assessment, losses to follow-up, treatment type, co-interventions). Statistical heterogeneity will be tested using the chi-square test (significance level: P=.1) and I^2 statistic (0%-40%, might not be important; 30%-60%, may represent moderate heterogeneity; 50%-90%, may represent substantial heterogeneity; 75%-100%, considerable heterogeneity). There will be no I^2 cutoff point to assess heterogeneity. Any source of heterogeneity will be explored using subgroup or sensitivity analysis.

A meta-analysis of studies with similar comparisons reporting the same outcomes will be conducted. The results from studies not suitable for inclusion will be reported in a table. The meta-analysis will be performed using Stata 16 (StataCorp). If appropriate, a subgroup analysis of age groups may be performed.

The outcome will be combined and calculated using the statistical software Stata 16, according to the statistical guidelines referenced in the current version of the Cochrane

Handbook for Systematic Reviews of Interventions [20]. The Mantel–Haenszel method will be used for the fixed-effect model if tests of heterogeneity are not significant. If statistical heterogeneity is observed (I^2≥50% or P<.1), the random effects model will be chosen. If heterogeneity is substantial, a meta-analysis will not be performed; a narrative, a qualitative summary will be done instead.

Effect sizes expressed as odds ratios or relative risk or other association measures and their 95% CIs will be calculated for analysis. Where effect estimates and standard errors are unavailable, they will be calculated from crude data and 95% CIs.

Metabias

A funnel plot will be generated within Stata 16 to assess publication bias if 10 or more studies were included in a meta-analysis. Statistical tests for funnel plot asymmetry (Egger test, Begg test) will be performed where appropriate.

Confidence in Cumulative Evidence

The quality of evidence for all outcomes will be assessed using GRADE (Grading of Recommendations Assessement, Development and Evaluation).

Results

This review will be conducted from September 2021 to December 2021. The PROSPERO registration number is CRD42020221064. Two reviewers (AJ and FK-D) will be blinded at each stage of the process. Regular team meetings will be held to settle any disputes or differences between the inclusions of the reviewers. This will serve to enhance the transparency of the review process. All discussions will be recorded as evidence. There is no conflict of interest within the team. Once the systematic review is completed, it will be submitted for publication.

Discussion

Although reviews from elsewhere have shown that PDs increased blood glucose levels in patients with T2DM, and that the treatment of PD has shown an improvement in metabolic control in this group of patients, a systematic review in the South African population had not yet been conducted to consolidate findings in this population [10].

A study conducted in India determined that periodontitis, measured by periodontal inflammatory surface area, was more associated with elevated blood glucose levels and retinopathy and nephropathies [21]. In that same study, patients with DM without periodontitis had significantly better metabolic control than those with chronic periodontitis [21]. India's socioeconomic background is similar to that of South Africa, and therefore, similarities can be expected between these 2 populations.

Although the importance of PD diagnosis and management in T2DM is well-documented elsewhere [11], the implementation has not been widely accepted in South Africa. To our knowledge, this will be the first systematic review conducted to evaluate the effect of PD on metabolic control in T2DM in South Africa.

Given the comorbid relationship between the 2 diseases, and the increasing burden of T2DM on the South African population, this review's relevance is emphasized.

The feasibility of future research on PD and DM in South Africa will be determined. Outcomes will also include the guidance of policy for the intervention and prevention of PD in patients with DM based on evidence produced by this review. Any required protocol modifications will be discussed by all reviewers and implementation of justifiable modifications will be documented and reported in the review.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P checklist.
[PDF File (Adobe PDF File), 54 KB - resprot_v10i7e27471_app1.pdf]

Multimedia Appendix 2
Search strategy.
[PNG File , 21 KB - resprot_v10i7e27471_app2.png]

Multimedia Appendix 3
Database retrieval tool.
[PNG File , 280 KB - resprot_v10i7e27471_app3.png]

Multimedia Appendix 4
Data extraction tool.
[PNG File , 84 KB - resprot_v10i7e27471_app4.png]

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Abbreviations

DM: diabetes mellitus
GRADE: Grading of Recommendations Assessement, Development and Evaluation
JBI: Joanna Briggs Institute
PD: periodontal diseases
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

T1DM: type 1 diabetes mellitus
T2DM: type 2 diabetes mellitus

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Protocol

Tobacco Control Policy Simulation Models: Protocol for a Systematic Methodological Review

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Abstract

Background: Tobacco control models are mathematical models predicting tobacco-related outcomes in defined populations. The policy simulation model is considered as a subcategory of tobacco control models simulating the potential outcomes of tobacco control policy options. However, we could not identify any existing tool specifically designed to assess the quality of tobacco control models.

Objective: The aims of this systematic methodology review are to: (1) identify best modeling practices, (2) highlight common pitfalls, and (3) develop recommendations to assess the quality of tobacco control policy simulation models. Crucially, these recommendations can empower model users to assess the quality of current and future modeling studies, potentially leading to better tobacco policy decision-making for the public. This protocol describes the planned systematic review stages, paper inclusion and exclusion criteria, data extraction, and analysis.

Methods: Two reviewers searched five databases (Embase, EconLit, PsycINFO, PubMed, and CINAHL Plus) to identify eligible studies published between July 2013 and August 2019. We included papers projecting tobacco-related outcomes with a focus on tobacco control policies in any population and setting. Eligible papers were independently screened by two reviewers. The data extraction form was designed and piloted to extract model structure, data sources, transparency, validation, and other qualities. We will use a narrative synthesis to present the results by summarizing model trends, analyzing model approaches, and reporting data input and result quality. We will propose recommendations to assess the quality of tobacco control policy simulation models using the findings from this review and related literature.

Results: Data collection is in progress. Results are expected to be completed and submitted for publication by April 2021.

Conclusions: This systematic methodological review will summarize the best practices and pitfalls existing among tobacco control policy simulation models and present a recommendation list of a high-quality tobacco control simulation model. A more standardized and quality-assured tobacco control policy simulation model will benefit modelers, policymakers, and the public on both model building and decision making.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42020178146; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020178146

International Registered Report Identifier (IRRID): DERR1-10.2196/26854

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KEYWORDS

smoking; modeling; health policy; policy making; systematic review

Introduction

Smoking remains a top public health priority, globally killing over 6 million people annually, with 450,000 smoking-related hospital admissions, representing 4% of annual adult admissions, in England [1,2]. Furthermore, smoking prevalence demonstrates worrying inequalities, reaching 25% among routine and manual workers but only 10% among those in managerial and professional occupations [3]. Future tobacco control policies will thus need to be both effective and equitable, and might therefore greatly benefit from useful simulation models for tobacco control. Using simulation modeling to tackle complex public health issues was also highlighted in the Chief Medical Officer's Report of 2018 [4].

Simulation models are mathematical frameworks estimating the potential impact of health care interventions, which are widely used in informing medical decision-making [5-8]. These models are commonly used in economics, transport, business, and meteorology, but less so in public health [5].

Tobacco control models, mathematical models that predict tobacco-related outcomes in defined populations, have attracted increased interest in recent years [9-11]. However, few reviews have systematically studied this topic. Feirman et al [10] published what is considered to be the first systematic review on models in the tobacco control field. They reviewed 263 studies published before July 1, 2013, and noted a diversity of model methods and applications. In general, the models aimed at projecting tobacco-related trends and policy/intervention effects with outcomes of behavior change, health effect, or economic impact. Unsurprisingly, similar to other medical decision-making models, tobacco control models are developed using diverse methods such as Markov chains, discrete event, and microsimulation. Berg et al [11] studied economics models used specifically in smoking cessation, and reported the state-transition Markov model as the most common model type, with quality-adjusted life years being the most common outcome used for assessments.

We define policy simulation models as models that estimate and compare the potential impact of existing or not-yet-implemented policies. The impacts can be health-related, equity-related, economic, environmental, or other [5]. Therefore, models potentially represent the best methodological approach for estimating the future benefits of diverse prevention policies [12]. Nevertheless, some model audiences and potential users remain concerned about model credibility. As stated by the Brighton Declaration, model transparency and reporting guidelines are major existing challenges [5]. Similarly, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)-Society for Medical Decision Making (SMDM) Modelling Good Research Practice Task Force emphasized the role of transparency in explaining how the models work and the importance of validity in demonstrating model accuracy [6,7,13,14].

Quality assessment is a strategy used in weighing the credibility of study findings [15]. There are several publicly available quality assessment tools, including the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist; Grading of Recommendations, Assessment, Development and Evaluations (GRADE); and the National Institute for Health and Care Excellence (NICE) Methodology Guide quality checklist. However, these checklists are not all applicable to the evaluation of tobacco control models. The NICE and CHEERS checklists are designed for evaluation of economics models, and the GRADE guideline mainly focuses on evidence certainty [15-17]. Neither of the previous tobacco control model reviews applied a quality assessment of model transparency, validation, or reporting standard. Feirman et al [10] did not assess study quality owing to high heterogeneity among studies. Similarly, Berg et al [11] only evaluated study limitations and economic parameters. Nevertheless, both papers discussed the importance of reporting quality on model process and output, thus highlighting the need for further research on model transparency, validation, and reporting quality.

Tobacco control policy simulation models, as a policy model subcategory of tobacco control models, is an active area of research. In this systematic review, we will update, expand, and enhance the work of Feirman et al [10]. Specifically, we will perform a systematic methodological review on tobacco control policy simulation models to (1) assess the modeling practices used in tobacco control policy simulation models, and (2) present a recommendation list of a high-quality tobacco control policy simulation model. Model users will be able to evaluate tobacco control models using this recommendation, which will better enable decision makers with tobacco policy decision making.

Methods

Study Design

We will perform a systematic methodological review of tobacco control policy simulation models following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist to ensure proper conduct. This checklist offers a systematic way to search each database, minimizing the impact of the researcher on the outcome of the search [18]. We will use a narrative synthesis to present the data.

Search Strategies

We expanded a search strategy from a peer-reviewed systematic review of population tobacco use prediction models to identify potential literature [9]. Five electronic bibliographic databases (Embase, EconLit, PsycINFO, PubMed, and CINAHL Plus) were searched. A sample of search terms used in PubMed is provided in Textbox 1; the full search terms are provided in Multimedia Appendix 1. The final search was performed on August 1, 2019 limited to the English language and publication date from July 2013 to August 2019. Papers identified by the searches were imported into Zotero (version 5.0.85), a data management program, to identify duplicates, and screen titles, abstracts, and full texts as appropriate.

Textbox 1. Sample of search terms used in PubMed.

((“models, theoretical”[majr:noexp] OR “models, statistical”[majr:noexp] OR “models, economic”[majr] OR “computer simulation”[majr:noexp] OR “monte carlo method”[mesh] OR “decision support techniques”[majr:noexp] OR “decision trees”[mesh] OR “systems theory”[mesh] OR “markov chains”[mesh] OR “system dynamics”[tiab] OR “agent-based model”[tiab] OR “agent-based models”[tiab] OR “agent-based modelling”[tiab] OR “agent-based modelling”[tiab] OR “simulation model”[tiab] OR “decision analysis”[tiab] OR “decision framework”[tiab] OR “markov”[tiab] OR “cost-utility analysis”[tiab] OR “cost-utility analyses”[tiab] OR “cost-effectiveness analysis”[tiab] OR “cost-effectiveness analyses”[tiab] OR “cost-benefit analysis”[tiab] OR “cost-benefit analyses”[tiab] OR “forecasting”[mesh] OR “microsimulation”[tiab] OR “micro simulation”[tiab] OR “monte carlo” [tiab] OR “life year”[tiab] OR “life years”[tiab] OR “smoking-attributable deaths”[tiab] OR “smoking attributable deaths”[tiab] OR “deterministic”[tiab] OR “probabilistic”[tiab] OR “stochastic”[tiab] OR “dynamic transmission model”[tiab] OR “state-transition”[tiab] OR “state transition”[tiab] OR “discrete event”[tiab] OR “continuous event”[tiab] OR “analytic horizon”[tiab] OR “cohort simulation”[tiab] OR “second-order simulation”[tiab] OR “threshold analysis”[tiab] OR “years of healthy life”[tiab] OR “decision problem”[tiab] OR “transition probabilities”[tiab] OR “discount rate”[tiab]) AND (“Smoking”[Mesh] OR “Smoking Cessation”[Mesh] OR “Tobacco”[Mesh] OR “Tobacco Products”[Mesh] OR “Tobacco, Smokeless”[Mesh] OR “Smoking”[TI] OR “Tobacco”[TI] OR “Smoker”[TI] OR “Smokers”[TI] OR (cigar[TI] OR cigar'[TI] OR cigarettes[TI] OR cigaret[TI] OR cigarete[TI] OR cigarets[TI] OR cigarett[TI] OR cigarette[TI] OR cigarette'[TI] OR cigarette's[TI] OR cigarettedagger[TI] OR cigaretteinduced[TI] OR cigarettes[TI] OR cigarettes'[TI] OR cigarettesmoke[TI] OR cigaretts[TI] OR cigarillo[TI] OR cigarillos[TI] OR cigarlike[TI] OR cigarra[TI] OR cigarret[TI] OR cigarrette[TI] OR cigarrilla[TI] OR cigarro[TI] OR cigarros[TI] OR cigars[TI]) OR “Smokeless”[TIAB] OR (e cigarette[TIAB] OR e cigarette's[TIAB] OR e cigarettedagger[TIAB] OR e cigarettee[TIAB] OR e cigarettes[TIAB]) OR (electronic cigarette[TIAB] OR electronic cigarettes[TIAB]) OR “Snus”[TIAB] OR “Nicotine”[TIAB]))

Study Selection and Inclusion Criteria

Studies were included when they contained peer-reviewed tobacco control policy simulation models that predict tobacco-related outcomes from smoking policy options and scenarios. We are interested in modeling the methodologies of tobacco control policy simulation models across a variety of population groups; therefore, we will include tobacco control policy simulation models with any subpopulation in any setting.

The retrieved studies were assessed using the PICOS (Participants, Interventions, Comparators, Outcomes, and Study design) approach (Table 1). Two reviewers (VH and AH) independently assessed the eligibility of the studies. Any discrepancies were resolved by consensus or by involving the senior author (CK).

Table 1. PICOS (Participants, Interventions, Comparators, Outcomes, and Study design) approach to set inclusion and exclusion criteria.

Category	Include	Exclude
Participants	Studies on any populations	Studies on animals and cells
Interventions	Tobacco control policies	Nontobacco control policies
Comparator	Studies where tobacco control policy simulation models are evaluated or compared	No tobacco control policy simulation models presented
Outcomes	Studies reporting any tobacco-related outcomes	Studies reporting no tobacco-related outcomes
Study design	Policy simulation models	Studies without policy simulation models

Data Extraction

A data extraction form facilitates the extraction of bibliographic and methodological information about each study, and ensures that data extraction is consistent among all reviewers and across all studies. Use of such a form could also aid subsequent analyses [19].

Three reviewers (VH, AH, and CK) designed a data extraction form based on our research questions, referring to existing guidelines and expert opinions. The form has already been piloted in several studies that will be included in this systematic review. The form will be used to collect thorough information on model structure, data sources, and transparency, including the following categories (see Multimedia Appendix 2 for the full extraction form): (1) general model information (eg, model name, code license, conflict of interest); (2) model simulation methods (eg, model type); (3) demographic characteristics (eg, age, gender, ethnicity/race, socioeconomic status); (4) risk factors; (5) diseases; (6) data sources; (7) model outcome types (eg, health, economics); (8) model checking (model transparency and validation/calibration); (9) reported model limitations. All data will be extracted into Microsoft Excel.

Reviewers VH and AH will independently perform data extraction on included studies. Each study will be extracted by only one reviewer. To ensure consistency, the reviewers will discuss and compare data extraction after reviewing five studies. When any unclear, missing, or insufficient data are encountered, the reviewers will contact the study authors for clarification.

Quality Assessment

We are not aware of any widely accepted quality assessment for policy simulation models. To elaborate, previous tobacco control policy simulation model review papers did not perform any quality assessment owing to study heterogeneity or a different study purpose.

Therefore, using the findings of our review, we are aiming to describe the ideal high-quality tobacco control policy simulation model. To be specific, we will employ criteria regarding the quality of (a) model inputs (hierarchy of evidence); (b) model structure (population representativeness, exposure granularity, disease epidemiology); and (c) model outputs (reporting

standards, uncertainty and sensitivity analysis, model validation) to analyze current models. We are aiming to use this model quality standard to facilitate future discussions on a policy simulation model quality assessment framework.

Data Synthesis

First, individual studies will be grouped by model names or common author names, as there are models that have been used in more than one published study. We will report patterns and trends related to modeling methods, outcome types, and funding sources (if the study is industry-funded). As modeling is an evidence-synthesis methodology, we will study the synthesis methods used among models by dissecting their approaches. We will critically review model data inputs, epidemiological principles, assumptions, and transparency. Moreover, we will identify the best practices and common pitfalls shared by identified models. Synthesizing the findings, we will provide a recommended list of the elements that a high-quality tobacco control policy simulation model should have. The model reporting quality will also be analyzed according to the criteria described in the Quality Assessment section above.

We will present our findings in complementary graphical formats using tables and charts.

Results

We are currently in the data collection stage. We are expecting to complete and submit our results for publication by April 2021.

Discussion

To the best of our knowledge, this is the first systematic review to focus on tobacco control policy simulation models. As well as summarizing model best practices and pitfalls, we will advise on the quality assessment of tobacco control policy simulation models. This assessment will be informed by referring to our study results, the published literature, and workshop reports published by the ISPOR-SMDM Modelling Good Research Practice Task Force and other relevant organizations.

This research could benefit modelers, policymakers, and the public from various backgrounds. The development and dissemination of a model framework, and the identification of best practices and weaknesses for model development may serve as a useful resource for future modelers to improve current models and plan more advanced and high-quality models. Our model reporting statement will enable the improvement of model credibility by emphasizing model reporting standards on transparency and validity.

Policymakers and journal editors may appreciate our characterization of a high-quality model. Furthermore, this work may help policymakers make quicker and more accurate decisions on model selection and model outcome evaluation, which will also ultimately benefit patients and the public.

Last but not least, reinforcing ISPOR-SMDM Modelling Good Research Practice Task Force principles, our results may help kickstart a more standardized and quality-assured tobacco control policy simulation model era. This could also inspire modelers working in other fields to enhance model quality.

This protocol for a systematic methodological review has several limitations. First, our search result is limited by publication language due to resource limits. However, there could be further research incorporating papers written in other languages to compare and verify our research findings. Moreover, we only searched and analyzed papers published from July 2013 to August 2019 in this study. We could expand our data extraction and synthesis to tobacco control policy simulation models identified in the study from Feirman and colleagues [10].

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Authors' Contributions

The protocol was drafted and finalized by VH and CK, with substantive contributions from AH, LH, SC, MF, and IB.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 15 KB - resprot_v10i7e26854_app1.docx]

Multimedia Appendix 2
Data extraction form.
[DOCX File , 20 KB - resprot_v10i7e26854_app2.docx]

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Abbreviations

CHEERS: Consolidated Health Economic Evaluation Reporting Standards
GRADE: Grading of Recommendations, Assessment, Development and Evaluations

ISPOR: International Society for Pharmacoeconomics and Outcomes Research
NICE: National Institute for Health and Care Excellence
PICOS: Participants, Interventions, Comparators, Outcomes, and Study design
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis
SMDM: Society for Medical Decision Making

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Protocol

Examining Challenges to the Incorporation of End Users in the Design of Digital Health Interventions: Protocol for a Systematic Review

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Abstract

Background: The process of designing a digital health intervention (DHI)—also referred to as mobile health or eHealth—spans needs assessments, technical functionality and feasibility, user satisfaction, effectiveness, impact, and value. These interventions are causing a rapid evolution in the landscape of health care. Multiple studies have shown their propensity to extend both the quality and reach of interventions. However, failure to improve DHI design is linked to failed uptake and health outcomes. This dilemma is further conflicted by the colliding backdrops of the digital and health industries, both of which approach, understand, and involve end users differently in the framing of a DHI.

Objective: The objective of this systematic review is to assess the challenges to incorporating end users in the design stage of digital health interventions, to identify key pain points, and to identify limitations and gaps for areas of future investigation.

Methods: The PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) checklist will be used to structure this protocol. A systematic search of the PsycINFO, PubMed (MEDLINE), Web of Science, CINAHL, Scopus, and IEEE Xplore databases will be conducted. Additionally, the PerSPEcTiF guidelines for complex interventions will be consulted. Two reviewers will independently screen the titles and abstracts of the identified references and select studies according to the eligibility criteria. Any discrepancies will then be discussed and resolved. Two reviewers will independently extract and validate data from the included studies into a standardized form and conduct quality appraisal.

Results: As of February 2021, we have completed a preliminary literature search examining challenges to the incorporation of end users in the design stage of DHIs. Systematic searches, data extraction and analysis, and writing of the systematic review are expected to be completed by December 2021.

Conclusions: This systematic review aims to provide an effective summary of key pain points toward incorporating end users in DHIs. Results from this review will provide an evidence base for a better approach to end user involvement in the interest of improving efficacy and uptake of DHIs.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42021238164; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=238164

International Registered Report Identifier (IRRID): PRR1-10.2196/28083

(JMIR Res Protoc 2021;10(7):e28083) doi:10.2196/28083

KEYWORDS

digital health; end user(s); user experience; UX; health behavior; intervention; co-design; mobile health; mHealth

Introduction

Background

Digital health interventions (DHIs), often referred to as mobile health (mHealth) or eHealth, are dynamic solutions that span needs assessments, technical functionality and feasibility, user satisfaction, effectiveness, impact, and value [1]. The domain of DHIs combines the expertise of digital and health professionals; these interventions are rapidly transforming health care, providing solutions that are emotional, decisional, or behavioral, and they are delivered with or without expert facilitation [2], bringing us closer to the dream of personalized medicine.

With one-third of individuals in the United States now using technology to manage their health, digital health revenues are expected to exceed US $500 billion by 2025 [3]. The World Health Organization declared that "people have the right and duty to participate individually and collectively in the planning and implementation of their health care" [4]. Digital health technologies (DHTs) are accelerating this vision. By enabling users to be better informed about their health, share experiences, and change perceptions (and stigmas), as well as enabling them to assess, monitor, and prioritize their health, DHIs are blending the solution space of patients and health care professionals [5].

Despite their promise, successful DHIs are challenged by a disparity in understanding and addressing users in the intervention space. A 2018 systematic review on mood disorders determined that acceptance, appropriateness, and availability framed the successful outcome of a digital solution [6]. Additionally, recent systematic reviews by Moore et al (2019) [7] and Vandekerckhove et al (2020) [8] explored forms of participatory design at the methodological level, seeking to understand current frameworks and their suitability. However, there is a need to "scratch beneath the surface" to understand and triangulate pain points toward successfully incorporating end users in DHIs at the design level.

More broadly, this approach can yield a better understanding of who the user is and how acceptance is obtained and defined. Because digital health is an inter- and transdisciplinary domain, the very definition of an end user (user/patient/human/subject) is approached differently from the perspectives of clinical, technical, and user-centered design, respectively. In an initial exploratory review of the problem space, we reviewed 54 papers. We identified a plethora of design frameworks, often with overlapping or nuancing approaches (human-centered, person-based, patient-centered, patient-led, etc), each framing the perspective of the end user differently. Nonetheless, concerns related to the uptake [9] of DHIs cut across the digital health domain regardless of the design approach. The role of incorporating the end user (the primary user of the intervention: patient, person, or sometimes practitioner) is key. This underscores the need for a systematic review to study and improve end user research in DHIs at the root level—from the perspective of the end user—exploring pain points unexclusive of a particular vantage point (health or digital) or framework.

Traditionally, within health care, randomized controlled trials (RCTs) are the gold standard approach to determining the clinical effectiveness of an intervention. Although this approach is quantitatively rigorous and statistical, it lends little to working with users (or patients) during the software development stage [10], where ideation and user feedback can be returned rapidly to ideate pivots in the intervention design. A health intervention that is proven to have clinical impact (through RCT results) will not result in uptake if users do not validate its usefulness. Contrastingly, within the digital industry, an interdisciplinary nondeterministic [11] agile approach weighs the qualitative feedback of user opinion, testing, interviews, and interaction to predict uptake [12]. Health validation also involves clinical and governmental approval [13], which challenges the laissez-faire approach to end user validation originating from mainstream app development and gaming. The health industry is rooted in rigor and research [14], validating health outcomes rather than user experiences. The thoroughness of health care juxtaposes the rapidity of agile development, creating a very different sense of how an end user should be incorporated.

The contrasting lens of what end users are and how to incorporate them is a byproduct of two different industries with two different definitions of a successful outcome. This is further complicated by the vast diversity of health stakeholders (clinicians, health experts, academics) and digital stakeholders (developers, designers, marketers, managers), which confounds the resolution space. From the health side of the room, the outcome is improved health or reduced costs, analyzed over many years. From the digital side of the room, the outcome is a digital product designed with user satisfaction in mind.

Thus, there is a clear need to understand the challenges the digital health industry faces in working with end users. Research has shown that limiting understanding of users, their needs, and the context of their solutions has induced failure in both uptake and effectiveness [15]. To this end, over the past 5 years, there have been several attempts to create agile processes tailored to the unique challenges of digital health development [13,14,16-20]. In each attempt, there is an understanding that uptake is directly connected to a successful co-design but also that typical agile industry approaches cannot simply be ported into the digital health domain unmodified, owing to the unique constraints of the health industry. The recent trend of shifting focus from user-centered to human-, person-, patient-centered, etc, to better accommodate the needs of digital health users has not eliminated the challenge to successful incorporation of end users. It is within this lens that we wish to triangulate the recurring pain points that challenge the integration of users in DHI design.

Research Questions

The aim of the to-be-performed systematic review is to examine challenges to the incorporation of end users in the development of DHIs. The review will focus on three main questions. Firstly, how are end users currently incorporated into iterative DHI design, and what is the effectiveness of current methods? Secondly, what are the most common pain points encountered while incorporating end users in DHI design? Finally, to inform future research, what are the current limitations and gaps in end

user research, such that better fluidity can be achieved in blending end users into the iterative design process in digital health, in the interest of greater efficacy and uptake?

Methods

Study Design

A preliminary search for existing systematic reviews on the topic of end user challenges in DHIs has been conducted in the following major databases: CINAHL, PubMed (MEDLINE), Web of Science, PsycINFO, Scopus, IEEE Xplore, PROSPERO, and the Cochrane Database of Systematic Reviews. We found no specific qualitative synthesis systematic reviews that collected the challenges in working with end users in DHIs. This systematic review protocol will follow the Cochrane Handbook for Systematic Reviews [21] and will use the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) checklist for reporting the protocol [22] (the PRISMA-P flow diagram is included in Multimedia Appendix 1) [22]. This protocol is registered on PROSPERO (registration number CRD42021238164). We will follow 6 stages in this systematic review: (1) literature search, (2) article selection, (3) data extraction, (4) quality appraisal, (5) data analysis, and (6) data synthesis. This review will gather evidence on the effectiveness, challenges, and gaps in designing DHIs with end users and the opportunities for further research and development.

Eligibility Criteria

Considering the complexity of DHIs, we have employed the PerSPEcTiF [23] guidelines for intervention (Table 1). We have selected this framework due to its suitability for qualitative synthesis in the health care domain.

Table 1. Details of the PerSPEcTiF framework as applied to this review.

Initial	Definition	Details
Per	Perspective	From the perspective of end users
S	Setting	In the setting of digital health
P	Phenomenon of interest/problem	What are the most prominent pain points?
E	Environment	Within an environment of designing DHIs[a]
(C)	Comparison (optional)	N/A[b]
Ti	Time/timing	During ideation and co-designing
F	Findings	In relation to understanding the challenges to successful incorporation of end users in the successful design of DHIs

[a]DHIs: digital health interventions.

[b]N/A: not applicable.

Studies will be included in this review that (1) address research on DHIs; (2) focus on interaction and co-design with end users; (3) explain results such that uptake, effectiveness, satisfaction, and health outcomes are discernable, positively or negatively; and (4) describe actionable procedures for better DHI design.

Because digital health is a rapidly evolving environment, we limited the search to studies conducted from 2015 until the date of the search commencement.

Search Strategy

We will systematically search the following electronic databases: PsycINFO, PubMed (Medline), Web of Science, CINAHL, IEEE Xplore, and Scopus. We have selected these databases according to preliminary searches and consultation with experts and librarians in this field. Keywords related to digital health interventions will be used. We will adapt the search strategy as needed to return a breadth of papers without retrieving an unmanageably large number of irrelevant articles.

A draft of the search terms that will be used in this review are grouped into three categories in Table 2.

The three clusters will be searched individually to compare and compile results from three different vantage points in digital health:

- Cluster 1: Health behavior (owing to behavior changes in health care resulting from digital health interventions)
- Cluster 2: User experience (owing to engineering, development, and design in digital health)
- Cluster 3: Methodologies and frameworks (owing to digital project facilitation and to health care intervention design and policy)

Table 2. Search terms and strings to be used in the systematic review.

Category	Keyword
Health behavior	"digital health" or "mHealth[a]" or "eHealth" and "end user*" or "end-user*"
User experience	"user experience" or "UX[b]" or "user centred" or "user centered" or "human centred" or "human centered" or "patient centred" or "patient centered" or "person based" or "person centered" or "person centred" or "participatory design" or "involvement" and "digital health" or "mHealth" or "eHealth"
Methodologies and frameworks	"agile" or "scrum" or "kanban" and "digital health" or "mHealth" or "eHealth"

[a]mHealth: mobile health.

[b]UX: user experience.

Inclusion Criteria

The primary criteria for inclusion will be (nonsingle) case studies; observational studies, including cross-sectional surveys; cohort studies; qualitative studies; and nonrandomized studies (before-and-after studies, interrupted time series studies). Only English language studies will be included. Due to the rapid innovation of digital health, only studies from January 1, 2015, to the date of the search commencement will be included. Any population group, geographical location, or topic that influences end user interaction in DHIs will be considered. There must, however, be an output that critically analyses the involvement of a user (inclusive of like terms: patient, person, human) in a DHI.

Exclusion Criteria

We will exclude studies that are not published in English. We will exclude single user/patient studies.

Screening and Article Selection

All articles identified and selected from the database searches will be stored in the reference management software EndNote (Clarivate Analytics), which will be used to eliminate duplicates, and tag and organize the research structure. Two independent reviewers will screen the titles and abstracts of all the studies. The full text of the remaining articles will then be examined to determine final eligibility. A PRISMA flow diagram will be used to record the details of the screening and selection process so that the study can be reproduced.

Data Extraction

To collate the results from qualitative studies on DHI end user challenges, we will extract data from studies that meet our inclusion criteria. Using a spreadsheet, the following data will be extracted: (1) title; (2); authors; (3) year of publication; (4) source of data; (5) country of study; (6) study characteristics (design, aim, population, primary user type); (7) outcomes (health outcomes, usability, user experience, feasibility, resource implication [including cost]); (8) limitations (functional, user-reported, health outcomes, potential improvements). As a pilot, we will extract data from a small number of studies before refining the final data extraction form. We will contact the authors and collaborators of publications to clarify data and feedback where necessary. Two reviewers will review the full text of all the papers included in the final section. Extracted data will be reviewed by one additional reviewer. Disagreements will be resolved by consensus discussion.

Quality Appraisal and Risk of Bias Assessment

Once the final selection of studies has been made, two independent reviewers will assess the risk of bias for included studies. If disagreement in judgment occurs, the reviewers will discuss disagreements before consulting a third reviewer. Because the majority of included papers are expected to be qualitative rather than quantitative (nonrandomized intervention assessment), we will use the Risk Of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool [24]. All papers will be assessed independently by two reviewers relative to the PerSPEcTiF guidelines in the eligibility criteria. A table will be created to summarize risk of bias graded as high, moderate or low.

Data Analysis and Synthesis

It is unlikely that a meta-analysis will be feasible due to the anticipated variety of study aims, methods, and reported outcomes. Therefore, a narrative synthesis will be performed to describe and summarize the identified studies. Rather than a statistical analysis, we will provide a structured narrative and/or summarized tables. The data synthesis will help assess areas of strength and weakness in both inter- and transdisciplinary approaches to working with end users in the design of DHIs, specifically identifying key pain points and suggesting approaches to resolve them. Finally, the identification of limitations and gaps in research will help establish a direction for the improvement of future DHIs in both efficacy and uptake.

Results

As of February 2021, we have completed a preliminary literature search examining challenges to the incorporation of end users in the development of DHIs. Systematic searches, data extraction and analysis, and writing of the systematic review are expected to be completed by December 2021.

Discussion

This systematic review will provide a systematic, transparent review of the literature to better understand the most prominent pain points encountered when integrating end users into the iterative design of DHIs. In this section, any researcher assumptions will also be discussed, as well as the conclusiveness of the data; limitations of the systematic review; gaps in the current literature; and possibilities for future research.

The three main contributions of our review will be the following: (1) investigation into current DHI end user incorporation and

its strengths and weaknesses; (2) detailing and triangulating the most common pain points encountered in seeking to incorporate end users in iterative design; (3) a discussion on the current limitations, gaps, and methods to inform better research toward a more fluid approach to incorporating end users in DHIs. Any amendments or modifications made in the protocol will be outlined and reported in the final papers. We anticipate that a limitation of this study will be the lack of quantitative studies available to cross-validate determinations made from qualitative studies. This is, fundamentally, a byproduct of the digital health arena, in which technological innovation outpaces long-term study timelines. Additionally, the restriction of studies published from January 1, 2015, forward, albeit by design (to focus on cutting-edge approaches), limits historical context to emerging DHI end user approaches. Based on the data synthesized, the key implications drawn will be discussed toward better design, incorporation, and evaluation of end user involvement in DHIs moving forward.

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Authors' Contributions

The study protocol was conceived by AD, GC, and SM. The research questions were designed by AD, GC, and SM. AD prepared and drafted the manuscript. All authors provided input into the design, edits, and revision of the manuscript. All authors read and approved the final manuscript. AD is the guarantor of the review.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) flow diagram.
[PDF File (Adobe PDF File), 100 KB - resprot_v10i7e28083_app1.pdf]

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Abbreviations

DHI: digital health intervention
DHT: digital health technology
mHealth: mobile health
PD: participatory design
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
RCT: randomized controlled trial
ROBINS-I: Risk Of Bias in Non-randomized Studies of Interventions

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Protocol

Evaluating Community-Facing Virtual Modalities to Support Complex Neurological Populations During the COVID-19 Pandemic: Protocol for a Mixed Methods Study

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Abstract

Background: The COVID-19 pandemic and concomitant governmental responses have created the need for innovative and collaborative approaches to deliver services, especially for populations that have been inequitably affected. In Alberta, Canada, two novel approaches were created in Spring 2020 to remotely support patients with complex neurological conditions and rehabilitation needs. The first approach is a telehealth service that provides wayfinding and self-management advice to Albertans with physical concerns related to existing neurological or musculoskeletal conditions or post-COVID-19 recovery needs. The second approach is a webinar series aimed at supporting self-management and social connectedness of individuals living with spinal cord injury.

Objective: The study aims to evaluate the short- and long-term impacts and sustainability of two virtual modalities (telehealth initiative called Rehabilitation Advice Line [RAL] and webinar series called Alberta Spinal Cord Injury Community Interactive Learning Seminars [AB-SCILS]) aimed at advancing self-management, connectedness, and rehabilitation needs during the COVID-19 pandemic and beyond.

Methods: We will use a mixed-methods evaluation approach. Evaluation of the approaches will include one-on-one semistructured interviews and surveys. The evaluation of the telehealth initiative will include secondary data analyses and analysis of call data using artificial intelligence. The evaluation of the webinar series will include analysis of poll questions collected during the webinars and YouTube analytics data.

Results: The proposed study describes unique pandemic virtual modalities and our approaches to evaluating them to ensure effectiveness and sustainability. Implementing and evaluating these virtual modalities synchronously allows for the building of knowledge on the complementarity of these methods. At the time of submission, we have completed qualitative and quantitative data collection for the telehealth evaluation. For the webinar series, so far, we have distributed the evaluation survey following three webinars and have conducted five attendee interviews.

Conclusions: Understanding the impact and sustainability of the proposed telehealth modalities is important. The results of the evaluation will provide data that can be actioned and serve to improve other telehealth modalities in the future, since health

systems need this information to make decisions on resource allocation, especially in an uncertain pandemic climate. Evaluating the RAL and AB-SCILS to ensure their effectiveness demonstrates that Alberta Health Services and the health system care about ensuring the best practice even after a shift to primarily virtual care.

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KEYWORDS

telehealth; evaluation; rehabilitation; musculoskeletal; neurological; COVID-19; spinal cord injury; advice line; webinar; artificial intelligence; machine learning; community engagement

Introduction

Background

The COVID-19 pandemic and concomitant governmental responses have created the need for innovative and collaborative approaches to deliver services, especially for populations that have been inequitably affected. The pandemic has triggered inconsistency in health service delivery and variable social distancing mandates, each fluctuating by time, geography, and social mores.

Vulnerable populations, such as individuals living with disabilities in the community, are at risk for negative health outcomes because they are unable to access necessary community resources during the COVID-19 pandemic [1,2]. It has been reported that 22% of Canadians have disabilities (eg, spinal cord injury and Parkinson disease) [3]. Mandated social distancing seen in the waves of COVID-19 has suspended clinics, homecare, and other support services, which are especially important for Canadians with disabilities. As services opened, virtual care and alternative service delivery formats offered opportunities and presented challenges for this population to socially connect and access the care needed. These challenges have put these patients at high risk for deterioration, possible hospitalization, and unnecessary emergency room visits. Extended isolation also exacerbates caregiver demands for people living with disabilities [4].

The influx of COVID-19 patients (with actual and expected surges) will introduce more patients requiring rehabilitation care into the system due to the physical, respiratory, and neurological symptoms after acute COVID-19 [5-11]. Early evidence suggests that patients with COVID-19 undergoing intensive care will likely experience functional decline due to organ dysfunction, deconditioning, cognitive changes, and psychological sequelae (depression and anxiety) for extended periods after hospitalization [5-7]. In addition to the patients experiencing post-COVID symptoms, there have been, and will continue to be, patients who present with physical and neurological sequelae unrelated to COVID-19, such as spinal cord injuries.

Utilizing and Evaluating Telehealth Modalities

The pandemic has catalyzed the rapid adoption of telehealth practices to ensure the continuity of appropriate care during this time [12]. Telehealth initiatives adopted during the pandemic have included telephone helplines; virtual meetings using platforms like Zoom, Google Meets, and Microsoft Teams; patient portals; chat boxes; webinars; and wearable devices [12]. Telerehabilitation and telehealth for self-management have been shown to be at least equivalent to in-person care [13-16]. Telehealth services provide several conveniences, including lower costs associated with individual visits. Helplines offer a highly accessible route to determine appropriateness and to promote accessibility of telerehabilitation [17]. Webinars represent a technology that provides the opportunity to engage with a variety of audiences to provide education, information, and support [18].

In order to assess whether the telehealth modalities adopted during the pandemic are efficient and effective at meeting the needs of the populations they serve, we need to employ the most relevant and rigorous evaluation modalities. Many studies have evaluated telehealth and telerehabilitation services [13,18-30]. A 2017 systematic review (n=137 articles) analyzed the successful evaluation methodologies utilized by telehealth projects and indicated that evaluation studies measured the quality of telehealth services through patient and provider satisfaction, economic benefit, and clinical outcomes [23]. Other studies mentioned similar outcome measures of interest for telehealth evaluations including patient and provider satisfaction [24,25]; cost-effectiveness [18-22,24-30]; adherence to, and communication of, care advice [24,25]; and timeliness and responsiveness of the service [25]. An evaluation specifically assessing a nurse-led telehealth line concluded that calling the line resulted in a change in the care management of patients [27]. These changes translated into a reduction in system-level health care costs [27]. A webinar-focused evaluation found that 90.1% of participants indicated that the webinar content was relevant to their interests and needs [18]. Knowledge, awareness of available resources, and confidence to discuss webinar topics increased after attending the webinar [18]. These studies can inform the evaluation approaches utilized to assess the novel telehealth modalities adopted during the pandemic.

Organizational Context

Rehabilitation aims to “enhance function for meaningful living” by focusing on the impacts that disease and disability have on function [13]. Rehabilitation is described as “…integral to all aspects of health and well-being, from health promotion and prevention to end-of-life care and across the lifespan” [13]. Rehabilitation is often an interprofessional collaboration including patients, families, and diverse disciplines [13].

Community rehabilitation and psychosocial care capacity has been severely challenged by the pandemic. In addition, the spinal cord injury community in Alberta, Canada expected that

the disruption of services due to the pandemic would cause more hospitalizations and emergency room visits of persons with lived experience. In response to inconsistencies in health service delivery and variable social distancing mandates, community rehabilitation stakeholders and members of the spinal cord injury community came together in the spring of 2020 to create novel solutions as follows: Rehabilitation Advice Line (RAL) and Alberta Spinal Cord Injury Community Interactive Learning Seminars (AB-SCILS). Multimedia Appendix 1 provides further details on both initiatives including the services provided, operating logistics, and target audience. In general, the RAL is a telephone advice line the helps to eliminate geographical issues with access and provide much needed advice to address the rehabilitation concerns of those living in the community during the COVID-19 pandemic. The AB-SCILS is a monthly webinar series aimed at improving the audience's knowledge about spinal cord injury, as well as empowerment and management strategies of persons with lived experience and their families.

Research Aim and Objectives

The aim of this protocol is to assess the short- and long-term impacts and sustainability of the RAL and AB-SCILS. We are interested in understanding the impact of the RAL on individuals with neurological conditions, particularly spinal cord injury, to correspond with the outcomes of the AB-SCILS evaluation.

The RAL program evaluation has the following three specific objectives to clarify impact and feasibility: (1) To clarify the population that uses the RAL in the first 6 months of operation (including personal and geographical demographics, and clinical conditions); (2) To understand the association between RAL use and patient-reported outcomes; and (3) To understand the impact, if any, on health service utilization after RAL use (including emergency room visits, hospitalizations, and primary care visits).

The AB-SCILS evaluation has the following three main objectives to clarify impact and sustainability: (1) To clarify the population attending AB-SCILS during a 6-month period; (2) To evaluate and understand the impact of the initiative on social connectedness, perceptions of disability, and overall quality of life (ie, for people with spinal cord injury) and interactions (for families, service providers, and others); and (3) To explore the long-term sustainability of the initiative.

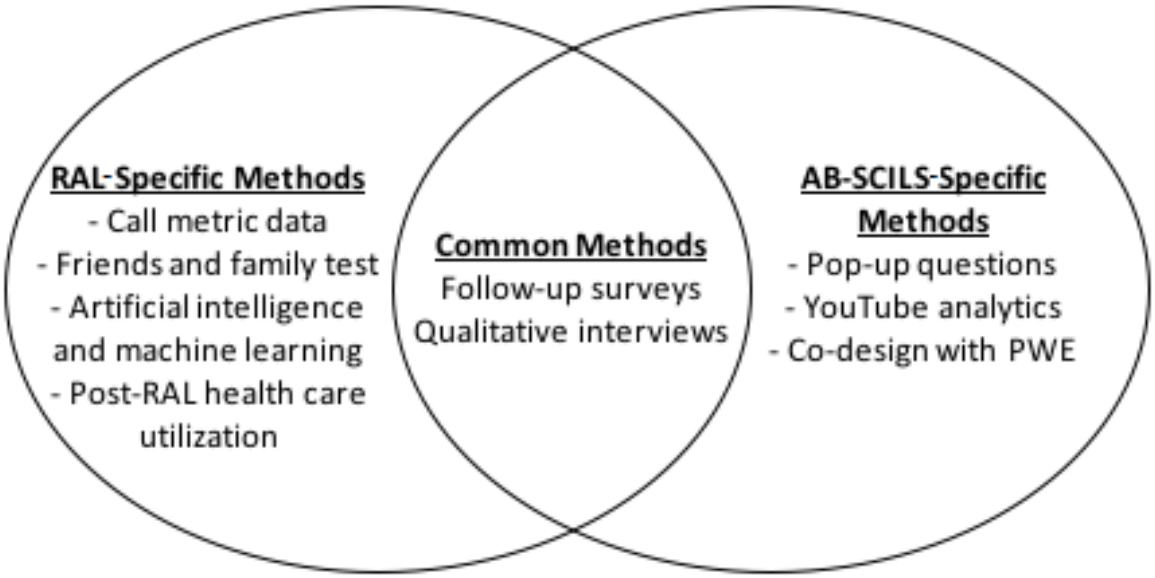
Methods

Overview

For both the RAL evaluation and the AB-SCILS evaluation, we will use an explanatory mixed-methods design [31]. These methods will include secondary data analyses, surveys, and interviews. For the RAL evaluation, we will also conduct narrative analyses of calls using artificial intelligence (AI) and machine learning (ML). AI/ML analysis will be used to provide deeper insights into data recorded during calls to the RAL to provide a more comprehensive analysis of the call data. For the AB-SCILS evaluation, we will also use a collaborative community engagement strategy to ensure that we are held accountable to the spinal cord injury community and to get real-time feedback on AB-SCILS. We have been in consultation with four persons with lived experience with spinal cord injury, and we want to ensure that this process is sustained. We also want to ensure that we are held accountable for the suggestions that these community members provide. As a result, we will be hosting bimonthly focus group discussions with these four members of the spinal cord injury community. The intentions of these focus groups will be to report back to the spinal cord injury community on how their input has been incorporated into the AB-SCILS, therefore working within the "involvement" stage from the community-engagement framework [32]. We will also be continually looking for new input and suggestions on how we can improve the AB-SCILS in the future.

The RAL and AB-SCILS evaluation methodologies are each separated into three sections based on specific evaluation aims. Figure 1 outlines the common and unique methods utilized by each evaluation to ensure readability and clarity.

Figure 1. Common and unique methods utilized by each evaluation. AB-SCILS: Alberta Spinal Cord Injury Community Interactive Learning Seminar; PWE: persons with lived experience; RAL: Rehabilitation Advice Line.



RAL Evaluation Method

Study Population

The study population includes callers to the RAL since its launch on May 12, 2020.

To be included as a caller in the study, participants must be 18 years of age or older and must receive advice through the RAL for neurological, musculoskeletal, and post-COVID-19 with rehabilitation concerns. They must also be able to read and understand English on their own or have support from their own family or friends. There are no exclusion criteria for this study.

Evaluation Aim 1: To Understand the Population Using the RAL

Recruitment

Our provincial health care system (Alberta Health Services) provides capabilities to obtain real-time data from its electronic medical records (ie, ECHO and the Tableau Dashboard), as well as call metric data through a cloud-based software (ie, Genesys Purcloud). This way, the RAL leadership is able to monitor productivity, clinical content discussed on the call, and caller demographics, allowing them to troubleshoot with clinicians to ensure the safety and quality of the service.

Data Collection

RAL data will be retrieved from the Tableau dashboard and Genesys by one of the study team members. Data will be downloaded into a password-protected Excel spreadsheet and shared between team members by SharePoint.

Table 1 describes the data we will retrieve for all of the calls made during the 6-month post-launch period. Call metrics (ie, offered calls, abandoned calls, and call hold duration) will also be retrieved for data analysis.

Table 1. Variables of interest for secondary data analysis.

Category	Variable for secondary data analysis
Caller/patient variables	1. Caller age
	2. Caller gender
Call metrics	1. Number of distinct callers
	2. Number of calls in total and per week
	3. Number of call backs in total and per week
	4. Average call length in total and per week
	5. Number of abandoned calls in total and per week
	6. Average call hold time in total and per week

Sampling

All data points will be included in the calculations. This will allow us to get a clear picture of the population utilizing the RAL service in the first 6 months after launch. Extrapolating from the data collected in the first month following the RAL launch, it is likely that we will have data on approximately 1200 RAL calls (approximately 200 callers per month for 6 months).

Data Analysis

Data will be analyzed using SPSS statistical software (IBM Corp). Data will be used to calculate descriptive statistics on the individuals who call the RAL in the 6 months after launch. We will calculate normality as well as the mean and standard deviation of any interval data analyzed such as caller age. We will also calculate the frequency of any categorical data analyzed such as caller gender and disposition of calls. We will look for associations between variables using the chi-square test and regression analysis. We may perform a time trend analysis on the descriptive data.

Evaluation Aim 2: To Understand the RAL Call Experience

To understand the RAL call experience, we will conduct interviews and surveys, as well as use ML. The surveys include patient-reported experience and outcome measures, particularly the friends and family test at the end of each RAL call and study-specific 3-month follow-up surveys with RAL callers. The interviews will be with RAL callers. We will analyze the RAL clinician clinical notes for each call using ML.

Friends and Family Test

Recruitment

The friends and family test will be administered to every RAL caller at the end of the call. We will conduct secondary data analyses of the results when we perform the data analysis described above. As part of standard practice, participants can choose to answer the question or not answer the question.

The friends and family test has been validated in the United Kingdom National Health Care System and is a direct test, which, when combined with follow-up questions, provides a tool to identify good and bad performance and encourage staff to make improvements when necessary [33]. The specific question is as follows: “Would you recommend this service to a friend or family member?” The response is yes or no.

Data Collection

Data are captured in our provincial medical records (ie, ECHO and the Tableau Dashboard) during every RAL call interaction as described above.

Sampling

All data collected through the administration of the friends and family test will be included in the calculations. This will allow us to get a clear picture of the population utilizing the RAL service in the first 6 months after launch. We expect approximately 1200 responses to the friends and family test at 6 months after launch. This number is an extrapolation based on data collected in the first month following the RAL launch (approximately 200 callers per month for 6 months).

Data Analysis

Data analysis will be completed using SPSS statistical software at 6 months after launch (see above). We will calculate the frequency of “yes” and “no” responses collected during the friends and family test. Results of the friends and family test will be compared and analyzed with patient demographics calculated earlier to see if the results are associated.

Follow-Up Surveys With RAL Callers

Recruitment

All RAL callers who consent to future contact will be offered the opportunity to complete the follow-up surveys at the 3-month time point following their call. A research assistant will go through the call memos for each month to identify which callers consented for future contact. This list will be cross-referenced with the email list from the RAL. Callers’ emails are added to the list if they are sent resources following the call. For the callers whose email addresses are available, we will send the survey link by email. For the callers whose email addresses are not available, we will call them to ask them if they would be interested in participating in the survey. If they say yes, we will ask for their email addresses and send the survey link. Callers will be sent the survey 1 to 3 months following their call to the RAL. We aim to recruit approximately 30% of all RAL callers for each month. Extrapolating from data collected during the first month after launch, 30% of callers would be approximately 60 callers a month or 180 callers over 3 months.

As part of standard practice, RAL clinicians ask callers if they consent to a follow-up call in a week. It is also standard practice for Alberta Health Services to send out follow-up satisfaction surveys. RAL callers will be free from coercion to participate since surveys will be administered by email and they can choose whether to complete the surveys at their discretion. We will consider the completion of surveys as implied consent.

Data Collection

A research assistant will be responsible for sending out the emailed follow-up surveys. Survey responses will be captured by the Alberta Health Services instance of REDCap. Each participant will receive automatic 1-week and 2-week reminder emails if the survey has not been completed through REDCap. The surveys of interest will take approximately 5 to 10 minutes for a caller to complete. The suite of surveys aims to capture how callers are doing 1 to 3 months following their call to the RAL, their perception of the RAL, and general demographic information. All developed surveys are considered valid and reliable [34-42].

- *Patient experience with telephone health line service*: The RAL Patient Experience Survey has been adapted with permission from the Health Link Patient Satisfaction Survey. The Health Link survey was a province-wide initiative conducted by Health Link staff for callers who contacted Health Link between April 1, 2013, and March 31, 2014 [41]. Survey objectives include measuring consumer satisfaction with Health Link and assessing Health Link’s impact on users’ health knowledge and whether they followed through with nurses’ advice [41]. Adapting this existing survey will allow for comparisons with the Health Link service.
- *Patient quality of life*: The EuroQol 5 Dimension 5 Level (EQ-5D-5L) is a standardized generic measure of health status that consists of two pages as follows: the EQ-5D-5L descriptive system and the EuroQol Visual Analog Scale (EQ-VAS) [40]. The EQ-5D-5L descriptive system contains five levels of severity for the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and

anxiety/depression [40]. A resultant five-digit number, with each number expressing a dimension, describes the respondent's health state [40]. The EQ-VAS records the respondent's self-rated health on a 20-cm vertical visual analog scale, with endpoints of "the best health you can imagine" (score 100) and "the worst health you can imagine" (score 0) [40]. Convergent validity of the 5L version of the EQ-5D appeared with the WHO-5 Well-Being questionnaire as all Spearman rank order coefficients were significant (P<.001) and ranged in value across the various dimensions of the 5L versus WHO-5 from 0.33 to 0.61 [40].

- *Self-efficacy to manage chronic health conditions*: The Self-Efficacy for Managing Chronic Disease-6 (SEMCD-6) scale is a six‐item scale measuring respondents' confidence in their ability to manage fatigue, pain, emotional distress, and other symptoms; to do things other than take medication to reduce illness impact; and to carry out tasks and activities that may reduce the need to see a doctor [37]. Respondents are asked to rate their confidence in performing certain tasks regularly at the present time [37]. Items are rated on a numerical scale ranging from 1 (not confident at all) to 10 (totally confident) [37]. The score for the scale is the mean of all items, with higher scores reflecting greater self‐efficacy [37]. A study reviewing eight independent studies investigated the psychometric properties of the scale. It was found that Cronbach alpha was a minimum of .88 across studies, the floor and ceiling effects were minimal, the measure was sensitive to change, and moderate and significant correlations provided convergent validity evidence when measured against selected health indicators [36].
- *Social support*: The Interpersonal Support Evaluation List-12 (ISEL-12) is a short-form version (12 questions) of the traditional ISEL and measures perceived social support [39]. Each question is measured from one to four, with one indicating "definitely false" and four indicating "definitely true" [39]. The ISEL-12 is scored by summing the items to create an overall social support score with high scores indicating high levels of social support [39]. The psychometric properties of the ISEL-12 have been previously determined [39]. The scale has high internal consistency (Cronbach alpha >.7) [39].
- *Telehealth usability questionnaire*: The Telehealth Usability Questionnaire-10 (TUQ-10) was shortened by Alberta Health Service's Virtual Health team in collaboration with the primary author, Dr B Parmanto [42]. The TUQ-10 measures the following domains: usefulness, ease of use/learnability, interface quality, reliability, and satisfaction/future use [42]. The TUQ-10 has a Cronbach alpha of ≥.8, which suggests it has good internal consistency and reliability [42].
- *Patient demographics*: We will collect participant demographic data to describe the follow-up survey sample. Self-reported demographic data will include age, sex, marital status, education level, current employment status, and ethnicity. All of these data are not collected in the original RAL call, so we will collect them separately. We will also check for associations between these patient demographic factors and other survey responses.

At the end of the follow-up surveys, participants will be asked if they consent to be contacted for an interview at a later date. We aim to recruit eight to 10 participants for follow-up interviews. They will also have the opportunity to enter their name into a random draw for one tablet computer or equivalent.

Data Analysis

Descriptive and inferential data analysis will be completed using SPSS statistical software. We will determine frequencies of responses on each of the surveys, patient gender, reason for call, and disposition of call. We will also calculate the mean where it is relevant to do so, for example, patient age. We will conduct analyses to test for associations between survey responses and patient demographics calculated earlier to see if outcomes are associated with particular types of calls, for example.

Interviews With Patients

Methodological Framework

We will use Sandelowski's framework for qualitative description. In qualitative description, a researcher does not deliberately choose to describe an event in terms of a specific framework or system but rather presents the facts of the study in layman's terms [43]. Qualitative description studies often draw their results from naturalistic inquiry or the studying of something in its natural state [43]. This form of study results in "thick" description, which is preferable to "thin" description obtained from solely quantitative research [43]. Data collection in qualitative descriptive studies often focuses on the who, what, and where or events and experiences, and includes moderately structured open-ended interviews [43]. Qualitative content analysis is the analysis method of choice as the goal is to summarize the information within the verbal data [43].

Recruitment

We plan to recruit eight to 10 patients to participate in interviews. Patients who complete follow-up surveys will be asked if they consent to be contacted for a follow-up interview, which would be organized by phone in the 4 weeks after their follow-up call. If patients consent to be contacted, their contact information will be shared with the study team. The research team will then follow-up with the participants to arrange a date and time for the phone interview. Patients will be emailed or mailed the study information sheet and consent form prior to their interview.

Data Collection

Participants who agree to an interview will be called at their agreed upon interview date and time. Prior to conducting the interview, the interviewer will go over the consent form with the participants to ensure they understand that the interview will be audio-recorded, that they can choose not to answer any questions that they do not want to, and that they can stop the interview at any time without reason, fear, or repercussions.

The interviews will be semistructured and will last approximately 30 to 60 minutes. The interviews will ask about call experiences, perceived successes and challenges of the call itself, and perceived values or suggestion for improvement of

the RAL. The interviewer will probe for further details as necessary. Interviews will be audio recorded on a secure device devoted to the study with the participants consent to capture what they say and exactly how they say it. Interview participants will receive a Can $20 gift card for their participation.

Data Analysis

Following interviews, audio recordings will be transcribed verbatim and subsequently deleted. Thematic analysis will be completed on the interview transcripts after every three interviews to inform any modifications or different questions to ask in subsequent interviews if deemed necessary during meetings with the research team.

Thematic analysis will be completed on all of the transcripts. Thematic analysis involves reading through the transcripts and grouping similar ideas together as codes. Codes are then later grouped together into overarching themes. One member of the research team will code all of the transcripts using NVivo software (QSR International). To ensure accuracy of coding, another member of the research team will code a portion of the transcripts using NVivo software. The two research team members will meet to discuss codes and develop a common analytical coding framework. The transcripts will then be reread to ensure that they have been coded appropriately based on the agreed upon analytical coding framework.

Rigor

Throughout the study, steps will be taken to ensure transferability, credibility, and dependability of the data, therefore enhancing rigor. Transferability refers to how well a study's findings can be applied in broader contexts [44]. By using a semistructured interview guide as well as probing questions, participants are prompted to provide in-depth answers. The high level of detail in participant answers allows potential knowledge users to gain better insights into how the conclusions of the study were reached and how these findings can be applied to broader situations. Dependability refers to the ability of findings to be replicated in the future [44]. Complete records will be kept throughout the study. This would allow anyone to track study progression in the future if they wish to do so. The credibility of the study will be enhanced by having multiple research team members involved in the coding process and the development of the coding framework. Moreover, audio recordings will be transcribed verbatim so that the researchers can capture what the participants say and exactly how they say it.

Analysis of RAL Call Documentation Through ML

Data Collection

Data are captured in our provincial medical records (ie, ECHO and the Tableau Dashboard) during every RAL call interaction as described above. Following input into the ECHO platform, data then flows to the Tableau dashboard. Key demographic information about the callers, such as their age and health care zone, call length, and free text clinical notes detailing the patient's reason for phoning the RAL; rehabilitation assessments; patient concerns; and the information/services provided by the RAL staff to the patient will be analyzed using a novel AI/ML system. The AI/ML system is used to provide caller experience and engagement information through processing the user note data after anonymization.

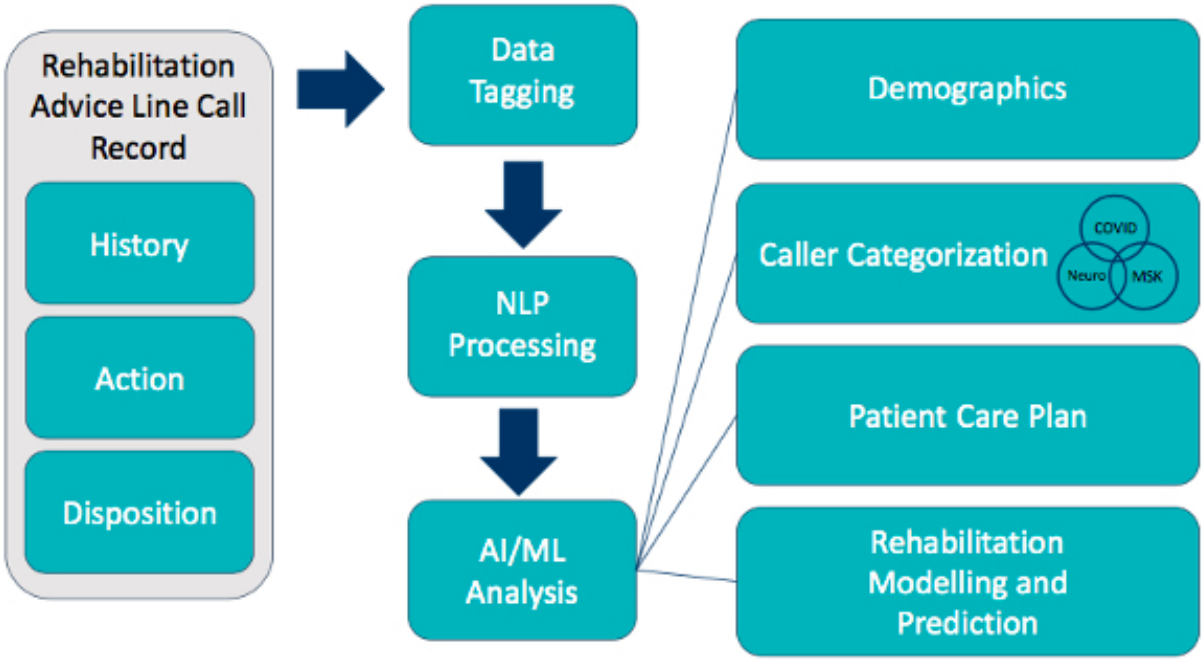
Sampling

Analysis of demographic and free-text note data will be completed on all calls received by the RAL from May 12, 2020, to October 31, 2020. Including all calls in the sample will allow us to get a clear picture of the RAL caller experience during the first 5 months after launch.

Data Analysis

The AI/ML natural language processing (NLP) system is designed as a case study to analyze the effectiveness of the RAL. The AI/ML system will combine and interpret data taken directly from the Tableau dashboard and the information from the free-form clinical notes captured during a call to the RAL. As shown in Figure 2, the processing pipeline for the RAL data system will consist of the following two main components: NLP-based preprocessing of clinical notes and an AI/ML-based system for modeling and analyzing the collected data.

Figure 2. Outline of the analysis to be performed on Rehabilitation Advice Line (RAL) caller data by the combined artificial intelligence (AI) and machine learning (ML) system. MSK: musculoskeletal.



NLP preprocessing will assist with analyzing the information contained in the free-text clinical notes entered into the ECHO platform. The call notes consist of unstructured data that can be classified into the following three broad categories: (1) *History* including previous patient diagnoses, medications, and existing symptoms; (2) *Action* taken by the RAL advisor during the call including discussion of current symptoms (including pain, weakness, difficulty performing activities of daily living, etc), subjective over-the-phone assessment, and cause of the condition (eg, if it was caused through injury); and (3) *Disposition* detailing the advice provided or service referrals given to the patient. By capturing this information, the RAL provides a means of monitoring and providing assistance to individual patients.

As an example of the analysis to be performed, the AI/ML system allows for a more meaningful interpretation of the RAL phone conversation by considering factors such as the frequency certain keywords are mentioned (such as patient-reported conditions or symptoms, comparison of keywords between different callers and geographic areas, and finding correlations between topics discussed in each call). The AI/ML system distills this analysis down into a list of common conditions, symptoms, and reasons for calling the RAL to get a metric of the underlying reasons persons are phoning into the RAL, what assessment was undertaken during the call, and what disposition was offered by the RAL. Along with traditional evaluation metrics that will be collected during patient surveys and interviews, the AI/ML NLP system allows for more in-depth understanding of the needs and services required and provided for persons phoning into the RAL. The system allows for automatically capturing demographic data by categorizing the reason for the call as resulting from musculoskeletal, neurological, COVID-19, or other conditions and analysis of the disposition to better understand the patient care plan.

Caller demographic information, including caller age, call length, and caller zone, retrieved from the ECHO platform will be used as part of the AI/ML analysis (see Multimedia Appendix 2 for further details).

An NLP tool will be used to analyze the clinical notes taken during the call and this information, in addition to the demographic information, will be used within the AI/ML system. The NLP tool works on the free-form text recorded by the RAL clinician, and will be used to identify medically relevant keywords and phrases within the call notes. The NLP analysis will be used to determine and categorize the reason for the call, caller's medical history, assessment, and disposition (see Multimedia Appendix 3 for further details).

Evaluation Aim 3: To Understand Health Service Utilization After the RAL

Data Collection

Patient personal health numbers are also captured by the provincial electronic medical record (ie, ECHO) during all RAL call interactions. With support from data analytics in Alberta Health Services, patient personal health numbers will be followed to determine how patients utilized health care services following the RAL encounter. The National Ambulatory Care Reporting System will be used as a source of data by the data analytics team in Alberta Health Services. The data analytics team will retrieve the data and share it in the form of a password-protected Excel spreadsheet with the research team through Alberta Health Services email to ensure we are working behind a firewall.

Sampling

All caller data will be included in the calculations to clarify how RAL callers are utilizing health care services following their call within the first 6 months of the RAL being available.

Data Analysis

Data will be analyzed using SPSS statistical software. Data will be used to calculate descriptive statistics on the health service utilization after the RAL launch of individuals who called the RAL in the 6 months after the launch. We will calculate the average frequency of emergency room visits before and after the RAL call. We will calculate the number of unique patients who visited the emergency room before and/or after their RAL call. We will also calculate the average number of days before and/or after someone visited the emergency room with respect to when they called the RAL and use that to calculate the mean difference (mean days after minus mean days before).

AB-SCILS Evaluation Method

Study Population

In consultation with persons with lived experience with spinal cord injury, we have determined that the AB-SCILS should not be solely targeted toward persons with lived experience since those who have lived with spinal cord injury for many years know a lot of the information being shared in the webinars. To build a broader spinal cord injury community that is equipped with appropriate knowledge to work with persons with lived experience, the AB-SCILS will target all persons with lived experience, including hospitalized patients and their families, health care professionals who are part of the spinal cord care journey (including general practitioners, nurses, rehabilitation experts, social workers, and physiatrists), and members of the broader community (ie, teachers, students, and city designers).

The study population includes attendees to the AB-SCILS. This population will be quite diverse and variable as AB-SCILS evolves. A detailed demographic analysis will be one of the factors we address in our evaluation. Attendees will likely include individuals living with spinal cord injury and their family members, health care professionals, and members of the broader community like teachers.

Participants must be 18 years of age or older and have attended at least one AB-SCILS session. They must also be able to read and understand English on their own or have support from their own family or friends. There are no exclusion criteria for this study.

Evaluation Aim 1: To Understand the Population Attending the AB-SCILS

Demographics

Data Collection

Patient demographics will be collected via pop-up questions at each webinar during the evaluation period (from November 2020 to April 2021). Demographics will include the following: (1) affiliation or interest in the webinar (person with spinal cord injury, family member of someone with spinal cord injury, health care provider, researcher, program manager, student, or other); (2) general location (urban, rural, or metropolitan center); (3) whether attendees are from Edmonton, Calgary, elsewhere in Alberta, or outside of Alberta; (4) attendance record (is this their first webinar, have they attended one to three webinars, have they attended four to six webinars, or have they attended more than six webinars); (5) whether they have accessed past webinars after the live session; (6) preferred availability for future webinars; and (7) preferred topics for future webinars.

Sampling

All demographic information collected during the 6-month evaluation period will be included in the evaluation to help us understand the population attending the AB-SCILS.

Data Analysis

We will calculate the frequency of responses for each of the pop-up questions to help describe the population attending the AB-SCILS. We will also perform chi-square tests to test for associations between variables if our data meets all of the assumptions of this test.

YouTube Analytics

Data Collection

We will clarify the demographics of those accessing the AB-SCILS through YouTube after the live session. We will pull data on where individuals are viewing the videos from (YouTube provides a general location), as well as how many unique views each video gets and when the videos are viewed. Data will be accessed through the AB-SCILS YouTube account. Aggregate data will be pulled from YouTube by a research assistant acting behind the Alberta Health Services firewall.

Sampling

We will analyze all YouTube analytics data collected during the 6-month evaluation period. All data contained in YouTube analytics are aggregate data, so we will be able to get a general picture of who is accessing the AB-SCILS after the live session.

Data Analysis

The analysis will include frequency calculations of where individuals are viewing the video from, as well as how many unique views each video gets and when. We will also perform chi-square tests to test for associations between variables if our data meets all of the assumptions of this test. All of these data will be analyzed on a video-to-video basis following the completion of the evaluation period.

Evaluation Aim 2: To Understand the AB-SCILS Webinar Experience

Recruitment

All AB-SCILS attendees will be offered the opportunity to complete follow-up surveys. Our goal is to have at least approximately 30% of all AB-SCILS attendees complete the follow-up surveys. It is possible that more attendees may fill out the follow-up surveys, and this additional data would be welcome as we seek a convenience sample. Attendees are able to complete the surveys more than once during the 6-month evaluation period and are encouraged to do so by having their names entered into a draw for a gift card following each webinar during the evaluation period, as well as a draw for a tablet computer at the end of the project. Having attendees complete the survey every month for 6 months would be ideal, as this would allow us to do some longitudinal analyses of the data. However, we recognize the infeasibility of every attendee

completing surveys after each AB-SCILS session. We will also examine the data cross-sectionally to get a snapshot of attendee perspectives with the AB-SCILS.

Data Collection

Participants will have the opportunity to click the survey link during and after each webinar. Survey responses will be captured by the Alberta Health Services instance of REDCap.

The survey package has been co-developed with persons with lived experience. This survey package includes questions about the ability of the AB-SCILS to foster social connectedness and change perceptions about disability. The surveys will also include more specific demographic questions such as age, gender, and educational background. The demographic information will be used to complete correlational analyses during data analysis. The surveys of interest will take approximately 10 to 15 minutes for an AB-SCILS attendee to complete, and informed consent will be implied with the return of fully or partially completed surveys.

At the end of the follow-up surveys, participants will be asked if they consent to be contacted for an interview at a later date. We aim to recruit eight to 10 participants for follow-up interviews.

Data Analysis

Descriptive and inferential data analyses will be completed using SPSS and Stata software (StataCorp). We will calculate frequencies of responses on each of the surveys where appropriate. We will also calculate the mean where it is relevant to do so. We will conduct chi-square analyses to test for associations between survey responses and patient demographics. We will perform regression analysis to test for statistically significant relationships between survey responses and demographic data.

Evaluation Aim 3: To Understand the Long-Term Sustainability of the AB-SCILS

Methodological Framework

We will utilize Sandelowski's framework for qualitative description to ground our qualitative work as discussed above [43].

Recruitment

We plan to recruit approximately eight to 10 AB-SCILS attendees, who have attended at least one AB-SCILS, to participate in interviews. Individuals who complete follow-up surveys will be asked if they consent to be contacted for a follow-up interview, which would be organized by phone in the 4 weeks after their follow-up call. If patients consent to be contacted, their contact information will be shared with the study team. The research team will then follow-up with the participants to arrange a date and time for the phone interview. Patients will be emailed or mailed the study information sheet and consent form prior to their interview.

Data Collection

Interview data collection for the AB-SCILS portion of the study will follow the same process as outlined above in the RAL evaluation methods. The interviews will ask about webinar experiences, perceived successes and challenges of the webinars themselves, and some takeaways from the webinars (ie, whether their views about spinal cord injury were challenged and how so), as well as the ability of the AB-SCILS to build a broader spinal cord injury community. Questions will be related to understanding the experiences of attendees in respect to the AB-SCILS, for example, "Could you describe your experience with AB-SCILS?" and "Did attending the AB-SCILS challenge your assumptions about what *normal* life with spinal cord injury could look like?"

Data Analysis

Following interviews, audio recordings will be transcribed verbatim by a research assistant and subsequently deleted. Thematic analysis will be completed on all of the transcripts as described above in the RAL evaluation methods. However, thematic analysis for the AB-SCILS evaluation will use Dedoose software (SocioCultural Research Consultants) rather than NVivo as described above.

Rigor

The same steps outlined above will be taken to ensure transferability, credibility, and dependability of our qualitative work, therefore enhancing rigor.

Results

At the time of protocol submission, we have completed qualitative interviews with 10 RAL callers and received 68 survey responses to the RAL follow-up surveys. Due to the integrative approach of our methods, we are currently completing all analyses to accumulate our findings to address the research questions.

For the AB-SCILS, we have begun administering surveys and have collected 25 survey responses at the time of protocol submission. We have also completed five qualitative interviews. We will continue to collect survey responses in the upcoming three webinars. Following each of the upcoming three webinars, we hope to interview two attendees to gain a more in depth understanding of their experience. Data analysis will commence shortly after the completion of data collection.

Discussion

Preliminary Gap Addressed

The study outlined in this protocol will help us learn how best to advance virtual care in Alberta by clarifying impact and feasibility, and informing sustainability of telehealth modalities. The pandemic has fostered the adoption of telehealth practices to improve the continuity of care for people with disabilities. Several studies have aimed to measure the impact and feasibility of telehealth initiatives adopted during the pandemic [12,45,46]. However, very few evaluation studies about telehealth initiatives adopted during the pandemic have been able to be carried out due to social distancing mandates, global lockdowns, and the reallocation of resources to aid in the pandemic response. The study discussed in this protocol will help to address this gap and will contribute to the knowledge base on the impact,

feasibility, and sustainability of telehealth initiatives during and after COVID-19.

Study Strengths

There are many factors that contribute to the strength of our proposed work. Implementing and evaluating different virtual modalities synchronously allows for the building of knowledge on the complementarity of these methods. This creation of knowledge provides an opportunity to improve each modality in order to synergize the positive effects of each. Both portions of the proposed study have unique qualities that contribute to the novel nature of the evaluation as a whole and will aid in learning how to best advance virtual care in Alberta. Bridging mixed-methods research with AI/ML modalities can assist in understanding the utility of such technologies when health care resources are being strained due to the pandemic [47]. Telehealth initiatives supplemented with AI/ML methods have been shown to be particularly useful for quality improvement for existing clinical practice and service delivery [48]. However, recent literature in telemedicine is still offering new potential applications for these methods, which suggests that their full potential for utility has not yet been attained [49]. Utilizing AI/ML technologies in our current work is justified as it will help contribute to the knowledge base of evaluating telehealth strategies with these technologies.

The co-design of the AB-SCILS webinar series also presents a unique opportunity. Previously published literature on patient engagement and co-design of health care services has demonstrated the need for strategies to build strong relationships between patients and health care professionals to ensure good communication and ultimately achieve positive outcomes [50]. The proposed study outlines one such strategy, and its overall effectiveness will contribute to the potential success of the evaluation. After the initial engagement with community members, they decided to continue working with us in the "involvement" category after discussing the IAP engagement framework [32]. This is an example of the diverse expectations and views from community members and shows that for some groups, being "empowered" or participating as equal partners in decision making is not possible due to their capacity to be engaged in such an intense manner. There is this trend to think that all community-based work has to be at least at the "collaboration" level if not the "empowerment" level [32]. We are demonstrating in this study that this is not the case as the members of the community did not feel they had the capacity or time to be engaged at the higher levels of the spectrum. We want to highlight that being "involved" versus "empowered" does not mean that the engagement is not meaningful. We as researchers must still ensure that we are held accountable for the suggestions that these community members provide and react accordingly.

Challenges and Limitations

We have faced challenges to date with our research. Conducting the RAL evaluation during the COVID-19 pandemic has not occurred without challenges. We have collected survey data for approximately 4 months and had 68 survey responses, while the RAL had 537 clinical call interactions during the first five and a half months of operation. The low survey responses are due to challenges in survey recruitment. We initially planned on collecting survey data by sending the survey link via email to RAL callers. However, we soon realized that we did not have many RAL caller email addresses since not all callers get resources sent to them after the call interaction. Further, not all RAL callers consented to be contacted about their call experience or did not want to participate in the survey due to their call interaction being months prior. Of the 537 clinical call interactions collected during the study period, only 304 had caller consent for follow-up contact. Through the RAL email list and by calling RAL callers, we were able to send the survey link to 162 individuals. These values represent a 42% response rate, which we consider satisfactory given the challenges associated with recruitment.

There are also potential limitations that go along with our proposed methodology. While the evaluation methods for both modalities are parallel in nature, bringing the results together may be challenging as the methods are not exactly the same. This may limit our ability to apply the learnings from each evaluation separately to improve our understanding of the effect of virtual health modalities in Alberta as a whole. To overcome this challenge, we continue to have monthly meetings with team members from both evaluations to share our learnings and inform our work moving forward, so that all parties understand how both evaluations complement one another. Our survey responses and qualitative interview data collected for the RAL evaluation may also have the issue of recall bias since we did not contact participants until 3 months after their call interaction. Participants may not have remembered important details of their call interaction, which may limit the quality of the data collected. However, the timing of survey administration and interviewing was deliberately chosen as we were interested in understanding how callers were doing 3 months following their interaction. If we would have administered the survey immediately following their call interaction, we would not know how the participants are doing in the longer term. The dual modality of the proposed study may offer a strategy to overcome this limitation since the AB-SCILS surveys and interviews will occur immediately following each webinar. We will be able to understand the short-term effects of an interaction with a virtual modality from the AB-SCILS evaluation and the longer-term effects from the RAL evaluation.

Conclusion

Understanding the impact and sustainability of the proposed telehealth modalities is important. The results of the evaluation will provide data that can be actioned and serve to improve other telehealth modalities in the future, since health systems need this information to make decisions on resource allocation, especially in an uncertain pandemic climate. Evaluating the RAL and AB-SCILS to ensure their effectiveness demonstrates that Alberta Health Services and the health system care about ensuring the best practice even after a shift to primarily virtual care.

Authors' Contributions

The manuscript was prepared by KB and JC. KPM, KC, ALS, PO, EP, RM, MT, and CH contributed to the conception and outline of the protocol. All authors contributed to protocol revision, as well as read and approved the submitted version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Detailed explanations of the Rehabilitation Advice Line (RAL) and Alberta Spinal Cord Injury Community Interactive Learning Seminars (AB-SCILS).
[DOC File , 35 KB - resprot_v10i7e28267_app1.doc]

Multimedia Appendix 2
Demographic information for artificial intelligence and machine learning analyses.
[DOC File , 28 KB - resprot_v10i7e28267_app2.doc]

Multimedia Appendix 3
Natural language processing categories.
[DOC File , 28 KB - resprot_v10i7e28267_app3.doc]

Multimedia Appendix 4
Peer-review reports.
[PDF File (Adobe PDF File), 96 KB - resprot_v10i7e28267_app4.pdf]

Multimedia Appendix 5
Authors' responses to peer-review report comments.
[PDF File (Adobe PDF File), 40 KB - resprot_v10i7e28267_app5.pdf]

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Abbreviations

AB-SCILS: Alberta Spinal Cord Injury Interactive Learning Seminars
AI: artificial intelligence
EQ-5D-5L: EuroQol 5 Dimension 5 Level
EQ-VAS: EuroQol Visual Analog Scale
ISEL-12: Interpersonal Support Evaluation List-12
ML: machine learning
NLP: natural language processing
RAL: Rehabilitation Advice Line
TUQ-10: Telehealth Usability Questionnaire-10

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Protocol

Predicting and Responding to Clinical Deterioration in Hospitalized Patients by Using Artificial Intelligence: Protocol for a Mixed Methods, Stepped Wedge Study

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Abstract

Background: The early identification of clinical deterioration in patients in hospital units can decrease mortality rates and improve other patient outcomes; yet, this remains a challenge in busy hospital settings. Artificial intelligence (AI), in the form of predictive models, is increasingly being explored for its potential to assist clinicians in predicting clinical deterioration.

Objective: Using the Systems Engineering Initiative for Patient Safety (SEIPS) 2.0 model, this study aims to assess whether an AI-enabled work system improves clinical outcomes, describe how the clinical deterioration index (CDI) predictive model and associated work processes are implemented, and define the emergent properties of the AI-enabled work system that mediate the observed clinical outcomes.

Methods: This study will use a mixed methods approach that is informed by the SEIPS 2.0 model to assess both processes and outcomes and focus on how physician-nurse clinical teams are affected by the presence of AI. The intervention will be implemented in hospital medicine units based on a modified stepped wedge design featuring three stages over 11 months—stage 0 represents a baseline period 10 months before the implementation of the intervention; stage 1 introduces the CDI predictions to physicians only and triggers a physician-driven workflow; and stage 2 introduces the CDI predictions to the multidisciplinary team, which includes physicians and nurses, and triggers a nurse-driven workflow. Quantitative data will be collected from the electronic health record for the clinical processes and outcomes. Interviews will be conducted with members of the multidisciplinary team to understand how the intervention changes the existing work system and processes. The SEIPS 2.0 model will provide an analytic framework for a mixed methods analysis.

Results: A pilot period for the study began in December 2020, and the results are expected in mid-2022.

Conclusions: This protocol paper proposes an approach to evaluation that recognizes the importance of assessing both processes and outcomes to understand how a multifaceted AI-enabled intervention affects the complex team-based work of identifying and managing clinical deterioration.

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KEYWORDS

artificial intelligence; clinical deterioration; rapid response team; mixed methods; workflow; predictive models, SEIPS 2.0

Introduction

Background

The timely identification of hospitalized patients who are clinically deteriorating is critical for facilitating prompt clinical interventions to improve patient outcomes but remains challenging for hospital systems to perform consistently. Artificial intelligence (AI), in the form of statistical models that predict clinical deterioration, is increasingly being considered by hospitals to aid in the early identification of these patients. Many such prediction models have been developed and reported in the literature, ranging from the sequential organ failure assessment score, which predicts inpatient mortality [1], to more recently developed machine learning models that predict a variety of outcomes, such as transfer to the intensive care unit (ICU), codes, and rapid response team (RRT) events [2-5]. However, few instances of these models have been shown to improve patient care, and there is little insight into how to implement interventions that use machine learning prediction models in the real-world setting [6]. A recently reported multisite prospective study of an intervention that used a model to predict inpatient clinical deterioration demonstrated improved clinical outcomes such as mortality rate and ICU length of stay in the intervention cohort, but there were no observed differences in the process measures, and it remains unclear which features of the implementation mediated the observed clinical benefit [7]. Therefore, although this particular intervention did demonstrate a clinical benefit at the participating study sites, there remains a pressing need for a deeper understanding of *how* such interventions can be effectively designed and implemented using AI to successfully disseminate them across other health care systems. As AI prediction capabilities in health care continue to grow, this implementation gap must be addressed to successfully leverage these capabilities to improve health care delivery.

One key question to address to close this implementation gap is how AI predictions can mediate changes within a complex work system to improve outcomes. Using a systems engineering lens, health care delivery—for example, for patients who are clinically deteriorating—can be viewed as occurring over a set of interconnected units (ie, people, technologies, and physical objects) that form distinct structures, processes, and patterns of behavior that lead to outcomes [8,9]. These health care work systems are typically considered to be *complex*, where the individual units dynamically interact with each other, self-organize, and adapt to the environment to form collective emergent properties that are difficult to predict and usually observed only after the system is live in the real world [10]. These systems are also described as *sociotechnical* because of the ways in which people and organizations (eg, patients and health care providers) interact with technology to make decisions, complete tasks, and form relationships and other organizational structures [11]. Emergent properties such as new workflows and habits, communication patterns, team structures, and cultures that arise from the introduction of new technologies may lead to unanticipated outcomes, barriers, or facilitators to the implementation of these technologies. In a systems thinking framework, the AI prediction model is not thought of as a standalone intervention but rather as an enabling component of a complex work system that mediates change [6].

Efforts to implement new technologies such as AI in health care often fail to consider the complexity of the sociotechnical systems in which these technologies are required to operate and underappreciate the unanticipated system-level effects that the technology may have on the health care delivery environment, and these effects can affect the success of the implementation [12]. For example, existing implementations of clinical deterioration prediction models typically assume a linear causal chain between the generation of an alert from the prediction model and the downstream actions of the receiving clinician who mediates the change in the outcome. However, they often do not explicitly consider and evaluate system-level properties such as the communication patterns and relationships among different members of the clinical team (eg, physicians and nurses), the degree to which the team members accurately share a mental model of risk, and the workflows and habits that evolve from the introduction of the AI prediction model. Evaluations of these implementations are therefore limited to only assessments of the clinical outcomes and select process metrics, and they do not capture the emergent properties that may help explain the barriers and facilitators to implementation and how the intervention mediates the changes in outcomes.

Objectives

This paper presents a theory-driven study protocol informed by systems thinking and implementation science to assess the clinical and implementation outcomes of an implementation of a sociotechnical work system enabled by an AI prediction model for the early identification of hospitalized patients at risk of clinical deterioration. This protocol has three aims to (1) assess whether the AI-enabled work system improves clinical outcomes, (2) describe how the clinical deterioration predictive model and associated work processes are implemented, and (3) define the emergent properties of the AI-enabled work system that mediate the observed clinical outcomes.

Methods

Theoretical Framework

The Systems Engineering Initiative for Patient Safety (SEIPS) 2.0 model will be used as an analytic framework for this study [13]. The SEIPS model takes a person-centered approach to understand work processes within a sociotechnical system that is well suited to studying the impact of a technical solution (predictive model in the electronic health record [EHR]) on human work processes (management of hospitalized patients). The SEIPS framework characterizes outcomes as a product of a work system made up of factors related to the internal and external environment, people, organization, tools and technology, tasks, and work processes [8]. The revised model (SEIPS 2.0) incorporates the concepts of configuration, engagement, and adaptation, which better reflect a more dynamic implementation process among people, their environments, and the outcomes they produce [13].

Setting

The intervention will be implemented in 6 primary general medicine adjustable acuity units at a quaternary academic hospital in the United States. The hospital has 605 beds, and most general medicine patients are cared for in 6 primary general medicine units. Each unit is served by physician teams, each with an average census of 12 and a maximum census of 20. The physicians spend most of their day rounding in many units and access the EHR through mobile devices, whereas the nurses spend most of their day in 1 unit working on a mobile desktop computer. These work setting characteristics were a key consideration in the intervention, implementation strategy, and study design.

Intervention Description and Model Validation

The intervention is conceptualized as a work system comprising the following three parts: an AI model that predicts clinical deterioration, a mechanism for delivering the model predictions to clinical teams, and a multidisciplinary workflow driven by physicians and nurses. The clinical deterioration prediction model, the clinical deterioration index (CDI), was developed by Epic Systems Corporation and built into its EHR platform. The CDI is a logistic regression that runs every 15 minutes for all hospitalized patients using the most recent available clinical data of 31 physiological measures captured in the EHR and generates a score between 0 and 100, with higher scores indicating an increased risk of clinical deterioration as defined by any one of the following: ICU transfer, inpatient code, RRT event, or death. Between January 2020 and May 2020, the model was prospectively validated on 6232 hospital encounters of patients admitted to the implementation site for its accuracy in predicting ICU transfer or RRT event within 6-18 hours of the prediction, which was deemed by the clinical stakeholders to be an appropriate time interval that would allow for a meaningful clinical response. Of these 6232 encounters, 152 (2.44%) were unplanned ICU transfers and RRT events. The area under the curve was 0.70, and a model score threshold of 65 (out of 100) was chosen to maximize the positive predictive value and sensitivity of 0.20. Of note, this validation strategy was an enhancement of the vendor's validation, which reported model accuracy in predicting the outcomes *without* the 6-hour to 18-hour time lag; this was thought to not be clinically meaningful because a model predicting an event to occur within the next 6 hours would not provide sufficient time for a clinical response to be effective.

Participatory design sessions using design thinking and process improvement methods were conducted with clinicians, including physicians, residents, and nurses. The participating clinicians generally preferred to be alerted only when patients were identified by the model as *high risk* rather than see the model prediction for every patient. Therefore, we designed the system to only flag patients whose CDI score was higher than 65, which, based on our validation, was the optimal cutoff to identify patients at the highest risk for unplanned ICU transfers and RRT events. As the area under the curve was only 0.70, the discriminatory ability of the model was not sufficiently robust to warrant showing the individual integer score values (ie, we did not want users to mistakenly interpret a higher integer score within the high-risk group as translating into higher risk) [2,4]. Rather, we incorporated a population-level description of patients in the high-risk group with the statement that the flagged patients have a *1 in 5 chance of requiring a RRT or ICU transfer within the next 6-18 hours*, which is derived from our validation.

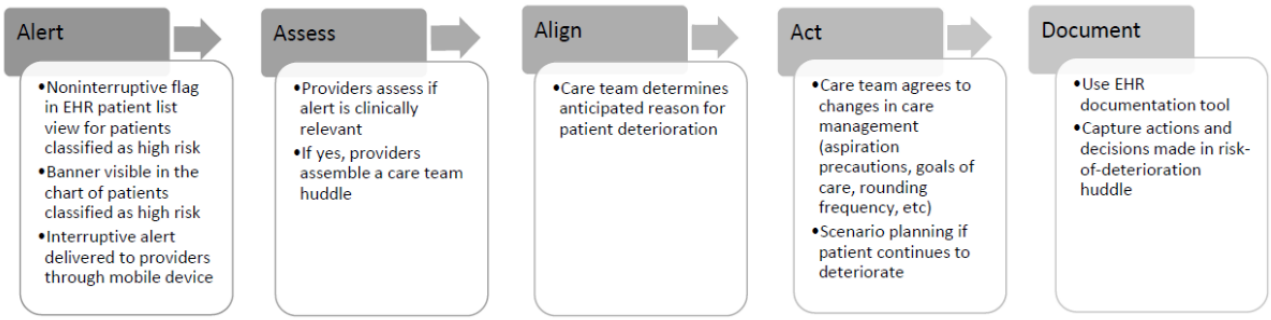
Three preferred alerting mechanisms for a patient identified by the model as high risk were identified: alert mode 1: a noninterruptive flag icon that appears on the screen next to patients classified as high risk in the EHR patient list view, which allows clinicians to quickly see the names of all patients classified as high risk on one screen; alert mode 2: a banner visible on top of the screen once the chart of a flagged patient is opened that provides additional information about what *high risk* means, the accuracy of the CDI model, and specific next steps that should be taken to assess the risk of deterioration; and alert mode 3: an interruptive alert delivered to mobile devices that includes the same information as the banner at the time a patient first crosses the high-risk CDI threshold.

Downstream workflows were designed to accompany these alert modes to improve the reliability and degree of team coordination in the clinical response for patients at risk of deterioration (Figure 1). Once the clinician receives the alert, they first assess the patient to judge whether the alert is clinically relevant and accurate and then conduct a huddle with the rest of the clinical team and use the following checklist to assess the patient's risk and review mitigation strategies:

1. Align on the anticipated reason for patient deterioration.
2. Assess vital signs, airway or oxygenation needs, intravenous access, and code status.
3. Agree on changes to care management (eg, aspiration precautions in place, critical care consultation, etc).
4. Agree on the steps to take if the patient continues to deteriorate.

The last step involves documentation using an EHR-based documentation tool that captures the actions to be taken and the decisions made during this risk-of-deterioration huddle.

Figure 1. Workflow for assessing and managing clinical deterioration following an alert from the Clinical Deterioration Index prediction model. EHR: electronic health record.



Implementation Strategy

The intervention implementation will be split into two stages to assess its impact when offered to the physicians only (stage 1) and later to the entire physician-nurse team (stage 2). In stage 1 (yellow shading in Figure 2), the three alert modes will be delivered only to the physicians for patients across all 6 patient care units, and subsequent workflows will be initiated only by the physician.

In stage 2 (green shading in Figure 2), the alert modes will also be delivered to the nurses on the clinical teams, and either the physician or the nurse on the team can initiate the downstream workflow, thus creating a team approach to identifying and managing clinical deterioration. Nurses are to perform a parallel clinical validation of the alert and contact the physician to conduct the aforementioned risk-of-deterioration huddle. Thus, assessment of the risk and initial steps to manage deterioration can be initiated by either the physician or the nurses in the team intervention model. Stage 2 will be rolled out in a stepwise manner to each of the 6 primary general medicine units.

Rolling out the intervention using a stepwise approach was chosen for pragmatic implementation and evaluation purposes. The physicians care for patients across all 6 patient care units, whereas the nurses are staffed based on individual units. For implementation practicality and patient safety, stage 1 (physician-only intervention) would thus be implemented across all 6 units, whereas the implementation of stage 2 (the addition of nurses) would be staggered by the patient care unit so that the nurses in each unit can be trained in the new workflow together. This implementation strategy also allows us to evaluate the additive impact of delivering AI predictions to the entire physician-nurse team using a stepped wedge design.

Figure 2. Stepped wedge design for the implementation and evaluation of a clinical deterioration model and workflow. Under *Baseline* column, blue shading includes data from the 10 months prior to the roll-out of the intervention for all 6 participating units (60-unit months for analysis). Under *Month* column, yellow shading represents stage 1 and the physician-only intervention for the physician-nurse team (25-unit months for analysis). Under *Month* column, green shading indicates stage 2 and the intervention for the physician-nurse team (41-unit months for analysis).

Unit	Baseline	Month										
		1	2	3	4	5	6	7	8	9	10	11
Medicine unit 1												
Medicine unit 2												
Medicine unit 3												
Medicine unit 4												
Medicine unit 5												
Medicine unit 6												

Study Design

To evaluate this complex, multicomponent intervention, we will use a mixed methods approach informed by the SEIPS 2.0 model to achieve our aims of assessing both the clinical outcomes and the processes that produced these outcomes. We found this model to be uniquely equipped to assess the impact of a new technology such as a predictive model because it takes into account both the social and technical aspects of implementation. Using a mixed methods approach will provide complementary data on the effect of the AI-enabled model on the management of clinical deterioration (ie, quantitative data will evaluate the clinical outcomes, and qualitative data will evaluate the processes) [14]. The intervention will be implemented consecutively in the medicine units based on a modified stepped wedge design featuring three stages (Figure 2): the baseline period (stage 0, blue shading) includes the 10-month period before the implementation of the intervention; in stage 1 (yellow shading), the intervention will be launched to all general medicine physicians across the hospital; and in

the third and final phase (green shading), the intervention will be launched to the full physician-nurse clinical team in a staggered approach by medical unit. The study began in March 2021 (month 1).

Sample

To evaluate this multidisciplinary intervention, data derived from multiple stakeholders, including providers, staff, and adult patients, will be included. The intervention will be implemented by providers and clinical staff in the 6 medicine units for all adult patients, as outlined in Figure 2. The clinical and process outcomes derived from the EHR and chart reviews will be captured at either the patient or unit level. The following patient inclusion criteria are based on the level of analysis:

- For unit-level outcomes, all patients admitted to the units will be included in the analyses.
- For patient-level outcomes, patients who cross the high-risk CDI threshold (CDI≥65) during their inpatient stay and will thus be eligible for the intervention will be included in the analyses.

For the qualitative evaluation, a stratified purposeful sample of approximately 20 providers and clinical staff who are typically responsible for identifying deterioration in patients will be selected for interviews (eg, hospital residents or interns, bedside nurses, critical care response team, clinical nurse specialists, and ICU fellows) [15].

Outcomes

The clinical outcomes will be derived from data extracted from the patients' EHRs related to inpatient hospital stay and up to 30 days after discharge to capture readmission. Using these data, the outcomes will be calculated and expressed at either the unit or patient level, as described herein. To facilitate generalizability and comparisons with other outcomes, the following outcomes, which are commonly assessed in other interventions for clinical deterioration [2,5,16], will be evaluated to address aim 1:

- Number of RRT activations in response to adverse events per unit per month (RRT/unit/month; unit level)
- Number of code events per unit per month (codes/unit/month; unit level)
- Number of ICU escalations per unit per month (ICU/unit/month; unit level)
- Mortality per unit per month (deaths/unit/month; unit level)
- Readmission rates (30-day rates) per unit per month (30-day readmissions/unit/month; unit level)
- Length of stay in acute inpatient setting (patient level nested in unit)

We will also explore the process outcomes informed by the SEIPS 2.0 model and the implementation outcomes described by Proctor et al [17] to assess the ways in which the model and workflow changed the work system and, subsequently, the work processes (aims 2 and 3). Where possible, these outcomes will be derived from the patients' EHRs and a secure text messaging platform to minimize the required data reporting by clinicians. A focused chart review of a subsample of patients will also be conducted for data not extracted through the methods described previously. Examples of these processes include the following:

- Completion of documentation in the EHR (unit/month; unit level)
- Number and type of staff engaged in the intervention workflow (patient level nested in unit)
- Actions taken by the team engaged in the intervention workflow (patient level nested in unit)
- Time elapsed between alert and completion of workflow procedures, including documentation (patient level nested in unit)

Data Collection and Procedures

Quantitative and qualitative data collection will be aligned to the SEIPS 2.0 framework. Mapping data to the framework aims to identify where multiple methods and sources of data can be used to explore each concept [14].

EHR Data Extraction

Quantitative data for processes and clinical outcomes will be extracted from the patients' EHRs (Epic Systems Corporation) and the records of the clinical teams' secure text messaging service (Voalte). Data extracted at the patient level will include notes, flowsheets of orders and referrals, and laboratory results, along with associated time stamps to assess the processes of the clinical teams' response to clinical deterioration. Collecting these outcomes will require the development of electronic tools that will permit the capture and storage of these data discretely in the EHR as opposed to encounter-note text, for example.

Chart Review

Nondiscrete exploratory outcomes captured in the encounter notes will be investigated through chart review. To further explore the clinical processes related to the interruptive alert and clinical workflow, 10% of the patient charts will be reviewed to describe the workflow within the EHR after an alert has been triggered. The charts will be identified from a list of all patients for whom a high-risk alert was triggered during the evaluation period and stratified by unit to explore the potential between-units variation. Data elements and a template for the chart review will be determined based on the outlined SEIPS 2.0 constructs and will capture the events and orders documented in the EHR related to the CDI trigger, the location of documentation within the EHR, the role of the documenter, and interactions between the clinical team members. The chart review will follow the guidance described by Vassar and Holzmann [18].

Qualitative Interviews

Interviews with the clinicians will be conducted before and after the model and workflow are deployed to determine if and how the work system has changed (aims 2 and 3). The topic guide will be aligned with the concepts in the SEIPS 2.0 framework and the implementation outcomes [13,17]. The interviews are expected to take approximately 30-45 minutes and will be conducted by phone or video conference for the convenience of busy clinicians. The interviews will be recorded and transcribed for analysis. In addition, the outputs from the process improvement methods for designing the nursing workflow

(process maps and pain point analysis) will be included as documentary data as part of the qualitative data set.

Analysis

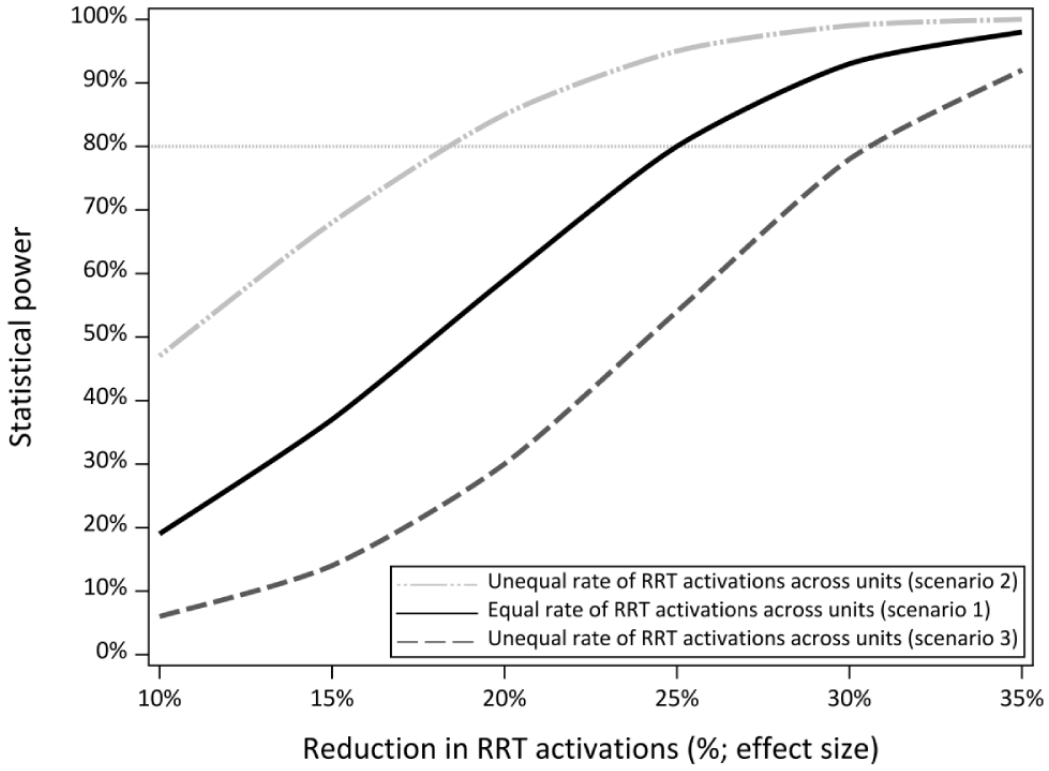
Quantitative Analysis

The primary aim is to assess the impact of the physician-only and team interventions on the unit-level clinical outcomes compared with baseline data. The secondary aim is to explore how the intervention is implemented by describing the process outcomes that were developed and launched as part of the intervention-specific workflow. For these process outcomes, the differences between the physician-only and team interventions will be statistically evaluated because baseline data will not be available for these outcomes. Poisson regression will be applied for unit-level count outcomes to determine the differences among the three phases of the study (baseline, physician-only, and team), followed by pairwise comparison. A multilevel, mixed-effects model will be used for patient-level outcomes to include the covariate unit to account for nesting. The level of statistical significance will be set at $P<.05$.

Power Calculation

On the basis of the aforementioned study design, we assessed the minimum effect size of the team intervention that can be detected with sufficient power (>80%). The percentage reduction in the number of RRT activations in response to adverse events per unit per month (RRT/unit/month) was chosen as the effect size measure because it is the most proximal of the clinical outcomes to the implemented workflow. As shown in Figure 2, our design provides a baseline period of 60 unit months and a team intervention period of 41 unit months. Assuming that the occurrence of RRT events follows a Poisson process, we conducted simulation studies with 10,000 replications to estimate the power curves using the following three scenarios. The first scenario assumes a mean rate of 4.5 RRT/unit/month during the baseline period for all 6 units. The second and third scenarios assume the following heterogeneous mean rates across the 6 units: 3.5 RRT/unit/month for 2 units, 4.5 RRT/unit/month for 2 units, and 5.5 RRT/unit/month for 2 units. In scenario 2, we assume that the team intervention is introduced to the units with lower rates at baseline first and the higher-rate units last, whereas in scenario 3, we assume the opposite. All scenarios use a two-sided α set at .05. Figure 3 shows the power curves for each scenario: scenarios 1, 2, and 3 indicate 80% power to detect a reduction in the RRT event rate of approximately 25%, 18%, and 30%, respectively.

Figure 3. Power curve for simulations with both equal and unequal rapid response team rates across units. RRT: rapid response team.



Qualitative Analysis

A SEIPS 2.0 codebook will be created to define each of the concepts and create a shared mental model of the framework for clinical deterioration. Using the documentary data outputs from the process improvement methods to develop the workflow (process maps and pain point analysis) as a starting point, we will develop SEIPS configuration maps that determine important factors for identifying clinical deterioration related to task, person, organization, internal and external environments, and tools and technology—as well as their interactions. The members of the process improvement and evaluation teams will first meet to discuss the SEIPS codebook and then individually produce SEIPS 2.0 configuration maps. These maps will then be consolidated into one agreed configuration map that

represents the current state of work for managing clinical deterioration. The SEIPS 2.0 configuration map will then be further refined with data from the interviews. NVivo (QSR International) will be used for data management and analysis. The interview analysis will use a deductive and inductive approach, using deductive codes derived from the SEIPS 2.0 framework and implementation outcomes while searching for emergent themes. The transcripts will be coded by one researcher with a portion of the transcripts coded by a second researcher to check for consistency in identifying themes [19]. The output from the qualitative analysis will be configuration maps before and after the implementation of the model and an assessment of the implementation outcomes, barriers, and facilitators.

Mixed Methods Analysis

Data will be mixed during the analysis phase using a mixed methods matrix [20]. Data collected using the aforementioned methods will be mapped to the SEIPS 2.0 framework (eg, data related to *tools and technology* will be gathered in the EHR by extracting number and pattern in the CDI views and in the interviews by asking questions about how the clinicians incorporate the CDI into their workflow and decision-making).

Results

This study was given a nonresearch determination by the Stanford University Institutional Review Board because the purpose of this study is to develop and evaluate a system to identify and manage clinical deterioration that is specific to the hospital setting. The study began a pilot period of the intervention in one unit in December 2020, and the stepped wedge study began in March 2021.

Discussion

This protocol paper proposes an approach to evaluation that recognizes the importance of assessing both processes and clinical outcomes to understand a multifaceted AI-enabled intervention aimed at the challenging problem of clinical deterioration. Our study design examines both clinical effectiveness and implementation outcomes because implementation outcomes such as clinician adoption, process metrics that reflect the impact of the machine learning model on workflow, and the clinical outcome of interest (eg, number of unplanned ICU transfers) are all intricately related as part of the work system. Evaluating these outcomes in tandem will help to understand how individual and team work processes mediate (or perhaps explain the lack of) any improvement in the clinical outcome, as well as any implications that the implementation may have for patient safety in the real-world setting. The implementation of this intervention reflects the real-world capabilities of currently available clinical deterioration prediction models, which have relatively low positive predictive value, and extends the question beyond the capabilities of the actual model to how AI models can inform, and be integrated into, the workflow. A complex systems approach using the SEIPS 2.0 framework to view the problem and the intervention will allow a more nuanced understanding of how a complex intervention involving AI and human behavior change interact to produce outcomes.

Traditional physician-nurse teams often face problems regarding hierarchy, communication breakdowns, and a lack of shared mental models for patient needs that result in challenges revolving around the management of high-stakes situations, such as clinical deterioration. Our evaluation will specifically assess if and how AI predictions, when incorporated into a team-based workflow, may help to reduce these barriers to effective team performance. This approach is a significant addition to the existing evaluations of AI interventions that primarily focus only on the effect of AI on clinical outcomes and do not sufficiently examine how the observed effects are mediated by AI and the associated work processes. Furthermore, the application of complexity and sociotechnical systems thinking in our evaluation allows for the generation of insights into how AI can be effectively incorporated into human work systems to deliver the desired improvements in processes and outcomes. The potential of AI to change the behavior of clinical teams is of particular interest to this evaluation.

The stepped wedge design demonstrates that limitations due to implementation requirements can be used as an opportunity to collect data to better differentiate the active ingredients (physician-only vs team) of a complex intervention. Our mixed methods approach aims to reflect the complexity of the system in which the AI-enabled CDI is deployed and provide detailed evidence of what works and why, thus providing the necessary foundation to ultimately support sustainability. Although we perceive that the team intervention will likely be specific to the hospital culture and setting in which it is implemented, using the SEIPS model as a theoretical approach to understand the impact on the work system will be of interest to a widespread audience looking to integrate AI into real-world clinical environments.

Acknowledgments

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Authors' Contributions

LMH, SMRK, and RCL designed the study; RCL, LS, and MS conceived and designed the intervention; RCL, LS, MS, and SV provided clinical input and workflow perspectives; MW and SMA provided methodological expertise; NS assisted in qualitative

aspects; DWG provided biostatistical support; LMH and SMRK drafted the manuscript; and all authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
CDI: clinical deterioration index
EHR: electronic health record
ICU: intensive care unit
RRT: rapid response team
SEIPS: Systems Engineering Initiative for Patient Safety

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Protocol

Patient and Family Engagement Approaches for Digital Health Initiatives: Protocol for a Case Study

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Abstract

Background: Digital health initiatives such as patient portals, virtual care platforms, and smartphone-based apps are being implemented at a rapid pace in health care organizations worldwide. This is often done to improve access beyond traditional in-person care and enhance care quality. Recent studies have indicated that better outcomes of using these initiatives and technologies may be achieved when patients and their family members are engaged in all aspects of planning, implementation, use, and evaluation. However, little guidance exists for how health care administrators can achieve effective engagement in digital health initiatives specifically.

Objective: The objective of this study is to document processes related to planning and implementing patient and family engagement (PFE) in digital health initiatives. This information will be used to develop tangible resources (eg, a field guide) that other organizations can use to implement PFE approaches for digital health initiatives in their organizations.

Methods: A previously developed multidimensional conceptual framework for PFE in health and health care contexts will be used to guide this work. To understand the intricacies involved in using PFE approaches in digital health strategies, a case study will be conducted. More specifically, this work will employ an embedded single-case design with PFE in digital health initiatives at a large Canadian mental health and addictions teaching hospital. Multiple digital health projects being undertaken at the study site will be explored to better understand where the PFE is intended to support the design, implementation, and operation of the digital health platform or technology. These projects will form the individual units of analysis. Data collection will involve field notes and artifact collection by a participant observer and interviews with the various digital health project teams. Data analysis will include a content and thematic analysis, triangulation of the findings, and a chronological mapping of data to a PFE process.

Results: Funding for this work was provided by the Canadian Institutes of Health Research (CIHR), via a Health System Impact Fellowship. As of August 2020, digital health projects that will form the case study units have been identified, and the participant observer has started to embed themselves into these projects. Although the development and collection of field notes and artifacts, respectively, have begun, interviews have not been conducted. The study is expected to conclude in September 2021. Once this study is complete, the development of a field guide and resources to support the uptake of PFE strategies in digital health will begin.

Conclusions: By better understanding the processes involved in PFE in digital health projects, guidance can be provided to relevant stakeholders and organizations about how to do this work in an effective manner. It is then anticipated that with the increasing use of PFE approaches, there may be improved uptake, experience, and outcomes associated with using digital health technologies.

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KEYWORDS

digital health; patient engagement; case study; patient and family engagement; mental health

Introduction

Background

The potential for digital health initiatives, such as electronic health record systems, mobile health apps, and virtual care platforms, to have a positive impact on aspects of health care delivery, including in effectiveness and patient safety, is well documented in the literature [1-4]. In this paper, digital health initiatives refer to several digital technologies including, but not limited to, mobile apps, online digital interventions, telemedicine or virtual care platforms, electronic health records, and patient portals [1]. These technologies may empower patients, providers, and other knowledge users by providing them with information to improve decision making in self-management, point of care, health policy, and beyond. In addition, some of these technologies (eg, virtual care platforms) may allow for improved access to care beyond the physical location in which it is typically delivered.

Numerous health care organizations have already implemented digital health initiatives; however, there have been varying degrees of success. A recent systematic review found that 81% of evaluations of these technologies showed significant improvements in efficiencies or effectiveness due to the adoption of the technology, with the remaining studies showing mixed or negative results [5]. Despite the potential benefit, many digital health initiatives have faced implementation barriers, hindering their update and adoption (eg, technology issues, mismatched values, changes in workflow, organizational culture issues, etc) [6]. Lessons learned from failed initiatives suggest that the active involvement of patients in the various aspects of developing and implementing digital health initiatives (or patient engagement) is critical to its success, especially those targeted for use specifically by patients and family members themselves [7-9]. Studies have shown positive outcomes when patients are engaged throughout the lifecycle of health technology projects [10-12]. Recently published work describing digital health initiatives showed that engaging patients in the design and implementation process has yielded positive results [12,13].

A 2019 scoping review exploring patient and family engagement (PFE) strategies in health information technology (IT) initiatives found that engaging patients and families has become a growing trend in recent years, with most (57%) of the included studies in that review being published since 2017. The review also found that there are varying degrees of engagement of patients and family members by health care organizations, with often limited engagement sustained throughout the entirety of the stages of digital health projects [14]. A recent Canadian study was conducted to understand how health care organizations can develop strategies to facilitate greater patient engagement in their health IT initiatives [15]. A core recommendation of the study was to develop a resource document, or guide, to support health care organizations in developing and integrating patient engagement strategies in digital health initiatives.

Although the increasing trend of engaging patients and families in digital health initiatives remains apparent, there lacks a validated patient engagement field guide or resource to inform administrators of effective strategies. A 2018 scoping review on patient engagement in Canada called for greater investments directed to the development, validation, and implementation of a practical patient engagement resource [16]. Thus, there is consensus on the importance of patient engagement beyond direct care (ie, shared decision making) to include patient partnerships in decision making at the organizational and policy level. For this reason, a validated patient engagement field guide is necessary to promote patient decision making at the organizational and policy level and to assist digital health initiatives in sustaining patient engagement. To develop this kind of resource or guide, more information is required to understand the key processes involved in engaging patients and families in digital health initiatives. The purpose of this study is to use a case study approach to generate an understanding of how PFE strategies are initiated and integrated into digital health initiatives at a specialty Canadian academic health science center.

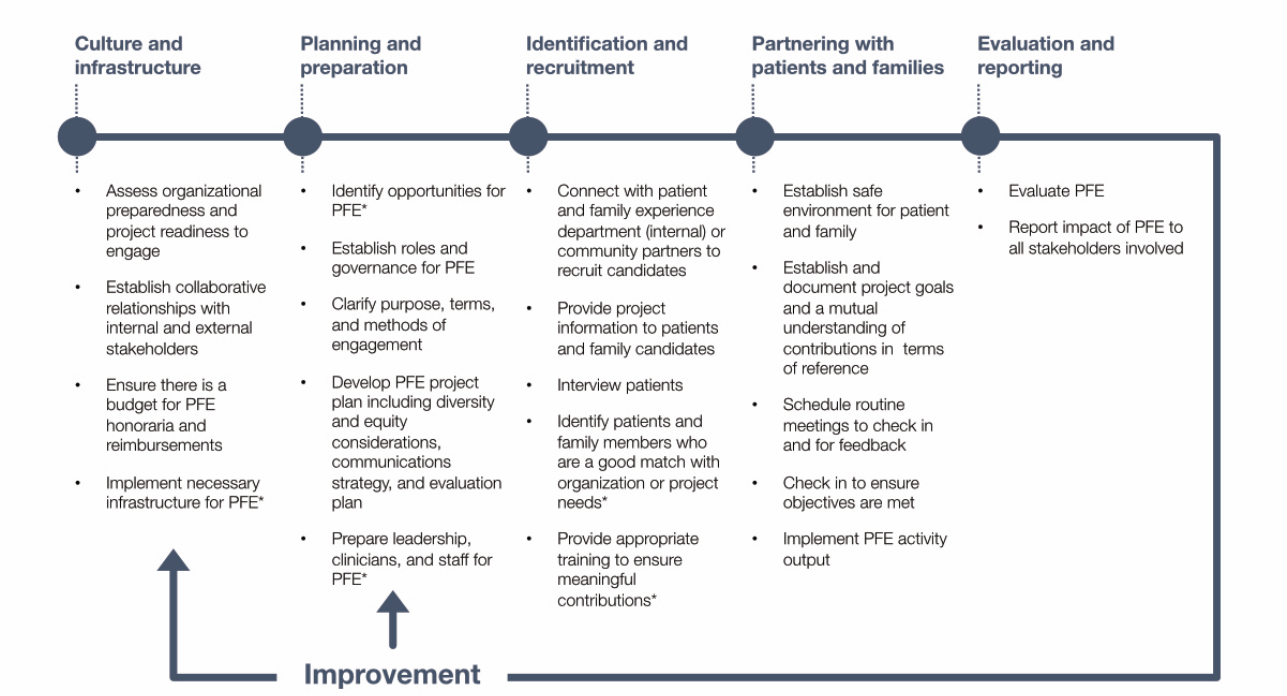
Conceptual Frameworks

The concept of patient engagement is being increasingly accepted in health care; however, it takes on different meanings for different stakeholders in different settings [17,18]. To provide some conceptual clarity, Carmen et al [19] proposed a multidimensional framework for PFE in health and health care. This framework has been used in health IT projects to inform PFE strategies in health IT adoption, implementation, use, selection, and evaluation [14]. The framework identifies a continuum of engagement that ranges from consultation, to partnership, to shared leadership. These 3 categories of engagement can occur at 3 different levels of the health care system: direct care, health care organizational design and governance, and policy making [19]. The current study will be framed in the context of PFE in organizational design and governance, and policy making, representing PFE in the design of the digital health technologies, processes, and policies at an organizational or systems level. Although PFE in direct care through digital health can empower and equip patients for better self-care, opportunities exist to explore and understand the meso- or macrolevel PFE contexts [20].

Although the Carmen framework provides types of PFE nested in different health care contexts, it does not offer guidance on the process of implementing PFE initiatives. Existing efforts to provide this guidance have come in the form of lessons learned, recommendations, and checklists; however, a more robust understanding of how to engage patients efficiently, effectively, and meaningfully is required [21]. A brief scan of academic and gray literature identified only a few resources that provide an in-depth guide to PFE [22-26]. The implementation process by the Agency for Healthcare Research and Quality [22] was selected to be the foundation, as it outlines practical in-depth guidance on implementing PFE to support hospital quality improvement and safety initiatives. To provide a more comprehensive process map, some adaptations were made to the process, such as establishing a culture for PFE, evaluation, and the cyclical nature of the process [23-26]. This preliminary process map was further adapted with a systematic scan of PFE tool kits identified in the gray literature. This iteration of the PFE process map (Figure 1) includes the information from the Canadian tool kits and guides identified [23,25,27-34]. The next

iterations of the map will be validated through consultation with the PFE teams at the study site and will be used as a framework for this case study.

Figure 1. Patient and family engagement process map: PFE: patient and family engagement. * denotes steps identified by the Agency for Healthcare Research and Quality guide [22].



Methods

Overview

This study is part of a larger project aimed at developing a field guide to support effective patient and family engagement in digital health initiatives. This project is funded through the Canadian Institute of Health Research Health (CIHR) System Impact Fellowship, where the objective is for embedded fellows to use an integrated knowledge translation approach to advance an organization's impact goals regarding health system improvement [35]. This study will take place at a mental health and addictions–focused Canadian academic health science center, where PFE was identified as a guiding principle in the 3-year strategic plan for the center and its digital innovation strategy. As such, the focal point of this project is to build capacity for PFE at the center. This project was approved as a quality improvement project by the Quality Project Ethics Board at the center and will be conducted between December 2020 and September 2021.

A case study will be conducted to understand the intricacies involved in employing patient engagement activities in digital health initiatives. Case studies typically involve the analysis of an object of study within a real-life, contemporary context or setting [36]. It is an exploration of a bounded system (a case) through detailed, in-depth data collection involving multiple sources of information (ie, observations, interviews, and artifacts) [37,38]. The resultant report will describe the experience and discuss themes within the experience.

This case study asks the following: what are the necessary elements to support effective PFE engagement in digital health initiatives? To answer this question, this project has 7 objectives: (1) map current PFE processes, (2) identify key steps for PFE, (3) understand digital health team needs in planning and implementing PFE, (4) understand the staff experience, (5) understand patient experience, (6) identify ways to improve PFE planning and implementation, and (7) identify core artifacts that support PFE organization and implementation.

This project will employ an embedded single-case design with PFE in digital health initiatives at the mental health and addictions academic health science center (see Figure 2). Within this case, this study will explore the development and implementation of PFE in multiple digital health projects, where the PFE is intended to support the design, implementation, and operation of the digital health platform or technology. Each project engaged in this case study will be a unit of analysis. Within each unit of analysis, a member of the research team will be embedded as a participant observer to support the project team in organizing and facilitating PFE activities while documenting the processes and tacit knowledge required through field notes and artifact collection. Interviews with each digital health team will be conducted to understand the experience and to triangulate with the observations.

Figure 2. Embedded case study design.

The motivation for this case study approach is instrumental and takes on a praxeological lens or action-based approach in understanding how PFE processes are conducted and how they can be improved [39]. The findings from this case study are intended to integrate first-hand experiential knowledge into the development of the field guide. As primary users of the field guide, this case study aims to understand the digital health project team's information needs and lessons learned through the projects.

Recruitment

A maximum variation purposive sampling strategy will be employed to identify digital projects at the academic health center. This strategy will be employed to identify cross cutting themes derived through a diverse range of experiences in implementing PFE. Recruitment will be based on the Carman et al [19] framework and will maximize variation across the different organizational domains (ie, "organization design and governance" and "policy making") and levels of engagement (ie, "involvement or "partnership"). This protocol acknowledges that recruitment will be dependent upon the types of projects available and that PFE activities at the higher levels of the engagement spectrum, as proposed here, are less frequent [40,41]. Depending on these factors, a convenience sample may be required.

Digital health projects will be identified through consultation with departmental leadership and the Digital Health Steering Committee at the academic health center. Project leads identified through consultation will be contacted via email to schedule a meeting to discuss their project and to assess the fit of the project for this case study. Preference will be given to projects that are still in their early planning stages of integrating PFE, as it would allow the research team to observe and participate in the entire process of organizing and implementing PFE in a project.

Data Collection

A key characteristic of a case study is the collection and convergence of multiple data sources to allow for a holistic understanding of the case [42]. This case study will employ participant observations and interviews as the 2 primary types of data collection methods which will yield 4 types of data: field notes, project artifacts, documentation, and interview transcripts. Table 1 shows the linkages between the data sources and research questions. In light of the COVID-19 pandemic, all data collection will be facilitated electronically through institution-approved email, cloud drives, and videoconferencing platforms.

Table 1. Linkages between case study objectives and data types.

Case study objectives	Data types			
	Field notes	Artifacts	Documents	Interview transcripts
Map current PFE[a] processes		✓	✓	✓
Identify key steps for PFE	✓			✓
Understand digital health team needs in planning and implementing PFE	✓			✓
Understand the staff experience	✓		✓	✓
Understand patient experience			✓	✓
Identify ways to improve PFE planning and implementation	✓	✓	✓	✓
Identify core artifacts that support PFE organization and implementation	✓	✓		✓

[a]PFE: patient and family engagement.

Participant Observations

A member of the research team (NS) will be embedded as a participant observer in the projects. As a participant, NS may assume a variety of roles on the digital health project and be actively involved in the planning and implementation of the PFE activity. As an observer, NS will take field notes following an observation protocol (see Multimedia Appendix 1 for these protocols). The field notes will document conversations related to the PFE activity and the processes involved in planning and implementing PFE activity (eg, questions asked about PFE and process, decision points, information requirements). Notes related to implementation factors will also be documented as they are critical to understanding the processes involved (ie, enablers, barriers, pain points, and breakthrough points). Additionally, physical and digital artifacts used throughout the projects will be collected. These artifacts are items that are used to facilitate planning and implementation (eg, technologies, templates, patient-facing material, process maps, project documents, PowerPoint slides decks). Documentation related to the project may also be used to provide context to the cases. Documentation includes agendas, meeting minutes, report of events, proposals, progress reports, evaluation reports, published articles, and news appearing in institutional announcements and mass media. [38].

Interviews

Semistructured interviews will be conducted to provide greater insights and context to the PFE processes and informational needs of digital health teams. Approximately 12 interviews will be conducted across the 4 digital health projects and will follow an interview script (see Multimedia Appendix 1). Interviews will be conducted with the project lead or manager and the staff supporting the project. Additionally, patient and family advisors will also be interviewed in projects where they are a member of the digital health team (ie, participating in meetings and contributing to the digital health project). Staff will also be asked about their current knowledge and knowledge gaps regarding the planning of PFE activities. The interviewer will ask participants about their experiences planning and implementing their PFE activities, what was successful, what they would do differently, and lessons they learned throughout the process.

The interviews will be conducted with the teams at the conclusion of a PFE activity or event. For projects with ongoing PFE, these interviews will be conducted after a project milestone has been met or at other logical end points. All interviews will be conducted and audio recorded via a web-based video or audio platform approved by the organization. Field notes will also be taken.

Data Management and Analysis

The data from the participant observations and interviews will be analyzed following a common data analysis method consisting of sequential deductive and inductive approaches. Data will first be deductively coded using a codebook derived from the PFE process map, where each step will be used as a code. Data that do not fit the scheme will be inductively coded as new categories.

The data collected in the participant observations will be analyzed using a qualitative descriptive approach with content analysis, which will provide a comprehensive summary that provides factual description of the data [43,44]. Data will be analyzed using a directed content analysis [45] that follows the sequential deductive-inductive approach. Relevant sections of the field notes will be coded line by line. Artifacts will be categorized based on where they were used in the process map.

The interview data will be transcribed verbatim and will be thematically analyzed following Braun and Clarke's framework [46]. The framework consists of 7 steps: transcription, reading and familiarization, coding, searching for themes, reviewing themes, defining and naming themes, and finalizing the analysis. The coding process will also follow the deductive-inductive approach. Using NVivo 11 (QSR International), the analysis will be conducted in pairs, where the independent coding will be compared and discrepancies will be resolved through discussion.

A case description strategy will be used to organize the participant observation and interview results into a descriptive framework [38]. The results will be triangulated to cross-validate the findings and provide a comprehensive understanding of PFE [47]. This will be accomplished through a journey mapping technique that will visually plot the results on a timeline (ie, a PFE process map will be used as the template) [48]. The data collected through participant observation will undergo a time

series analysis in which a chronological sequencing technique will be used to trace the data over the timeline for each project [38,49]. Critical milestones and decisions points within the process will be identified through commonalities in the field notes across multiple projects. Artifacts and key documents will also be mapped to the process based on when they would be relevant. Similarly, insights from the interviews will also be mapped to the journey map where they would be relevant. The comparison of multiple units strengthens the inferences that can be made about the process while addressing threats to internal validity; furthermore, the final journey map will undergo a round of member checking by the project teams and validation by the PFE teams. This final step will be used to identify any oversights and resolve any contradictions [38].

Results

Three digital health projects that will form the case study units have been identified, and the participant observer has started to embed themselves into these projects. One project used a consultation approach to PFE; the other two projects used multiple approaches. One involved consultation and involvement, while the other had all three approaches of consultation, involvement, and partnership. The interviews have not been conducted and are anticipated to occur in Spring 2021. This study is expected to conclude in September 2021. Once this study is complete, the development of a field guide and resources to support the uptake of PFE strategies in digital health will begin.

Discussion

Principal Findings

Digital health is increasingly gaining prominence in today's health care landscape. Its importance has been emphasized with the COVID-19 pandemic, during which health care organizations and providers are leveraging virtual and digital means to coordinate a response to the unprecedented challenge [50]. Engaging patients ensures the valid design of patient-centered digital health innovations, where the discrepancy between user and clinical realities are minimized [51]. Furthermore, patient engagement in the ideation, development, implementation, and governance in new digital health innovations is critical in addressing the social, cultural, technological, and ethical challenges of digital health implementation [52]; moreover, it ensures that the end product and the processes that support it are desirable, feasible, and viable for all stakeholders involved [53]. This case study aims to identify all the critical factors to ensure that PFE can be implemented effectively and meaningfully to support digital health innovations.

The findings from this proposed case study can fill an identified knowledge gap in health informatics and PFE literature [14,21]. This case study builds upon the work of a scoping review [14] and a stakeholder engagement activity [15] on how to facilitate PFE in digital health initiatives, cross-validating the recommendations from these previous works through the practical experience of implementing PFE strategies. As identified in the work to date, there is currently no common framework or resource to support health care organizations through the implementation of PFE strategies in their digital health initiatives. Taking a case study approach allows for the convergence of multiples sources of data and perspectives in developing a framework.

This protocol was published for the following reasons. First, the peer-review process offers the opportunity to improve the quality and applicability of this work through the insights of the reviewers. Second, this paper will inform the scientific community that this research is underway and to encourage collaboration from those interested. Last, publishing study protocols has the benefit of disseminating contemporary ideas and approaches to the complex problems [54]. Although case study research has been increasingly used by researchers, publishing a case study is important, as it is a relatively underused form of inquiry that is valuable for untangling dynamic and complex topics [55,56]. This protocol is intended to highlight how a case study approach can be pragmatically used to map out processes and form a foundation for developing a field guide.

Through the work outlined in this protocol, this case study will adapt existing processes for planning and implementing PFE for the digital health context. Future work will engage digital health teams, patients, and families in the co-design of the field guide. The field guide addresses an identified knowledge gap and will encourage greater PFE in digital health initiatives, thereby also addressing a practice gap in a field where adoption, scale, and spread are challenging.

Limitations

This study has a few anticipated limitations to consider. First, the case study will be undertaken in a very specific context, where the digital health initiatives are focused on mental health and addictions and are implemented in an academic hospital setting. Moreover, the findings from this study will not be generalizable to a broader setting; however, this study is intended to be exploratory, providing a preliminary understanding of the process nuances and key steps rather than seeking causal relationships [57,58]. Future work will include cross-validating the findings and recommendations through an environmental scan of past digital health PFE projects across Canada (and perhaps beyond), offering the opportunity to extend the understanding of PFE processes in digital health. Second, the proposed PFE process presented in this protocol is still in a preliminary state and will undergo further adaptations based on other PFE guides identified throughout the case study. The adapted PFE process map will be further validated by the PFE teams to ensure a comprehensive and valid PFE process is available for the proposed time series analysis. Moreover, the PFE teams will be engaged throughout the case study to provide external validation of the interview and participant-observer findings. Finally, various strategies will be undertaken to address the common methodological issues related to case studies. Strategies to improve validity include triangulation of multiple data sources, member checking, data analysis in pairs, disclosure of researcher bias or reflexivity, and external validation [57].

Conclusions

The findings of this study will extend the current understanding of PFE in digital health and will contribute broadly to health informatics, participatory medicine, patient experience, design, and implementation-science literature. The case study approach will compare the current understanding of PFE processes with the lived experience of implementing PFE, thereby exploring and uncovering the tacit nuances of initiating and integrating PFE into practice. The exploratory case study approach also offers the opportunity to further develop the conceptual and theoretical understanding of PFE in digital health [38,58], an area that has not been systematically documented or understood [59-61].

With a better understanding of how PFE occurs within digital health projects, a resource guide can be developed to support the successful uptake of these strategies by other organizations. If PFE becomes commonplace in all stages of the life cycle of digital health technologies, there may be improved uptake, satisfaction, and engagement with these technologies by patients and their family members.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Protocols.
[DOCX File , 22 KB - resprot_v10i7e24274_app1.docx]

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Abbreviations

CHIR: Canadian Institutes of Health Research
PFE: patient and family engagement
IT: information technology

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Protocol

Geospatial Analysis of Neighborhood Environmental Stress in Relation to Biological Markers of Cardiovascular Health and Health Behaviors in Women: Protocol for a Pilot Study

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Abstract

Background: Innovative analyses of cardiovascular (CV) risk markers and health behaviors linked to neighborhood stressors are essential to further elucidate the mechanisms by which adverse neighborhood social conditions lead to poor CV outcomes. We propose to objectively measure physical activity (PA), sedentary behavior, and neighborhood stress using accelerometers, GPS, and real-time perceived ecological momentary assessment via smartphone apps and to link these to biological measures in a sample of White and African American women in Washington, DC, neighborhoods.

Objective: The primary aim of this study is to test the hypothesis that living in adverse neighborhood social conditions is associated with higher stress-related neural activity among 60 healthy women living in high or low socioeconomic status neighborhoods in Washington, DC. Sub-aim 1 of this study is to test the hypothesis that the association is moderated by objectively measured PA using an accelerometer. A secondary objective is to test the hypothesis that residing in adverse neighborhood social environment conditions is related to differences in vascular function. Sub-aim 2 of this study is to test the hypothesis that the association is moderated by objectively measured PA. The third aim of this study is to test the hypothesis that adverse neighborhood social environment conditions are related to differences in immune system activation.

Methods: The proposed study will be cross-sectional, with a sample of at least 60 women (30 healthy White women and 30 healthy Black women) from Wards 3 and 5 in Washington, DC. A sample of the women (n=30) will be recruited from high-income areas in Ward 3 from census tracts within a 15% of Ward 3's range for median household income. The other participants (n=30) will be recruited from low-income areas in Wards 5 from census tracts within a 15% of Ward 5's range for median household income. Finally, participants from Wards 3 and 5 will be matched based on age, race, and BMI. Participants will wear a GPS unit and accelerometer and report their stress and mood in real time using a smartphone. We will then examine the associations between GPS-derived neighborhood variables, stress-related neural activity measures, and adverse biological markers.

Results: The National Institutes of Health Institutional Review Board has approved this study. Recruitment will begin in the summer of 2021.

Conclusions: Findings from this research could inform the development of multilevel behavioral interventions and policies to better manage environmental factors that promote immune system activation or psychosocial stress while concurrently working to increase PA, thereby influencing CV health.

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KEYWORDS

wearables; global positioning system; ecological momentary assessment; accelerometer; biomarkers of stress; mobile phone

Introduction

Background

Promoting physical activity (PA) is a critical public health goal because insufficient PA participation affects all age groups and various racial and ethnic groups in the United States (US) [1]. Approximately 10% of deaths are attributed to insufficient PA in the US [2], and engaging in regular PA (ie, meeting the PA guidelines of at least 150 min/week of at least moderate intensity PA) can reduce the risk of numerous chronic diseases (eg, cardiovascular disease [CVD]) [3]. Furthermore, in 2018, the newly released Physical Activity Guidelines for Americans, 2nd edition documented that regular PA has immediate health benefits, including lowering blood pressure, increasing sleep quality, decreasing anxiety, and improving cognitive function and insulin sensitivity [4]. Despite the well-demonstrated PA benefits, most US adults do not engage in sufficient PA, when measured by accelerometers [5,6]. In particular, African American adults have a lower PA level than their White counterparts, with 7.7% of African American adults and 8.2% of White adults meeting the PA guidelines [6].

The application of a multilevel social-ecological framework to determine changes in the environment and policy that would promote PA participation has been supported by authoritative US health institutions and international organizations over the past two decades [7-9]. This conceptual framework identifies relevant factors at multiple levels, ranging from genetic, intrapersonal, interpersonal, social, and cultural, to environmental factors [10]. The key principle of the social-ecological model posits that each level can impact behavior, and individuals can impact and are influenced by their environment, particularly when considering psychosocial effects [11]. Recent interventions are increasingly focusing on the role that the neighborhood social environment (eg, poverty, social disorder, and crime [12]) may play as a source of stressors that shape low levels of PA at the population level [8,13].

Although the neighborhood social environment is an important factor in promoting PA [13], a key limitation in neighborhood social environment research is that the majority of such research systematically focuses on residential areas (ie, home) when investigating relationships between objectively measured environmental exposures via geographic information system (GIS) and PA [13]. However, individuals are generally mobile and engage in daily activities that are not restricted to places close to residential areas (eg, workplace) [14]. This generates a geospatial mismatch between exposures to the neighborhood social environment and locations where health behaviors occur [13,15,16]. Previous studies have also used self-reported PA, resulting in potential recall and social desirability bias [17].

When coupled with the neighborhood social environment as a source of stressors, psychosocial factors, such as chronic stress and depression, have an inverse relationship with PA and ultimately CVD [18]. Furthermore, a recent study in adults without CVD and our research in African American women in Washington, DC, demonstrated that amygdala activity (ie, chronic stress–related neural activity) assessed via 18-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET/CT) were significantly associated with subsequent CVD events [19] and vascular inflammation, a subclinical marker of atherosclerosis [20,21]. In addition, another recent study showed that neighborhood-level socioeconomic status (SES) was inversely associated with amygdala activity and arterial inflammation [22]. These findings are important for validating the relationship between chronic stress because of neighborhood factors and CVD events. However, the major limitations of the previous study were that they did not account for individual-level SES in the analytic models. Instead, they used neighborhood-level SES as a proxy for individual-level SES and examined the associations between neighborhood SES and amygdala activity. Furthermore, participants were chosen from a clinical database, which was not representative of the general US adults, and they were predominantly White adults [22]. Further research is needed to elucidate the associations between psychosocial factors, amygdala activity, and biological markers of adverse cardiac events in diverse populations and to assess both individual- and neighborhood-level SES.

Objectives

To address these limitations, researchers have increasingly used an objective PA monitor (ie, accelerometer) linked to data from GPS units to track locations where PA occurs [23,24]. GPS units are often used to quantify an individual's daily activity space (ie, defined as locations where individuals travel or move throughout the day) [23-28]. Ecological momentary assessment (EMA) also helps researchers to better understand psychosocial factors (eg, stressors and mood) in real time and psychosocial-environment contexts for health behaviors [29], such as PA and sedentary behavior. Therefore, the simultaneous use of three distinct methods (accelerometer, GPS, and EMA) reduces recall bias and the geospatial mismatch between exposures to the neighborhood social environment and PA [13]. In our study, we plan to measure both individual- and neighborhood-level SES among a diverse sample of adult women.

This pilot research will address current gaps in understanding the determinants of health disparities for populations from both high- and low-SES neighborhoods in Washington, DC, by applying geospatial tools and methods (ie, accelerometer, GPS, and EMA) and by linking to biomarkers of stressors. This research is innovative because it will apply geospatial tools and methods for tracking individual daily mobility and examine their linkage with biological measures, integration of neighborhood social measures for more comprehensive and objective assessment of factors that may lead to stress-related neural activity and poor CV outcomes. Therefore, the aims of this pilot study are as follows:

Aim 1: To test the hypothesis that living in adverse neighborhood social environment conditions is associated with higher stress-related neural activity among 60 healthy women living in high- or low-SES areas in Washington, DC.

Sub-aim 1: To test the hypothesis that the association is moderated by objectively measured PA via an accelerometer and psychosocial factors via EMA.

Aim 2: To test the hypothesis that residing in adverse neighborhood social environment conditions is related to differences in vascular function.

Sub-aim 2: To test the hypothesis that the association is moderated by objectively measured PA and psychosocial factors via EMA.

Aim 3: To test the hypothesis that adverse neighborhood social environment conditions are related to differences in immune system activation.

Implications

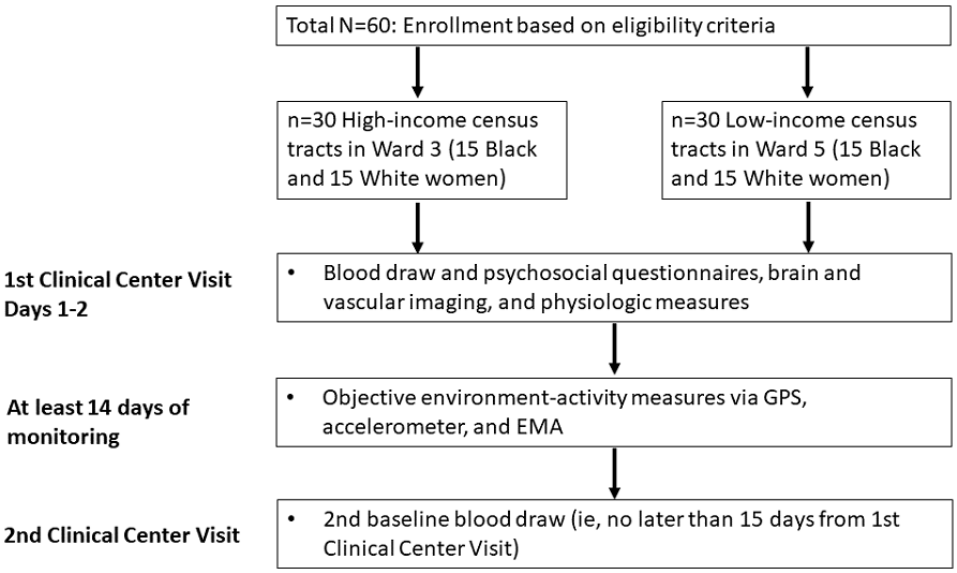
This geospatial pilot study has a strong impact because the associations between neighborhood social contexts and stress-related neural activity (ie, marker of chronic stress–related neural activity) are highly understudied. This study is also novel because the linkages between neighborhood factors, detailed immune markers related to amygdala activity, and vascular function are limited. In addition, this geospatial pilot study will be among the first to include innovative geospatial technologies and tools to further characterize exposure to adverse neighborhood contexts within an individual's daily mobility and link these data to an individual's stress and mood through EMA data. Findings from this research could accelerate the development of multilevel behavioral interventions and environmental policies to better manage environmental factors that promote psychosocial stress or interventions that increase PA, which in turn can promote cardiovascular health.

Methods

Study Design

This is a cross-sectional study designed to investigate the impact of neighborhood environment on cardiovascular health and PA in African American and White women residing in Washington, DC, neighborhoods. Study participants will first visit the National Institutes of Health (NIH) Clinical Center where baseline health information will be collected and three devices will be distributed (accelerometer, GPS, and EMA app; Figure 1). After 14 days, participants will return to the Clinical Center for a final blood draw and cardiovascular examination. The NIH Institutional Review Board (IRB) approved this study, and this study has been registered on ClinicalTrial.gov (NCT04014348).

Figure 1. Flowchart of events.



Study Participants

A sample of women (at least n=30; 15 White women and 15 African American women) will be recruited from higher SES census tracts within a 15% range of the median household income in Ward 3 (median household income=US $126,184) [30]. The other participants (at least n=30; 15 White women and 15 African American women) will be recruited from lower SES census tracts within a 15% range of the median household income in Ward 5 (median household income=US $68,375) [31]. Participants from Wards 3 and 5 will be matched based on age, race, and BMI.

Eligibility

Individuals eligible for this protocol will meet the following inclusion criteria: (1) a healthy White female or healthy Black female of African descent; (2) must be aged between 19 and 45 years; (3) must not have any chronic health condition, including lung disease or active infection; (4) must be living in Washington, DC, Wards 3 or 5; (5) must have access to a smartphone; (6) must be able to provide informed consent; and (7) must speak English. Individuals who meet the following criteria will be excluded from this study: (1) pregnant or breastfeeding; (2) physically unable to perform PA for any reason; (3) weight changes greater than 20% over the past 3 months; (4) obesity (measured BMI≥30.0 kg/m^2); (5) high or low blood pressure; (6) diabetes; (7) history of mental illnesses, treated with medication and therapy; (8) history or evidence of hyper or hypothyroidism; (9) current medication use for chronic illness; (10) HIV; and (11) food allergies or highly restrictive diets that may prevent the ability to consume a controlled metabolic diet.

Recruitment

Recruitment strategies include (1) distribution of recruitment flyers targeting potential participants in public locations throughout Wards 3 and 5, concentrating on areas in or near the targeted census tracts; (2) inclusion of study information on ClinicalTrials.gov, NIH Search the Studies, and a dedicated recruitment website on the Clinical Center Office of Patient Recruitment website (Current Protocols area); (3) use of ResearchMatch. for identification of healthy volunteers meeting criteria; (4) use of NIH (National Heart, Lung, and Blood Institute [NHLBI]/Clinical Center) social media accounts—Facebook, Twitter, and Craigslist with IRB-approved messages; and (5) distribution of recruitment messages on NIH listservs. This study was approved by the NIH Intramural IRB (NCT 04014348). Before enrollment in this study, our trained research staff will obtain written informed consent from all participants.

Devices

Participants will receive an accelerometer (ie, objective activity monitor; ActiGraph wGT3X-BT) to measure PA, sedentary time, and sleep duration for at least 14 days. The ActiGraph accelerometer has been previously used to objectively assess PA [23,24], sedentary time [23,24], and sleep duration [32] among adults. The data will be collected at 1-minute epochs. Two distinct cut-points based on approaches by Troiano [5] and Matthews [33] will be used to determine the intensity of PA. Participants will be instructed to wear the monitor on their dominant wrist with a wristband at all times, except when bathing or swimming. A valid day of accelerometer monitoring is defined as ≥10 hours of wear time [33]. The time-stamped recordings from the accelerometers will be linked with GPS data.

Participants will also receive a GPS unit (ie, tracking device, Qstarz BT-Q1000eX GPS Logger). The GPS unit receives a satellite signal to identify latitude and longitude coordinates for a given period. GPS units will monitor participants' daily activities via locations where they travel throughout the day for at least 14 monitoring days. GPS units will also record distance, speed, elevation, and time. The data will be collected at 1-minute intervals. This device has been used successfully in a recent study [34]. This GPS device is small and can be worn on a belt or placed in a backpack or bag. It will provide a timestamp and GPS coordinates. A valid day of GPS tracking is defined as ≥10 hours of wear time [35].

We will use a smartphone app to record EMA data via a mobile phone; these methods have been previously used for adults [36,37]. We will use two approaches for participants to record their PA, neighborhood environment, and stress. The first is an event contingency assessment. With this assessment, participants will be expected to record within the smartphone app when they engage in a certain behavior (eg, PA) within 15 minutes of the event occurring. The other type of assessment involves random survey prompts. Participants will respond to a series of questions on each day of the week. They will receive EMA random prompts for each assessment for that day (up to three random prompts for each assessment [morning, afternoon, and evening] and a maximum of nine prompts each day). The survey may take approximately 2-3 minutes to complete each time. Each item assesses the type of neighborhood context for the physical environment (eg, home, work, and outdoor), vegetation (amount of trees), traffic (amount of traffic), and safety (feeling safe and violence). Mood (positive and negative affect) and stressors (eg, daily hassles) from the EMA survey will be used specifically as psychosocial factors for each sub-aim. Previously validated EMA surveys and protocols for adults will be used in the proposed study [36,37].

Compliance

EMA compliance rates will be based on answered surveys divided by the total number of scheduled EMA surveys for each participant. We will also monitor participation rate, missing data, latency period (defined as the time between receiving EMA prompts and the items answered), and attrition rate [38]. In additionally, we will follow up each participant daily, irrespective of the compliance rate, to ensure that they do not have issues with device use. Basic statistical analyses will be performed to better understand participant compliance, such as compliance rate, missingness, participation rate, and latency period. In addition, as an exploratory analysis, the missingness of EMA surveys will be examined using pattern mixture random-effects modeling [39]. Furthermore, mindless EMA responses to surveys may occur. To address this issue, we have selected survey items that are crucial to our study aims to minimize participants' burden.

Preliminary Study

Before this pilot study, we conducted the DC CV Health and Needs Assessment (DC-CHNA) study (NCT019227783) to investigate bio-psychosocial and neighborhood conditions resulting in poor CV health. The objective of the previous work was to determine ways to use mobile health technology to promote CV health for populations in lower SES DC Wards 5, 7, and 8 [40-44]. First, the DC-CHNA created a community advisory board, the DC Cardiovascular Health and Obesity Collaborative (DC-CHOC), to give feedback on developing and implementing the DC-CHNA and subsequent community-based projects. The DC-CHOC consists of representatives from the DC faith-based community, US government agencies, academia, and health advocacy organizations, all of whom are devoted to addressing obesity and CV health in at-risk DC communities [44-47]. In this study, 11 participants from DC-CHNA were asked to carry GPS units and use the EMA app and then test the feasibility of both a GPS device and an EMA app for African American women.

Schedule of Events

Participants will visit the NIH Clinical Center where we will instruct them on how to use the devices and measurement tools (accelerometer, GPS, and EMA; Table 1). During the inpatient visit, we will conduct a cardiovascular examination, draw blood, and conduct a vascular stiffness test. Participants will also undergo 18F-FDG-PET/CT testing to measure chronic stress–related neural activity (ie, amygdala brain activity) and vascular inflammation. On the first day of the inpatient visit, study volunteers will follow a controlled eucaloric diet containing 55% carbohydrate, 15% protein, and 30% fat and providing 150% of their estimated resting energy needs in preparation for testing to accurately measure energy expenditure on inpatient day 2. Resting energy expenditure has not been included in the aims of this study. However, this measure can be evaluated as a moderator for the sub-aims of aims 1 and 2.

Table 1. Schedule of events.

Events	First Clinical Center visit		At least 14-day monitoring	2nd Clinical Center visit
	Day 1	Day 2		
Recruitment	Ongoing	Ongoing	Ongoing	Ongoing
Informed consent	✓			
Vital signs	✓			
Anthropometric measures	✓			
Clinical blood testing	✓			✓
Cardiovascular examination	✓			✓
Blood pressure	✓			✓
Blood glucose	✓			✓
Hemoglobin A_{1c}	✓			✓
Lipid panel	✓			✓
Resting energy expenditure		✓		
18-fluorodeoxyglucose positron emission tomography-computed tomography		✓		
Pulse wave velocity	✓			
Survey assessments[a]				
Sociodemographic characteristics	✓			✓
Medical history	✓			✓
Health behaviors	✓			✓
Self-rated health	✓			✓
Smoking status	✓			✓
Alcohol use	✓			✓
General physical activity level	✓			✓
Illicit drug use	✓			✓
Sleep duration and quality	✓			✓
Dietary intake	✓			✓
Perceived Stress Scale	✓			✓
Center for Epidemiological Studies-Depression Scale	✓			✓
Hamilton Anxiety Rating Scale	✓			✓
Adverse Childhood Experiences	✓			✓
Life Orientation Test-Revised (a measure of optimism)	✓			✓
MacArthur Scale of Subjective Social Status	✓			✓
Perceived Ethnic Discrimination Questionnaire Community Version	✓			✓
Positive and Negative Affect Schedule	✓			✓
Superwoman Schema	✓			
Perceived Neighborhood Environment	✓			✓
COVID-19 surveys	✓			
Physical activity, sedentary behavior, sleep, and neighborhood disorder assessments				
Physical activity and sedentary behavior via accelerometers			✓	
Sleep duration via accelerometers			✓	

Events	First Clinical Center visit		At least 14-day monitoring	2nd Clinical Center visit
	Day 1	Day 2		
GPS monitoring			✓	
Ecological momentary assessment			✓	
Engagement with the DC Cardiovascular Health and Obesity Collaborative Community Advisory Board	Ongoing	Ongoing	Ongoing	Ongoing

[a]The surveys can be completed at the first or second clinical visit and will not be repeated.

During their baseline visit, participants will also undergo anthropometric measurements, including height, weight, waist circumference, and hip circumference for weight-related outcomes; complete questionnaires to measure demographics and medical history, health behaviors (eg, PA [48]), perceived neighborhood measures, psychosocial factors (eg, perceived general stress [49]), and COVID-19 questionnaires [50,51]. The majority of the participants will complete the survey questionnaires during the baseline visit (visit 1). For some reason, if participants do not complete the surveys during visit 1, we allow them to complete surveys during the 2nd visit to avoid protocol deviation. A second blood draw will be performed within 14 days from the first draw, as a second baseline to account for the variability of sensitive biological measures. This study follows a tiered compensation format where total compensation depends on the number of assessments the participant completes.

After the baseline assessment (ie, clinical visit days 1 and 2), participants will wear an accelerometer to objectively measure PA and carry a GPS unit to assess locations where they engage in PA for at least a 14-day period [52]. Concurrently, participants will carry a smartphone to receive EMA surveys that have been previously validated to measure psychosocial factors, including mood and stress, for a 14-day period. Subsequently, we will create GIS-derived neighborhood environmental variables, psychosocial variables (EMA), PA or sedentary behavior, and diet outcomes using data from the surveys, EMA, accelerometers, and GIS unit. We will then examine associations between environmental exposures and biological measures, psychosocial factors, PA or sedentary behavior, and dietary intake.

Measures

Outcomes

Participants will visit the NIH Clinical Center for 18-FDG PET/CT to measure stress-related neural activity. In brief, we will assess amygdala uptake as published [19,53]. Immune activation testing from collected blood will be performed within the NIH Clinical Center.

Two measures of vascular inflammation and function will be used (Table 2). First, the target-to-background ratio for aortic vascular inflammation will be measured through the whole body FDG PET/CT to examine amygdala activity [54]. Second, the pulse wave velocity and augmentation index as a measure of large-vessel vascular function will be determined by the Sphygmocor system (AtCor Medical), a noninvasive tool [55]. The noninvasive measure of vascular function has been validated and used widely.

Table 2. Biological measures, physical activity, residential and GPS activity space, and ecological momentary assessment measures.

Measures	Description
Outcomes	
Stress-related neural activity	• Amygdala activity (18F-FDG[a] PET/CT[b])
Vascular inflammation and function testing	• Vascular inflammation: arterial Inflammation (18F-FDG PET/CT) • Vascular function: pulse wave velocity and augmentation index (Sphygmocor)
Immune system activation	• Flow cytometry-based characterization of immune cell populations and their receptor expression profile (two flow cytometry panels) [56]: (1) CD3, CD14, CD15, CD16, CD19, CD42b, CD45, CD56, CD203c, and CD193 and (2) CD3, CD14, CD16, CD56, CD98 heavy chain, CD64, CCR2[c], CCR5, and TLR2[d]
Immune cell function	• Natural killer cell function profiling by detecting degranulation and cytolytic activity [57,58] • Monocyte function profiling [59], including ability of monocytes to perform chemotaxis and migration, as well as determination of inflammasome activity
Biomarker-based immune system activation	• Cytokine and chemokine profiling [60] eg, TNF-α[e], IL-6f, IL-10, IL-8, IL-1β, IFN-α[g], IFN-γ, MCP-1[h], VEGF-A[i], IL-RA[j], IL-18, TGF-β[k] • Stress-induced neurotransmitter profiling, including epinephrine, norepinephrine, dopamine, and cortisol [61]
Exposures	
Residential and GPS activity space (model: BT-Q1000XT)	• Neighborhood Deprivation Index [62,63] based on US census [62], social disorder based on virtual neighborhood audits [41,64], crime rate around GPS activity space based on police crime report [65], and modified retail food environment index. All measures will be created based on GPS activity space [66] • Count and density of parks, gyms, and recreation facilities [67] around GPS activity space
Moderators	
PA[l] via accelerometer or survey	• A minute-by-minute PA (A[m]), daily mean moderate-to-vigorous PA minutes (A), total PA minutes (A), active transportation PA, and leisure-time PA minutes [46] (S[n])
Psychosocial factors via ecological momentary assessment	• Perceived neighborhood social environment [68,69]; mood states [70], perceived stress [49], and daily hassles [71]

[a]FDG: fluorodeoxyglucose.

[b]PET/CT: positron emission tomography-computed tomography.

[c]CCR2: C-C chemokine receptor type 2.

[d]TLR2: toll like receptor 2.

[e]TNF-α: tumor necrosis factor α

[f]IL-6: interleukin-6.

[g]IFN-α: interferon-α.

[h]MCP-1: monocyte chemoattractant protein-1.

[i]VEGF-A: vascular endothelia growth factor-A.

[j]IL-RA: receptor antagonist.

[k]TGF-β: transforming growth factor β.

[l]PA: physical activity.

[m]A: assessed by accelerometer.

[n]S: assessed by survey.

The outcomes for immune cell activation studies will be the proportion of each detected immune cell, their receptor expression, and platelet adhesion (eg, proportion of classical clusters of differentiation, such as CD14+CD16- monocytes of all monocytes, or proportion of natural killer cells of all CD45+ cells; Table 2). Immune cell function for purified and isolated monocytes and natural killer cells will also be determined for each participant. For instance, the ability of monocytes to perform chemotaxis, migrate toward the monocyte chemoattractant protein-1 gradient, will be determined based on a chemotaxis coefficient, as well as the activity of the inflammasome by measurement of interleukin (IL)-1β and IL-18 release by enzyme-linked immunosorbent assay upon appropriate stimulation. In biomarker profiling, plasma or serum levels of the proposed cytokines, chemokines, and stress-related

neurotransmitters, and hormones will be measured as concentrations in pg/mL.

Exposures

Two distinct types of neighborhood exposures will be created (Table 2): (1) residential neighborhood variables around participants' homes [25-27] and (2) GPS activity space (ie, places where participants travel throughout the day) [25-27]. Each type of measure will be linked to accelerometer data with respective time and measured intensity of PA levels (Figure 2; Table 2). Both residential and GPS activity space measures will include neighborhood poverty (eg, neighborhood deprivation index from US census [62,63]), physical disorder (by virtual neighborhood audits [41,64]), police-reported crime (from DC databases [65,72]), and the modified retail food environment index (defined as the ratio of healthy to unhealthy food stores) [73]. In addition, parks, gyms, and recreation facilities will be used to create the count and density of these PA facilities to better understand how participants engage in PA [67]. As a measure of feasibility and practicality, we used 11 participants from a protocol (ClinicalTrials.gov identifier NCT03288207) to create residential buffers around participants' homes (ie, circular [25-27] and line-based road network buffers; Figure 3 [74]) and GPS activity space buffers based on SD ellipses [66,75] (Figure 4) and individuals' daily paths (Figure 5) [66]. Figures 2-5 were based on hypothetical data to show each different buffer and buffer type (actual study participant data are not shown). Some points occurring around residential areas will be weighted.

Figure 2. Minute-by-minute accelerometer data linked to GPS coordinates. Note: each point represents a minute of physical activity, ranging from sedentary to vigorous intensity levels.

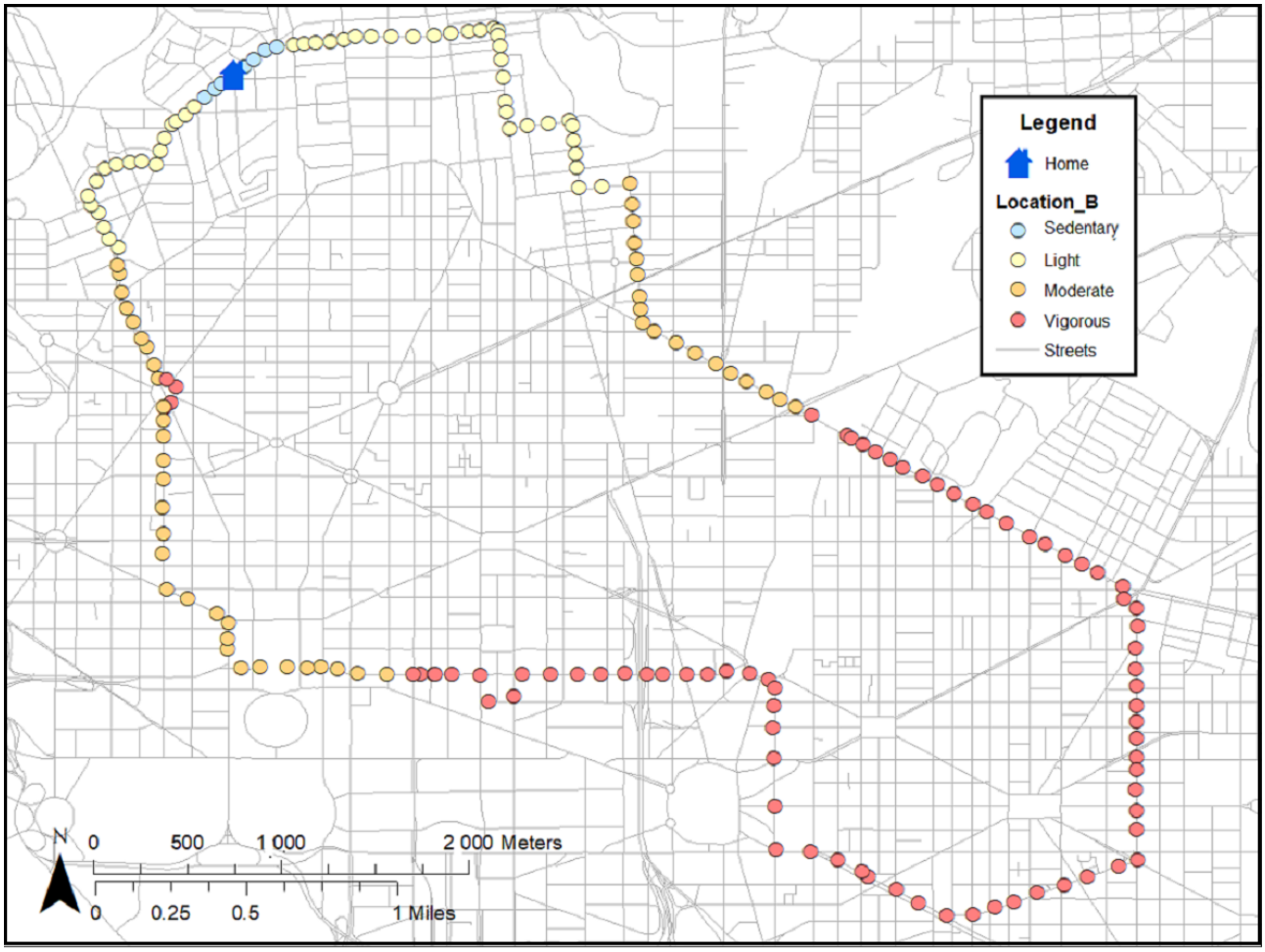


Figure 3. Residential buffers around participants' home based on circular and line-based road network buffers.

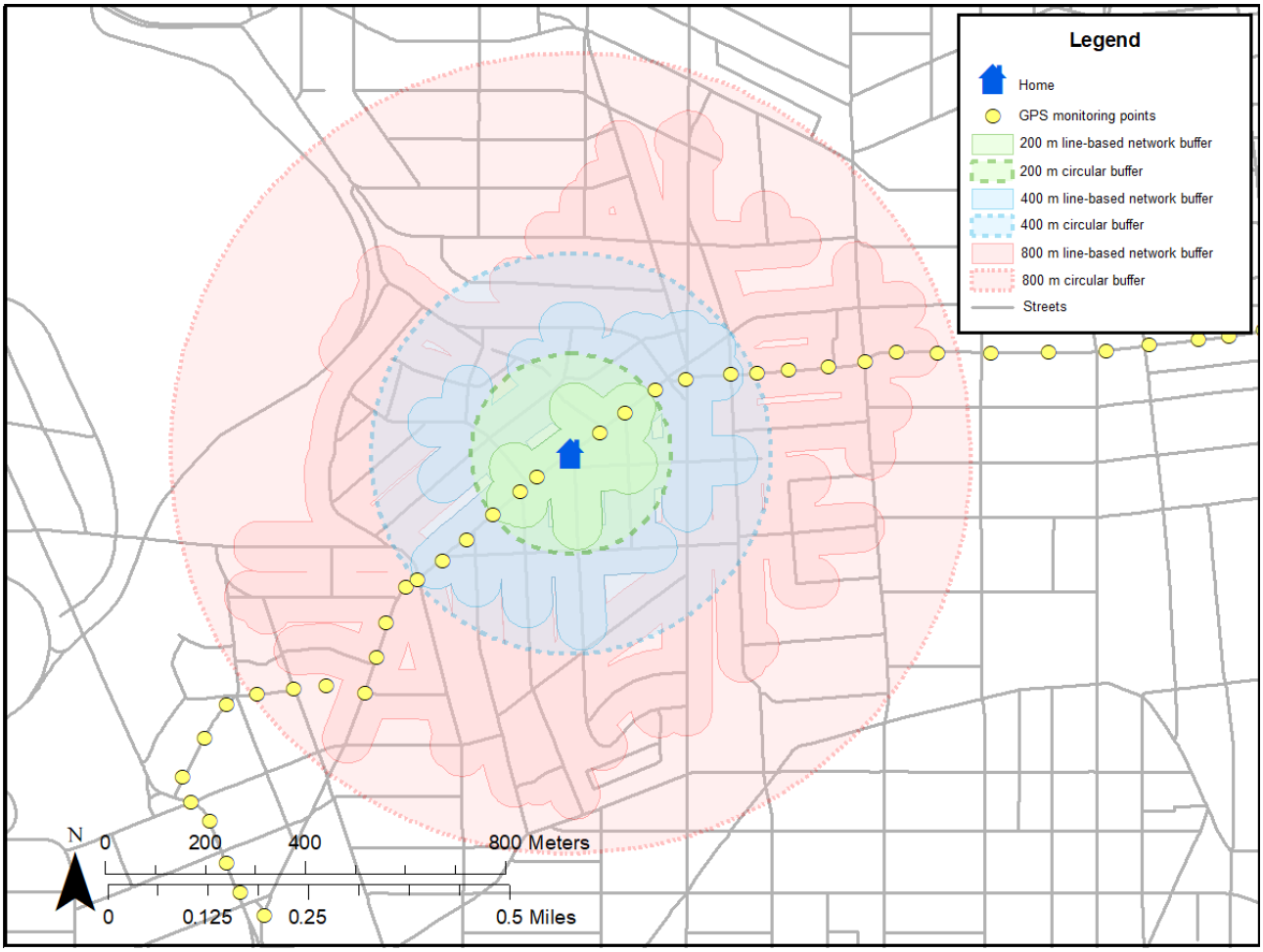


Figure 4. GPS activity space buffers based on SD ellipses.

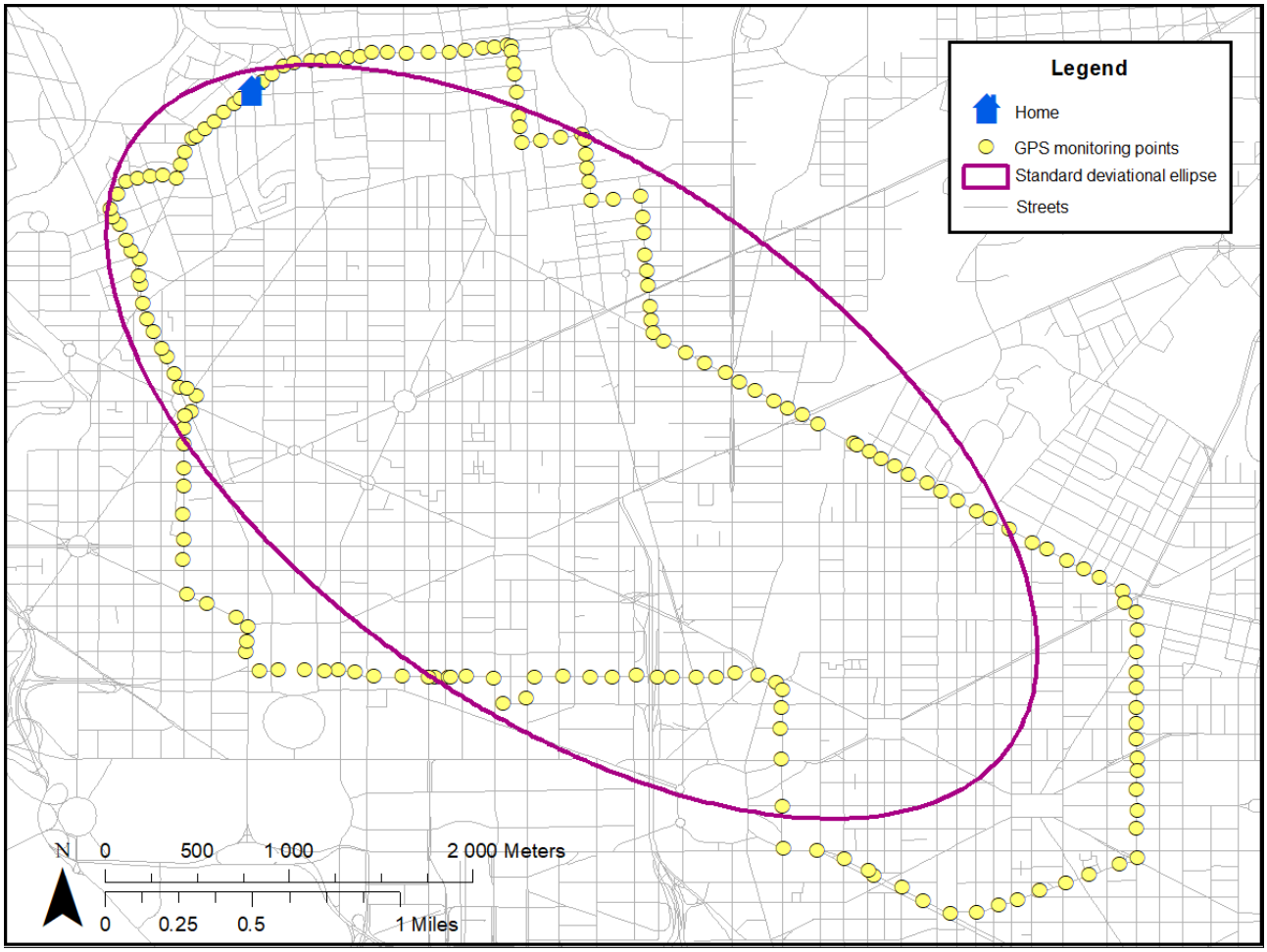
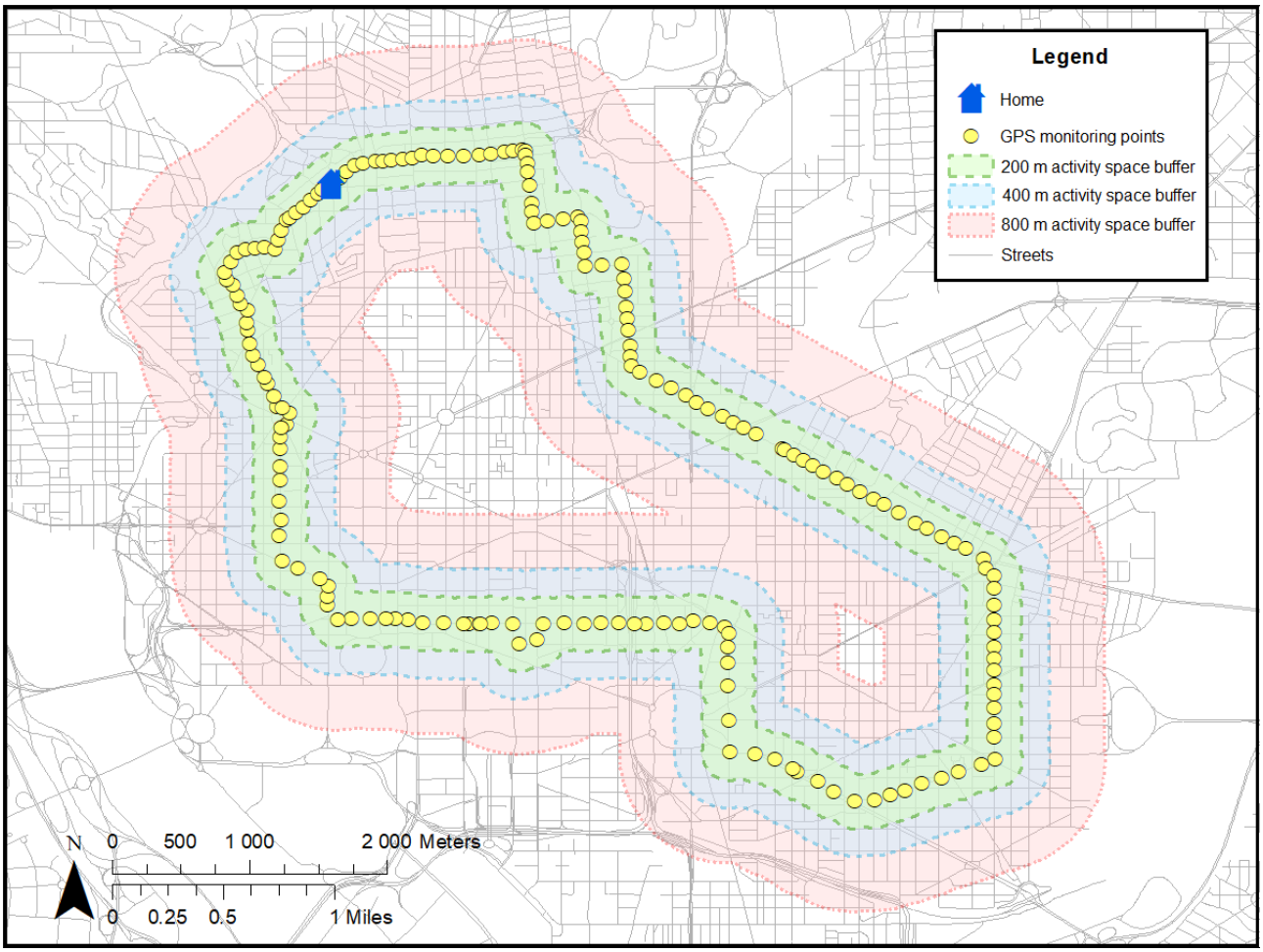


Figure 5. GPS activity space buffers based on individuals' daily paths.



In Table 3, real-time EMA measures will include perceived neighborhood social environment (eg, violence and safety), mood states (positive or negative affect [70]), perceived stress (eg, stressed and irritated [49]), and daily hassles (eg, work load [71]) with three random prompts within defined timeframes (7-9 AM, 11 AM-1 PM, and 5-7 PM) throughout the day (Table 3; Figure 6) [36]. Participants will initiate their own EMA recording when they start engaging in a certain activity (ie, event contingency; Table 3; Figure 6) [68,69]. The event contingency approach is based on a self-initiated response to behaviors and contexts. Participants will be instructed on how to initiate the EMA recording and respond to a certain activity and when to initiate their EMA recording. For example, when participants commute to work by car, they initiate it by themselves and record their mode of activity in the smartphone app. EMA measures will be merged with GPS activity space measures with the respective timestamps. Before the full pilot study, we tested GPS units and EMA using a smartphone app (ilumivu, Inc) to identify any potential barriers to use.

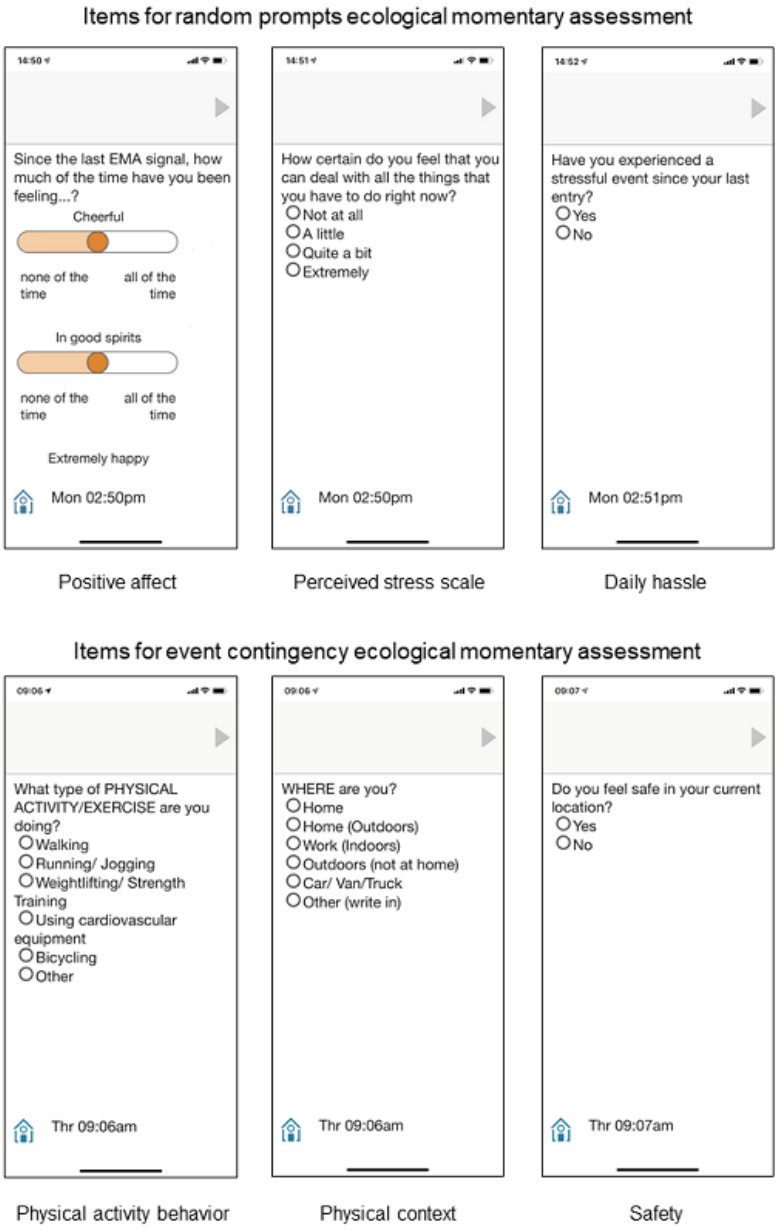
Table 3. Random prompts and event contingency items for ecological momentary assessment.

Variable	Item	Response options
Items for random prompts		
Positive and negative affect [70]	"Since the last EMA[a] signal, how much of the time did you feel...?" • Cheerful • In good spirits • Extremely happy • Calm and peaceful • Satisfied • Full of life • So sad • Nervous • Restless or fidgety • Hopeless • Worthless • Everything was an effort	• Very slightly or not at all • A little • Moderately • Quite a bit • Extremely
Perceived stress scale [49]	"How certain do you feel that you can deal with all the things that you have to do right now?"	• Not at all • A little • Quite a bit • Extremely
Perceived stress scale [49]	"How confident do you feel about your ability to handle all of the demands on you right now?"	• Not at all • A little • Quite a bit • Extremely
Daily hassles [71]	"Have you experienced a stressful event since your last entry?"	• Yes or no
Daily hassles [71]	"Have you experienced a stressful or problematic social interaction since last entry?"	• Yes or no
Items for event contingency [68,69]		
Physical activity behavior	"What type of physical activity/exercise are you doing?"	• Walking • Running or jogging • Weightlifting or strength training • Using cardiovascular equipment • Bicycling • Other (write in)
Physical context	"WHERE are you?"	• Home (indoors) • Home (outdoor) • Work (indoor) • Outdoors (not at home) • Car, van, or truck • Other (write in)
Physical context	"WHERE are you AT HOME?" (Indoors)	• Bedroom • Family or living room • Kitchen • Garage • Other (write in)
Physical context	"WHERE are you AT HOME?" (Outdoors)	• Pool • Deck, patio, or balcony • Yard • Driveway • Other (write in)
Physical context	"Where are you OUTDOORS?" (Outdoors not at home)	• Park or trail • Road • Sidewalk • Parking lot • Other (write in)

Variable	Item	Response options
Vegetation	"How many TREES AND PLANTS are there in the area where you are right now?"	• No trees or plants • A few trees and plants • Some trees and plants • A lot of trees and plants
Traffic	"How much TRAFFIC is on the closest street to where you are right now?"	• No traffic • A little traffic • Some traffic • A lot of traffic
Litter	"How much LITTER or GARBAGE is on the ground where you are right now?"	• No litter • A little litter • Some litter • A lot of litter
Safety	"Do you feel safe in your current location?"	• Yes or no
Safety	"Is violence a problem in your current location?"	• Yes or no

[a]EMA: ecological momentary assessment.

Figure 6. Selected random prompts ecological momentary assessment and event contingency ecological momentary assessment. EMA: ecological momentary assessment.



Merging Multiple Data

Complete master data will be created based on multiple data sources, including PA via accelerometers (ie, 1-minute epochs), GPS units (1-minute epochs), and EMA via a smartphone app (3 times/day). First, each recording of the GPS points will be linked to the respective time-stamped accelerometer data for each minute. Then, EMA data (three times through morning, afternoon, and evening assessments) will be linked to the corresponding GPS and accelerometer data. The complete data will then be collapsed by hours, time of day (morning, afternoon, and evening), and days.

Statistical Analysis

To test aim 1 hypothesis, we will first test the differences in stress-related neural activity by Wards 3 and 5. Subsequently, we will examine associations between each neighborhood social environment variable based on residential and GPS-derived measures as well as EMA measures separately and stress-related neural activity, adjusting for all covariates. Covariates will include sociodemographic variables (eg, age, race [White or Black adults], and individual-level income) and health-related variables (eg, PA). Each model will be assessed based on the value of the Akaike information criterion (AIC) to select the most parsimonious model. Third (sub-aim 1), after determining a statistically significant neighborhood exposure variable, we will test for an interaction between the specific neighborhood exposure variable and objectively measured PA and psychosocial factors (a potential moderator). If the interaction term is significant, we will stratify the association by high or low objectively measured PA based on the mean and by high or low psychosocial factors (eg, perceived stress scale scores) based on the mean.

To test aim 2 hypothesis, we will first test the differences in the measures of vascular inflammation and function (Table 2) by Wards 3 and 5. Second, we will examine associations between each neighborhood social environment variable based on residential and GPS-derived measures as well as EMA separately and each vascular measure, adjusting for all covariates. The same covariates will be used as in aim 1. Each model will be assessed based on the value of the AIC to select the best-fit model. Third (sub-aim 2), after we identify a statistically significant exposure variable, we will test for an interaction between the specific exposure variable and objectively measured PA and psychosocial factors. If the interaction term is significant, we will then stratify the association by high or low objectively measured PA based on the mean and by high or low psychosocial factors (eg, perceived stress scale scores) based on the mean.

To test aim 3 hypothesis, we will first test the differences in immune cell activation, immune cell function, and biomarker-based immune activation (Table 2) by Wards 3 and 5. Second, we will examine associations between each neighborhood social environment variable based on residential and GPS-derived measures as well as EMA separately and the measures of immune system activation, adjusting for all covariates. The covariates are described in aim 1. Each generalized linear mixed model will be assessed based on the value of the AIC to select the best-fit model.

Sample Size Calculation

This pilot study (n=30 in each of the two groups) will examine the differences in biological measures to perform power calculations for a larger study. This will also serve as a feasibility study to determine the feasibility of applying GPS, GIS, and EMA for a larger sample of adults. A sample size of 30 per group allows for estimation of the SD of the amygdala FDG in each group, with an upper bound on the SD 20% larger than the estimate, based on the normal distribution large sample 90% upper confidence bound of:

where  is the 10% quantile of the chi-squared distribution with n−1 degrees of freedom and s is the SD estimate. We plan to recruit approximately 90 participants, assuming that approximately 20% of participants will be lost to follow-up during the study.

Plans for Data Management

The NHLBI IRB has approved this protocol. The data with patient identifiers will be securely stored in the eHealth and data management systems at the NIH, which are protected by passwords and data encryption. These data will be shared only with approved members of the research team. The entire data set for the participants included the clinical information, GPS or accelerometer data, data through the EMA mobile app, and survey data.

A Food and Drug Administration–approved biospecimen tracking inventory system will be used to securely store all collected biological specimens at the NIH. The NIH IRB will review and approve any future testing of undefined biospecimens in the protocol before any data collection. The participants are allowed to refuse future use.

This research is scheduled to begin in 2021, with plans for completion by 2023. However, because of the COVID-19 pandemic, it may be delayed depending on the current pandemic situation. Participants who receive unintended consequences from study participation will be treated according to best practices under the NIH Clinical Center. This study is low risk; thus, it does not require a data monitoring committee. The principal investigator will monitor accrual and safety data. The protocol will be reviewed and monitored annually by the IRB and the NHLBI Office of the Clinical Director's Protocol Audit Team, along with any amendments requiring IRB approval. The results and conclusions of this research will be disseminated to community members through DC-CHOC meetings and a quarterly newsletter as well as at national and international conferences and in peer-reviewed publications.

Results

Feasibility of GPS Use

We tested the feasibility of using a GPS device and an EMA app with 11 participants from a PA-related study among African American women (ClinicalTrials.gov identifier NCT03288207). The mean age of the women was 56 years, and most of the participants had at least a high school education (Table 4). The majority of participants had a total household income of US $60,000-89,999; were employed part-time; and resided in Prince George's County, Maryland.

Table 4. Sociodemographic characteristics of participants (N=11).

Participant characteristics	Values
Age (years), mean (SD)	56.3 (12.3)
Gender (female), n (%)	11 (100)
Race, n (%)	
Black or African American	11 (100)
Education, n (%)	
College degree	4 (36)
Graduate or professional school degree	3 (27)
Some college degree	2 (18)
High school diploma or Tests of General Education Development	1 (9)
Some graduate or professional school	1 (9)
Total household income (US $), n (%)	
20,000-59,000	3 (27)
60,000-89,999	5 (46)
90,000-99,999	0 (0)
≥100,000	3 (27)
Employment status, n (%)	
Yes, full-time	3 (9)
Yes, part-time	4 (12)
No, retired	3 (9)
Other	1 (3)
Participant's residence (county, Maryland or Ward, Washington, DC), n (%)	
Prince George's County	6 (54)
Ward 5	3 (27)
Ward 7	2 (18)

Mean areas varied by the size of the buffers (200 m, 400 m, and 800 m) and types of buffers based on residential (circular and line-based road network buffers) and GPS activity space (Table 5). As expected, the areas for a line-based road network buffer were smaller than that for a circular buffer. Areas for residential buffers (circular and network buffers) were also smaller than the GPS activity space areas. We plan to explore different sizes and types of buffers.

Table 5. Mean areas for participants' residential (circular and network) and GPS activity space buffers (N=11).

Type of buffer	Size (km^2), mean (SD)		
	200 m	400 m	800 m
Circular buffer	0.13 (0)	0.50 (0)	2.01 (0)
Network buffer[a]	0.05 (0.02)	0.17 (0.08)	0.64 (0.33)
GPS activity space	20.48 (8.09)	53.32 (20.77)	123.02 (46.72)

[a]On the basis of a line-based road network buffer around the residence of a participant.

Protocol Approval

Full support for this study has been received from the NIH IRB (ClinicalTrial.gov identifier NCT04014348).

Discussion

Principal Findings

This pilot study would contribute significantly to scholarship regarding the association between neighborhood social environment (eg, poverty and crime) and stress-related neural activity, a measure of chronic stress–related neural activity.

This is important because there is limited research on this topic. This study is also novel because the relationships between neighborhood social environment conditions, detailed immune markers linked to physiological stress–related neural activity response, and vascular function are extremely understudied.

Lessons Learned From Feasibility of GPS Use

When 11 participants from our study (ClinicalTrials.gov identifier NCT03288207) returned the GPS units to research staff members, GPS tracking was generally accepted. Pilot device testing revealed several concerns that will be addressed in this study. For instance, participants mentioned that they often forgot to charge the GPS device each night, as required by their limited battery life. They also sometimes forgot to bring the GPS with them when they left the house each morning.

For the overall study, we plan to address these device issues using the EMA app. The morning EMA prompt will include a message reminding participants to bring all of their devices, and the evening prompt will include a message reminding participants to charge their GPS units. These messages will hopefully curtail user errors and increase device compliance.

Strengths, Limitations, and Expectations

Strengths

One strength of this study is that it focuses on both healthy White and African American adult women who reside in high- and low-SES neighborhoods in Washington, DC This study accounts for biological phenotyping based on age, race, and BMI to elucidate the differences in biomarkers of amygdala activity in relation to differential exposure to neighborhood social environment and PA. Furthermore, this pilot study may be one of the first to use three distinct geospatial wearable and activity monitoring devices for real-time assessment of environmental exposures via GPS, activity levels through accelerometers, and perceptions by the EMA smartphone app, followed by linkage to biomarkers of stress (ie, amygdala activity).

Limitations

This study had several limitations that need to be addressed. We may have some difficulties in recruiting African Americans residing in Ward 3, as the number of African American women living in Ward 3 is lower than that in Ward 5 in Washington, DC. However, our research group has strong relationships with organizations throughout Washington, DC, which will allow us to help with recruitment efforts in Ward 3. Furthermore, we will closely work with the recruitment liaison at the NHLBI at the NIH to resolve this issue. We should be able to recruit both White and African American female participants from Ward 5 from low-SES (household income of US $50,000-74,999 [about 15% of total residents in Ward 5]) to high-SES neighborhoods (household income of US $100,000-149,999 [about 15% of total residents in Ward 5]). In addition, this study has a cross-sectional design, thus limiting causal inference. Another limitation is that this study has a relatively small sample size (approximately 60 women) to assess differences in vascular function and immune cell activation based on exposure to adverse neighborhood social environment in Washington, DC. Note that the intent of this study is to establish feasibility and sample size needs for a larger study. We will also compare the extremes of neighborhood social factors to see if there are differences in vascular measures (eg, 5% highest poverty vs 5% lowest poverty) and assess racial differences in vascular inflammation and function within each ward. Finally, our analyses are at the person level, which do not intend to elucidate the within-day variability of PA and psychosocial factors in relation to biomarkers of stress. For a larger study, we plan to investigate the associations between within-day variability and outcomes.

Expectations

We anticipate that aim 1 will improve our current knowledge of the links between adverse neighborhood social environment features (eg, physical disorder) and stress-related neural activity (ie, amygdala activity), based on our prior experience demonstrating differences in amygdala activity between the DC-CHNA cohort and age- or sex-matched healthy volunteers [53]. Throughout this pilot study, we will disseminate the findings to the DC-CHOC members to gather input on the relevance of study findings to city practitioners and policy makers. These data will provide new insights into the role of the neighborhood social environment as a source of chronic psychosocial stress that can impact CV health.

In aim 2, we will be able to compare differences in vascular function between participants from Ward 3 (high-SES neighborhood) and Ward 5 (low-SES neighborhood). In addition, we will test the moderation effects of objectively measured PA using accelerometers because it is well known that PA influences vascular structure and function [76]. We expect that those living in adverse neighborhood social environments may have worse vascular function, which can be moderated by levels of PA. Those engaging in higher PA may have better vascular function, even if they reside in adverse neighborhood social environments.

In aim 3, we will be able to compare differences in immune activation between populations from two distinct neighborhood conditions (Wards 3 vs 5). We will also determine precise neighborhood social environment exposures within one's residential and GPS activity spaces that relate to immune system activation, while adjusting for objective PA levels. On the basis of our previous data showing differences in inflammatory biomarkers between the DC-CHNA cohort and healthy volunteers [20], we expect that aim 3 will also be hypothesis-generating and will identify potential pathways involved in immune cell activation and function along the neural-hematopoietic-inflammatory axis, influenced by adverse environmental conditions.

Conclusions

This pilot study will contribute to limited research on biomarkers of stress in relation to neighborhood social environment by applying geospatial methods and wearable devices, such as GPS, EMA, and accelerometers, to elucidate the mechanism by which adverse neighborhood social environment conditions impact the differences in stress-related neural activity by high and low SES in Washington, DC. If this pilot study can lead to

an explicit understanding of biomarkers of stress, we may expand this study to other at-risk large populations in other areas of the Washington, DC, metropolitan area.

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Authors' Contributions

KT and TMPW made substantial contributions to the conceptualization of the work. KT drafted the initial manuscript. KC and SJN created the tables and figures. All authors (KT, KC, SJN, NPV, VMM, BSC, CGH, JFT, YB, FOB, BST, VG, BAT, EOC, DB, NNM, VV, SNZ, and TMPW) provided feedback on the study design and editorial revisions of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AIC: Akaike information criterion
CVD: cardiovascular disease
DC-CHNA: DC CV Health and Needs Assessment
DC-CHOC: DC Cardiovascular Health and Obesity Collaborative
EMA: ecological momentary assessment
FDG: fluorodeoxyglucose
GIS: geographic information system
IL: interleukin
IRB: Institutional Review Board
NHLBI: National Heart, Lung, and Blood Institute
NIH: National Institutes of Health
PA: physical activity
PET/CT: positron emission tomography-computed tomography
SES: socioeconomic status

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Protocol

Assessment of Preparedness for Remote Teaching and Learning to Transform Health Professions Education in Sub-Saharan Africa in Response to the COVID-19 Pandemic: Protocol for a Mixed Methods Study With a Case Study Approach

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Abstract

Background: The current COVID-19 pandemic is affecting all aspects of society worldwide. To combat the pandemic, measures such as face mask–wearing, hand-washing and -sanitizing, movement restrictions, and social distancing have been introduced. These measures have significantly disrupted education, particularly health professions education, which depends on student-patient contact for the development of clinical competence. The wide-ranging consequences of the pandemic are immense, and health professions education institutions in sub-Saharan Africa have not been spared.

Objective: This paper describes a protocol for assessing the preparedness of selected health professions education institutions in sub-Saharan Africa for remote teaching and learning during the COVID-19 pandemic.

Methods: A mixed-methods design with a case study approach will be used. The awareness, desire, knowledge, ability, and reinforcement model of change was selected as the conceptual framework to guide the study. Eight higher education institutions in 6 sub-Saharan countries have participated in this study. Data will be collected through electronic surveys from among whole populations of academic staff, students, and administrators in undergraduate medicine and nursing programs. Qualitative and quantitative data from each institution will be analyzed as a case study, which will yield an inventory of similar cases grouped

for comparison. Quantitative data will be analyzed for each institution and then compared to determine associations among variables and differences among programs, institutions, or countries.

Results: Our findings will provide information to higher education institutions, particularly those offering health professions education programs, in Africa regarding the preparedness for remote teaching and learning to influence efforts related to web-based teaching and learning, which is envisaged to become the new normal in the future.

Conclusions: This study has not received any funding, and any costs involved were borne by individual consortium members at the various institutions. Ethics approval from the institutional review board was obtained at various times across the participating sites, which were free to commence data collection as soon as approval was obtained. Data collection was scheduled to begin on October 1, 2020, and end on February 28, 2021. As of this submission, data collection has been completed, and a total of 1099 participants have been enrolled. Data analysis has not yet commenced.

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KEYWORDS

Africa; COVID-19; emergency remote teaching; formal online learning; pandemic

Introduction

Background

The World Health Organization declared COVID-19 a pandemic on March 11, 2020, and countries had to adopt containment and mitigation measures such as restrictions on movement of persons and human congregation [1,2]. Consequently, many educational events that required people to congregate were put on hold or canceled, and the governments of many African countries decided to close educational institutions in an effort to contain the disease outbreak. Health professions education was no exception to these drastic measures, and planned teaching and learning activities have been almost totally disrupted. For most institutions in Africa, COVID-19–related restrictions were too rapid to institute any well-planned contingency measures to ensure the continuity of teaching and learning activities. Many students experienced complete stoppage of planned teaching and learning activities for unknown timespans. Students and teachers were physically isolated and disconnected from the mainstream university setting, where face-to-face instruction was the dominant approach to teaching and learning. The COVID-19 pandemic arguably exposed the unpreparedness of many higher education institutions (HEIs) in Africa to alternative teaching and learning approaches [3].

Consequent to the COVID-19 pandemic, many HEIs adopted emergency remote teaching and web-based learning by using a blended approach with reduced physical presence of students and educators on campus [4]. For educators to continue engaging with their students even during the pandemic, creative approaches such as “emergency remote teaching” (ERT) or “formal online learning” (FOL) needed to be adopted for continued teaching and learning. ERT is described as a short-term solution aimed at providing temporary access to instruction in a manner that is rapid to set up and reliable during an emergency crisis such as the COVID-19 pandemic, while FOL is a formal system of web-based learning, which is well-established and takes months to prepare [5]. While suggestions for FOL have taken on an increased impetus, they are not new. The World Health Organization, in its recent publication [6], recommended FOL as a tool for interprofessional education, particularly if it is delivered in an open-access environment [6].

Remote teaching and learning, however, are not without their challenges even in high-income countries. A McKinsey and Company report [7] in May 2020 noted that in the United States, students’ ability to succeed in a remote learning environment was affected by differences in household income; less than half (40%) of students from low-income households reported being able to access the necessary equipment for remote learning compared to 72% of students from high-income households, while only 56% of students from low-income households reported having reliable internet access and only 45% reported that their home environment supported remote learning, compared to 77% and 64% of students from high-income households, respectively [7]. This pattern is unlikely to be different or even worse for students in most HEIs in Africa, where additional issues such as power supply, internet connectivity, sociocultural dynamics such as gender roles, educators’ and leaners’ competence related to remote teaching, and security may be of concern [8,9].

Literature on how HEIs, particularly those offering health professions education programs, have adopted FOL and ERT and remote learning during the COVID-19 pandemic is fast emerging. However, most of this literature is emerging from high-income countries that have better resources and different socioeconomic contexts from those of African countries. Experiences with FOL and ERT in resource-poor countries, including those in sub-Saharan Africa, have been less documented, even though students have somehow continued to engage in the learning process [10,11]. Although HEIs in Africa continue to struggle to fully embrace FOL [8,9], there have perhaps been efforts implemented to utilize platforms that are currently available to most students and teachers to ensure that learning material, assessments, and feedback reach the intended audience. One such effort may be the use of ERT as a foundation to the development of comprehensive web-based learning in the long term and it being considered the “new normal.” However, a question arises, which will guide this study: what progress has been made by HEIs in sub-Saharan Africa to

transition to ERT or FOL within the current situation resulting from the COVID-19 pandemic?

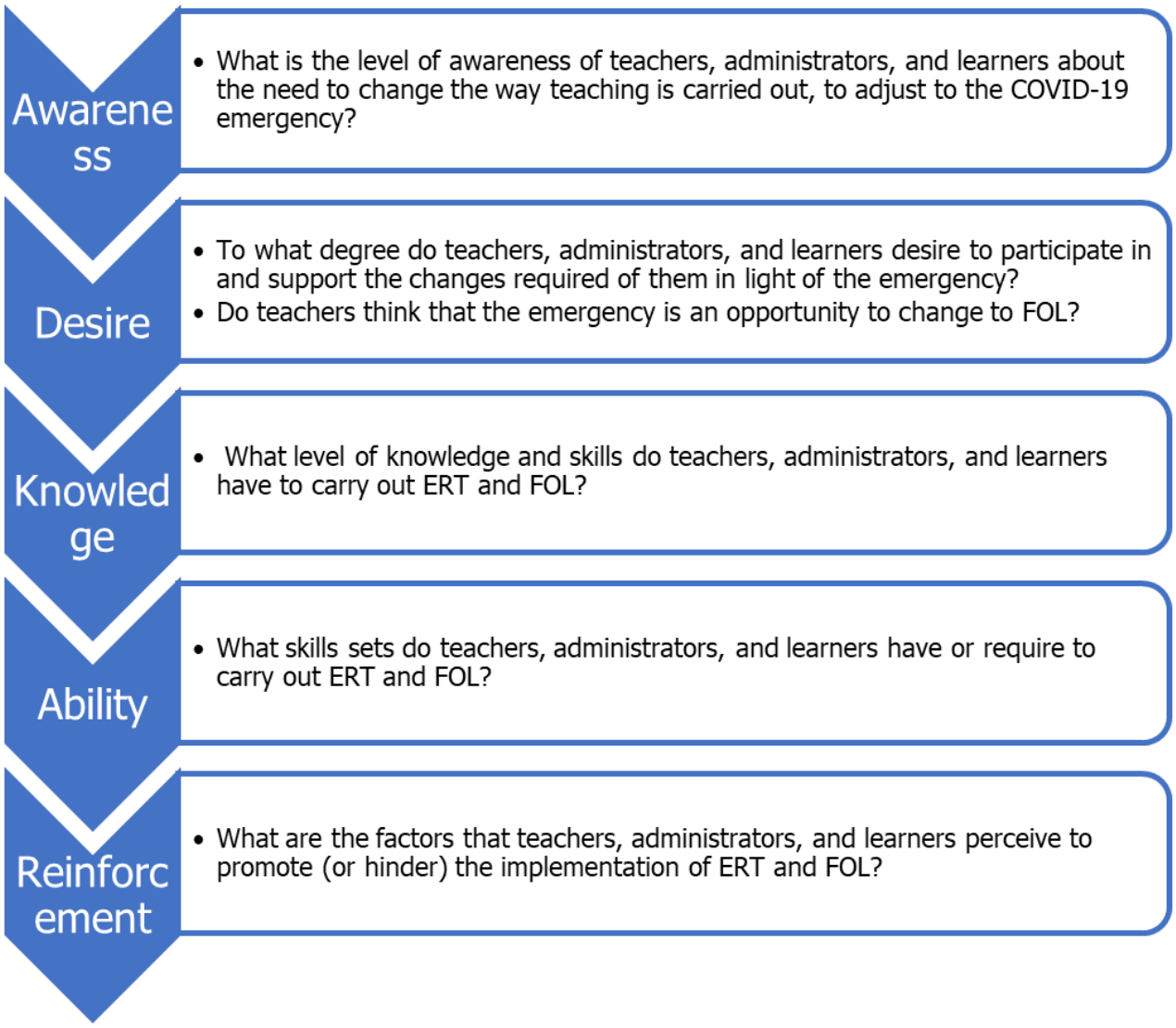
The need to respond to the effects of the COVID-19 pandemic urgently may imply that institutions adopt web-based learning approaches, and that ERT presents an opportunity for web-based learning even in circumstances of limited internet connectivity [5]. We argue that ERT and remote learning is a possible foundation for future formal web-based teaching and learning strategies in most HEIs in Africa, and insights obtained from our experience with this approach in sub-Saharan Africa could influence the adoption of appropriate web-based teaching and learning models throughout Africa.

This study aims to describe the preparedness of selected health professions educational institutions in sub-Saharan Africa for remote teaching and learning during the COVID-19 pandemic. This paper describes a research protocol that was designed by a consortium of health professions education researchers from 8 HEIs in 6 sub-Saharan African countries.

Conceptual Framework and Research Questions

The awareness, desire, knowledge, ability, and reinforcement (ADKAR) model of change was selected as the conceptual framework underpinning the study [12,13]. The ADKAR model focuses on change that is driven by the needs of the individual, whereby an evaluation is performed for the following attributes: awareness of the need for change, desire to participate in and support the change, knowledge necessary for change, ability or skills available or required to implement the change, and reinforcement to sustain the change. The use of this model will reveal factors that are critical for the success of FOL and remote teaching [14-16]. Figure 1 illustrates the ADKAR model that was used to generate the research questions to be answered in this study.

Figure 1. The conceptual framework of the study based on the awareness, desire, knowledge, ability, and reinforcement model [11]. ERT: emergency remote teaching, FOL: formal online learning.



Methods

Ethical Considerations

Relevant safeguards required in studies involving human participants, as outlined in the Belmont report of 1979 and the International Conference on Harmonization (ICH) of 2002, will be applied as the overarching ethics framework for this study [17,18].

Ethics approval was obtained from the institutional review board at various timepoints across the participating sites, which were free to commence data collection as soon as ethics approval was obtained. Data collection was scheduled to begin on October 1, 2020, and end on February 28, 2021. As of this submission, data collection was concluded, and a total of 1099 participants were enrolled. Data analysis had not yet commenced.

Study Design

The study will use a concurrent mixed-methods design. The ADKAR organizational change model will guide the approach to data collection, analysis, and reporting [13,14]. Data will be collected for 2 purposes: first, to construct case studies from each institution, which will provide an in-depth multifaceted insight into the preparedness of selected health professions education institutions in sub-Saharan Africa for remote teaching and learning during the COVID-19 pandemic and how they plan to conduct their training in the future [19]; and second, to compare quantitative data statistically by analyzing associations among variables and differences among programs, institutions, and countries.

Study Setting

The study will be conducted at 8 health professions training institutions in 6 sub-Saharan African countries: University of Botswana, Botswana; University of Namibia, Namibia; University of the Free State, South Africa; Makerere University, Uganda; University of Zambia and Cavendish University, Zambia; and University of Zimbabwe and the National University of Science and Technology, Zimbabwe.

Study Population and Sampling

The study population (Table 1) will consist of administrators, educators, and students from the medicine and nursing programs at the selected HEIs. For the total study population, purposive sampling will be used, which will target all the students, educators, and administrators at the aforementioned 8 HEIs. At each of the selected HEIs, whole populations of administrators and educators of undergraduate medical and nursing students before and during the COVID-19 pandemic will be invited to participate in the study. Whole populations of undergraduate medicine and nursing students will also be invited to participate in the study (N=9095).

Table 1. Study population.

Group	Medicine	Nursing	Total
Administrators, n	134	41	175
Educators, n	690	238	928
Students, n	4866	3126	7992
Total, n	5690	3405	9095

Data Collection

Data will be collected using questionnaires with structured and semistructured elements (Multimedia Appendix 1). Instruments will be pretested by excluding 1 person in each sampled program from the sampled study population. This will assist in instrument validation. The questionnaires will be sent via the most practical route to all sampled participants. All data will be entered into an electronic database.

Data Analysis and Presentation

Data analysis will be undertaken in stages. For each program, quantitative data will be summarized using a frequency distribution and averages, and qualitative data using thematic analysis.

In the first stage, a case study will be constructed for each of the 8 HEIs represented and will be presented discursively in paragraphs. Numbers will be used to indicate the strength of statements, and quotes shall be used to emphasize common issues. The case study framework will be based on the ADKAR model (Multimedia Appendix 1).

In the second stage, programs will be grouped in accordance with the extent to which they have planned for and implemented ERT and FOL. This will facilitate comparisons among categories of cases. Each institution will have the liberty to perform subgroup analysis based on data obtained from the institution.

In the third stage, quantitative data on each of the 5 ADKAR elements will be analyzed statistically to determine differences and associations among the programs. This will strengthen the understanding of the preparedness of selected health professions education institutions in sub-Saharan Africa for remote teaching and learning during the COVID-19 pandemic.

Results

We hope to obtain detailed information regarding the ADKAR elements among the administrators, faculty, and students for remote teaching and learning during the COVID-19 pandemic at selected health professions education institutions in sub-Saharan Africa. This will be achieved in the form of case studies that will provide a detailed insight in to each program, institution, or country. Comparisons will be made, highlighting similarities, differences, and associations among the various ADKAR elements to further enhance our understanding of the level of preparedness by the various programs, institutions, or countries.

Discussion

Principal Findings

We propose to write a comprehensive report, which will be shared with program leaders at the various participating institutions. We hope that our findings provide information to HEIs, particularly those offering health professions educational programs, in Africa regarding their preparedness for remote teaching and learning. We believe that our findings will influence efforts related to web-based teaching and learning, which is envisaged to become the "new normal" in the future. We shall develop papers intended for submission to peer-reviewed journals to share our findings with a wider audience.

As of this submission, data collection was concluded, and a total of 1099 participants have been enrolled. Data analysis had not been commenced.

Limitations

At each institution, only 2 of the many programs will be sampled: nursing and medicine. The information may not be fully representative of the level of preparedness of all the programs at these institutions. If response rates are low, statistical comparisons may not be possible or valid. This study involves a change in culture or tradition, which is quite complex since multiple factors are involved: environment, teachers' attitude toward ERT and students' ability to remain focused and self-motivated, parental support, and government support.

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Authors' Contributions

MNK participated in the drafting of the original protocol, data collection, and refining and approval of the final manuscript. SC was the team leader and conceived the idea and participated in protocol writing, revision, and approval of the final manuscript. DP was involved in drafting of the original protocol, as a scribe for the committee and edited the text of the paper. CNN participated in drafting the original protocol, analysis, manuscript writing, developing the electronic data capture tools, and approval of the final manuscript. RG participated in data collection and drafting of the original manuscript. EK was involved in drafting the original manuscript, proof-reading, and approval of the final manuscript. PKM participated in critical reading, providing scholarly insights, and refining the final manuscript. RM participated in data collection, drafting of the original manuscript, and proof-reading the final manuscript. LP participated in data collection, refining research instruments, and proof-reading the final manuscript. QW was instrumental in data collection, refining the original idea, drafting of first paper, and proof-reading the final paper. KSD participated in data collection, critical reading of the paper, and approval of final paper. CM participated in data collection, drafting of the methodology, and critically reading final version of the paper. AGM participated in modifying the original idea, refining the manuscript, and proof-reading the final version of the manuscript. GK participated in drafting the protocol, data collection, manuscript writing, and final reading of the manuscript. SNM participated in drafting the protocol and its revision, data collection, critical reading of the manuscript, and approving the final version. LvdM participated in developing electronic data capture tools, data analysis, and refining of the final version of the paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The case study framework.
[DOCX File , 13 KB - resprot_v10i7e28905_app1.docx]

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Abbreviations

ADKAR: awareness, desire, knowledge, ability, and reinforcement
ERT: emergency remote teaching
FOL: formal online learning
HEI: higher education institutions

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Protocol

Design, Implementation, and Examination of a Remote Patient Monitoring System for Pediatric Obesity: Protocol for an Open Trial Pilot Study

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Abstract

Background: Pediatric obesity is a critical public health issue. Augmenting care in multidisciplinary pediatric obesity clinics with innovative evidence-based technology to improve weight status and health outcomes is needed.

Objective: This study describes the design and methods of an open trial pilot study to examine a remote patient monitoring system (RPMS) for children aged 8-17 years who are receiving treatment in a multidisciplinary pediatric obesity clinic.

Methods: Participants will include 45 youth with obesity and their parents. Families will receive standard care in the clinic and the RPMS for 3 months. The RPMS consists of a tablet, weight scale, and pedometer. The system provides daily educational content and involves the use of the pedometer and weekly weigh-ins. Children and parents will complete baseline, posttreatment (month 3), and follow-up assessments (month 6). The primary aim of the study is to examine feasibility and satisfaction with the RPMS and assess its initial effectiveness.

Results: We hypothesize high feasibility and satisfaction, with rates over 75%. Furthermore, after RPMS treatment, children will exhibit improved weight status, health outcomes, dietary intake, physical activity, health-related quality of life, self-efficacy, and home-food environment compared to before treatment. These gains are expected to persist at follow-up.

Conclusions: This study is novel in that it is the first to design, implement, and examine an RPMS in a pediatric obesity clinic. If the RPMS is feasible, effective, and easily accessible, it may prove to be a practical, acceptable, and cost-effective weight management treatment for youth seeking treatment for severe obesity.

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KEYWORDS

digital health; eHealth; obesity; pediatric obesity; pediatrics; remote patient monitoring; telemedicine; weight management

Introduction

Pediatric obesity is a critical public health issue in the United States. Serious comorbid health conditions including type 2 diabetes, heart disease, stroke, and cancers are common [1]. Younger individuals with obesity burden the health care system [2]. Specifically, pediatric obesity accounts for health care costs of over US $14 billion annually in the United States [3]. Efficacious pediatric obesity interventions are necessary to mitigate long-term health consequences and reduce health costs.

Standard care in multidisciplinary pediatric obesity clinics decrease adiposity in approximately 50% of treated youth [4,5]. However, providing and maintaining consistent care can be challenging when working with underserved children and families [6,7]. In Mississippi, over 50% of the state is rural, more than 35% of the population is Black or African American, and almost one-third of children live in poverty [8]. Mississippi also has the highest rates of pediatric obesity in the United States [9]. There is a significant need for innovative evidence-based technology to improve health and weight status.

Telemedicine use has increased owing to high rates of computer ownership, tablets, and cellphones, as well as easier internet access [10]. Insurance companies and health care organizations use telemedicine to support chronic disease management by developing remote patient monitoring systems (RPMSs) [10]. RPMSs provide patients with hardware and software that medically monitor health outcomes, provide educational information, automatically analyze health data, and alert patients and care providers of concerns [10]. RPMS efficacy studies have demonstrated improved health status in adults with chronic health conditions [11], such as diabetes [12], congestive heart failure [13], and obesity [14]. Nonetheless, applications of RPMSs in pediatric populations are limited. Four published studies have examined the applications of RPMSs in youth, having particularly focused on those with sleep apnea [15], cardiovascular implants [16], cancer [17], and type 1 diabetes [18]. These studies demonstrated feasibility, effectiveness, and reduced health care costs in pediatric populations; however, RPMSs have not been integrated into pediatric obesity clinics.

The primary objective of this study is to describe the design and methods of an open trial to test an RPMS designed to provide supplemental care to youth receiving treatment in a pediatric weight management clinic in Mississippi.

Methods

Ethics Approval and Trial Registration

This study was approved by the institutional review board at the University of Mississippi Medical Center (protocol# 2017-0083) and is registered on ClinicalTrials.gov (protocol# NCT04029597).

Study Aims

The primary objective of this open trial is to pilot test an RPMS designed to provide supplemental health care to youth who are receiving specialty medical care in a multidisciplinary pediatric obesity clinic. Specifically, we will assess initial feasibility and satisfaction and examine initial effectiveness of the RPMS for 3 months. We hypothesize high feasibility with the use of the RPMS and satisfaction rates over 75%, and after treatment children are expected to exhibit improved health outcomes compared to before treatment and their parents are expected to report improvements in their children's health-related quality of life and home-food environment.

Study Design

This study will utilize an open trial design to examine the initial feasibility and effectiveness of implementing an RPMS in a pediatric obesity clinic. Participating families will receive standard care and the RPMS. After providing consent and assent, children and parents will complete questionnaires and objective measures as part of the pretreatment assessment. After using the RPMS for 3 months, families will complete the posttreatment assessment during a regularly scheduled follow-up appointment with health care providers at the pediatric weight management clinic. After an additional 3 months, participating families will also complete a follow-up assessment, similar to the pre- and posttreatment assessments, during a regularly scheduled clinic visit.

Study Setting

The study will be conducted at the University of Mississippi Medical Center (UMMC) Pediatric Weight Management Clinic, a multidisciplinary outpatient medical clinic designed to treat children with obesity and related medical comorbidities. The clinic providers include a pediatric nurse practitioner and pediatric dietician who see every patient, as well as a clinical psychologist and mental health specialists who assess and treat patients with suspected mental health concerns. The study is being conducted in partnership with the UMMC Center for Telehealth, who assisted with the development of the RPMS intervention materials and provides oversight regarding RPMS equipment and participants' use and interaction with the RPMS.

Participants

The study will recruit 45 families with a child aged 8-17 years who attends an outpatient pediatric obesity clinic and has a weight status in the obese range (BMI equal to or above the 95th percentile for age and gender), and parents and children who are fluent in English. Exclusion criteria are the following: (1) the child or parent having a history of cognitive impairment (developmental delay or intellectual disability) reported by the parent, which would impact their ability to understand and complete questionnaires or interact with the RPMS; and (2) the child having a medical condition, reported by parents, which may prohibit wearing of the actigraph device (eg, pacemaker).

Potentially eligible participants will be recruited through the pediatric weight management outpatient multidisciplinary clinic. When families present for a scheduled appointment, providers will provide them information about the study and ask if they are interested in knowing more about it. A trained research team member will discuss the study in more detail and obtain child assent, parent permission, and parent consent to participate. The research assistant will then assist the child and parent with the completion of baseline questionnaires and assessments.

Remote Patient Monitoring

The RPMS was developed in collaboration with UMMC Center of Telehealth. Patients enrolled in this open trial of the RPMS will interact with the system on a daily basis and with UMMC Center for Telehealth nurse care coordinators and research and clinical staff on an as-needed basis. The RPMS consists of an electronic tablet, weight scale, and pedometer. Patients will be asked to wear the pedometer daily to track engagement in physical activity and weigh themselves weekly to track weight during the 3-month period. Educational information specific to pediatric obesity–related medical complications and healthy eating and engagement in physical activity will be presented daily through brief presentations and video clips. Educational material and information were developed on the basis of behavioral family weight management treatments for pediatric obesity [19,20] and the social cognitive theory [21]. Daily assessments, which will include questions regarding health status and health behaviors, will be self-reported by the patient through the software program on the electronic tablet. Responses and vital signs and symptoms will be monitored by nurse care coordinators. The program contains a care management platform software that allows for data trends to be developed and analyzed to identify at-risk patients requiring action, such as follow-up phone calls to patients from the nurse coordinator and nurse coordinator informing the research and clinical team about patient symptoms. Solutions discussed and provided by the nurse coordinator and clinical research team may consist of the following: personalized interventions, targeted education, health coaching, behavior modification, medication adherence, and content to motivate patients. All health sessions are designed for patient engagement by providing quality educational content and self-management skills. The UMMC Center for Telehealth RPMS is linked to patients' electronic medical record (ie, Epic) to facilitate communication between the nurse care coordinators and the medical team at the pediatric obesity. In addition, if patients have questions or need to contact the medical team the nurse care coordinators can facilitate that process, but patients and families are also able to contact (via secure messages, call, etc) the medical team providers, consistent with standard clinic procedures.

Data Collection and Measures

Children and parents will complete the following measures and assessments at pretreatment (baseline), posttreatment (month 3), and follow-up (month 6) unless otherwise specified.

Child-Completed Questionnaires and Assessments

Height and Weight

Height without shoes will be measured using a stadiometer. Weight will be measured using a certified digital scale with 1 layer of clothing on and without shoes. Measurements will be conducted by trained clinical staff or research personnel. Data will be used to calculate child BMI, BMI *z* scores, and BMI percentiles using age- and gender-specific norms.

Health Outcomes

Standard procedures in the pediatric obesity clinic will be used by trained nursing or medical professionals to measure resting heart rate and blood pressure of children. In addition, results from routine blood tests assessing glucose and hemoglobin A_{1c} levels will be obtained from the child's medical records.

Dietary Intake

Children will complete a 24-hour dietary recall by using the Automated Self-administered 24-hour Recall (ASA24) system. ASA24 is a free, secure web-based tool developed by the National Cancer Institute for research use. The ASA24-2018 was developed for children and adults aged 10 years and older and guides participants through the completion of a 24-hour dietary recall by asking about food intake and estimated portion sizes during the previous day. Responses are scored using the US Department of Agriculture's Food and Nutrient Database for Dietary Studies.

Physical Activity

Children will wear an ActiGraph GT3X+ Activity Monitor on their waist for 24 hours a day for 1 week. The ActiGraph GT3X + Activity Monitor [22] measures child energy expenditure. After wearing the device for 7 days, families will return the actigraph via a self-addressed stamped envelope provided by research personnel at each assessment time point.

Self-Efficacy

To assess self-efficacy for eating healthier and engaging in physical activity, children will complete the Child Dietary Self-Efficacy Scale [23], which consists of 15 items that children answer using a 3-point Likert scale. Children will also complete the Self-Efficacy for Physical Activity Scale [24], which consists of 5 items specifically regarding the management of physical activity–related barriers. Both measures have been used previously in pediatric research and have acceptable reliability and validity.

Health-Related Quality of Life

To assess child quality of life, the Pediatric Quality of Life Inventory (PedsQL) [25] will be utilized. The PedsQL consists of 23 items and has been utilized with a variety of pediatric populations, including obesity, and it has good reliability and validity.

Treatment Satisfaction

Upon posttreatment assessment, children will complete the treatment satisfaction questionnaire, which was developed for this study and based on a previous study [26]. The questionnaire asks children to rate how much they agree or disagree with 10 statements.

Parent-Completed Questionnaires and Assessments

Demographic and Health History Information

At the baseline assessment, parents will complete a demographic questionnaire to obtain information about the child and parent. In addition, parents will answer questions about their child's and their own medical history. Parents will also be asked to provide their contact information, specifically postal address, phone numbers, and email addresses and the name and phone number of another family member the research team can contact if we are unable to contact the parent.

Height and Weight

Parent height and weight will be measured using the same aforementioned methods used for children. Measurements will be used to calculate parent BMI and determine parent weight status.

Home-Food Environment

The Home Food Inventory [27] will be completed by parents to assess the availability of healthy and unhealthy food at home. The measure was developed for use in health promotion research and has demonstrated adequate reliability and validity.

Child Health-Related Quality of Life

Parents will complete the parent-proxy form of the PedsQL [25] to provide perceptions of their children's quality of life. The parent-proxy form of the PedsQL has demonstrated good reliability and validity.

Treatment Satisfaction

Parents will also complete the treatment satisfaction questionnaire developed for this study upon posttreatment assessment [26]. The questionnaire asks parents to rate how much they agree or disagree with 12 statements about the RPMS.

Compensation

Families will receive compensation for completing each assessment. Total compensation for participating in the study will be US $90 during the 6-month study period.

Statistical Analyses

To examine aim 1, descriptive statistics (including mean [SD] and percentage values) of engagement with the RPMS will be used to examine feasibility and satisfaction scores on the basis of child and parent reports completed during the posttreatment assessment. To examine aim 2—initial effectiveness of the RPMS—repeated-measures analysis of variance will be conducted to determine whether there are significant differences in outcomes over time. Two-sample *t* tests will be used to compare differences in outcomes from pre- to posttreatment, pretreatment to follow-up, and posttreatment to follow-up. If necessary (eg, outcome data are skewed), nonparametric tests will be used to compare pretreatment, posttreatment, and follow-up scores. Maximum likelihood techniques will be utilized for missing data to provide unbiased and accurate estimates of variables regardless of the pattern of missing data (ie, random or completely random). Statistical significance will be set at $P<.05$.

Results

The study received ethics approval from the institutional review board in January 2019. Recruitment and enrollment began in August 2019. As of April 2021, 42 youth and their caregivers were enrolled in the study; however, participants continue to receive the RPMS intervention, and posttreatment and follow-up assessments are underway. Future outcomes will be published in professional peer-reviewed health-related research journals and presented at national, regional, or state-level professional meetings and conferences. Preliminary findings will be used to inform the development of a future study that will include a randomized controlled trial containing a larger sample of families and a standard care control group, evaluation of a refined RPMS, and cost-effectiveness analyses.

Discussion

Here we describe the rationale and design of an open trial examining the feasibility, satisfaction, and effectiveness of an RPMS for youth receiving multidisciplinary treatment for obesity. There is a need to develop and implement treatments that complement clinical treatment, which are feasible, accessible, and useful for families from rural and underserved areas, who have obesity and related comorbidities. There is a lack of accessible treatments that address severe pediatric obesity. Bariatric surgery is effective [28,29] but is not currently available for youth in our state; hence, the implementation of more intensive treatments is necessary to address morbid pediatric obesity for our patients.

The RPMS is novel in its use of telehealth technology, connection with the electronic medical record, and easier access to health care information and health care providers for patients and their families. The RPMS developed in this study provides daily education and support for implementing lifestyle changes among individuals with severe obesity, who need more intensive approaches than those that are available in outpatient clinics and are constrained by time and space demands. Outpatient pediatric weight management clinics are typically not able to provide the amount of treatment recommended by the US Preventative Task Force, which is 26 hours of treatment in a year [30]. Thus, a feasible, appealing, and effective web-based intervention, such as our RPMS, may serve as a suitable method for pediatric obesity clinics to provide the recommended amount of treatment.

It is important to identify potential limitations of the current study and potential directions for future studies. First, the sample size for this pilot open trial design is relatively small. However, the proposed sample size is larger than that in previous studies on pediatric RPMSs [18]. If feasibility, satisfaction, and effectiveness data are promising, the research team intends to pursue additional grant funding to expand the sample size and use a randomized design to continue to evaluate the feasibility and effectiveness of the RPMS in this population. Second, the RPMS being evaluated here was designed by the pediatric obesity clinic providers at this specific clinic for its specific target population. Generally, among the patients treated at this clinic, approximately 60% are African American or Black, and approximately 35% live in rural areas of the state [31]. Thus, this specific RPMS may not be generalizable to clinics located in other parts of the country. Third, the length of treatment with the RPMS is 3 months. Though the treatment is intensive (ie, every day), it may not provide sufficient time to result in long-term behavioral changes.

This open trial will examine the initial feasibility, acceptability, and effectiveness of the RPMS for racially diverse youth with severe obesity. We expect that this pilot study will provide our team with significant collaboration with telehealth and experience to support a larger randomized controlled trial in an underserved population that includes youth with obesity who

are racially diverse and are receiving specialty medical care. An intervention that is feasible and effective, as well as easily accessible through web-based telehealth for diverse and underserved families may be a practical, acceptable, and cost-effective weight management treatment for youth seeking treatment for severe obesity.

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Conflicts of Interest

None declared.

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Abbreviations

ASA24: Automated Self-administered 24-hour Recall
RPMS: remote patient monitoring system
UMMC: University of Mississippi Medical Center

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Protocol

Use of Social Media for Cancer Prevention Through Neighborhood Social Cohesion: Protocol for a Feasibility Study

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Abstract

Background: Social cohesion is associated with healthier behaviors and better health outcomes, and therefore may offer a mechanism for promoting better health. Low socioeconomic status (SES) communities face higher rates of chronic disease due to both community- and individual-level factors.

Objective: The aim of this study is to leverage social cohesion to promote healthier behaviors and prevent chronic disease in a low SES community. This protocol outlines the methodology for a pilot study to assess the feasibility of an intervention (Free Time For Wellness [FT4W]) using a social networking platform (Nextdoor) with mothers living in an urban, low-income community to improve social cohesion and promote healthy behaviors.

Methods: The study will involve three phases: (I) co-designing the intervention with mothers in the neighborhoods of interest, (II) implementing the intervention with community leaders through the social networking platform, and (III) evaluating the intervention's feasibility. Phase I of the study will include qualitative data collection and analysis from in-depth, semistructured interviews and a co-design group session with mothers. Phases II and III of the study include a pre- and postintervention survey of participating mothers. Neighborhood-level data on social cohesion will also be collected to enable comparison of outcomes between neighborhoods with higher and lower baseline social cohesion.

Results: As of March 2021, recruitment and data collection for this study are complete. This protocol outlines our original study plan, although the final enrollment numbers and intervention implementation deviated from our initial planned methodology that is outlined in this protocol. These implementation learnings will be shared in subsequent publications of our study results.

Conclusions: Ultimately, this study aims to: (1) determine the barriers and facilitators to finding free time for wellness among a population of low-income mothers to inform the co-design process, and (2) implement and study the feasibility of an intervention that leverages social cohesion to promote physical activity in a community of low-income mothers. The results of this study will provide preliminary feasibility evidence to inform a larger effectiveness trial, and will further our understanding of how social cohesion might influence well-being.

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KEYWORDS

social cohesion; mothers; neighborhood; physical activity; social media; social; behavior; health outcomes; socioeconomic status; community health; chronic disease; social network; feasibility; wellbeing; cancer

Introduction

This protocol outlines the methodology for a pilot study to assess the feasibility of an intervention (Free Time For Wellness [FT4W]) using a social networking platform (Nextdoor) with mothers living in an urban, low-income community to improve social cohesion and to promote healthy behaviors.

Social cohesion describes the extent of connectedness and solidarity with groups [1], such as feelings of trust and inclusion in social settings [2]. Measures of social cohesion assess the degree to which individuals experience trusting relationships, cooperation, and participation in their communities [3]. High or average social cohesion is positively related to good self-rated health [2,3]. Social cohesion has also been found to be correlated with healthier behaviors and better health outcomes such as higher rates of physical activity [4]; lower rates of smoking, drinking, and depression [5]; lower BMI [6]; and lower rates of myocardial infarction [7]. Living in a cohesive community may improve health through the diffusion of health information and resources that enable individuals' engagement in healthy behaviors [3,8]. Social cohesion may also impact neighborhood safety [9] or social norms that reduce risky behavior and increase mutual respect, thereby reducing stress [3].

Given the linkages between social cohesion and health outcomes, our study aims to build social cohesion to promote healthy behavior using the social media app Nextdoor. As the prevalence of social media has risen in our society, its use has been studied for health issues such as tobacco use, diet, physical activity, and sexual practices [10]. A recent study of a social media–based pilot intervention for weight loss among adults with low socioeconomic status (SES) was found to be feasible, with results demonstrating high rates of engagement, increases in social support, and decreases in body weight among participants [11]. In addition, a recent meta-analysis of 22 studies of social media interventions for weight loss or related behaviors found a modest but statistically significant weight loss effect of 1 kilogram [12]. Facebook is the most commonly used tool for similar social media lifestyle intervention research [13]; therefore, this study will add to this body of literature by designing and evaluating an intervention using a newer social media tool (Nextdoor) that prioritizes connections between people in the same geographic area through address verification.

This study will focus on co-designing and implementing the intervention in the urban, low-income community of Washington Heights, New York City (NYC). Communities of low SES are at increased risk of developing conditions such as cancer, heart disease, diabetes, and other chronic diseases [3,14,15]. This increased risk is due to factors at many levels, including the environment, community, family, and individual [16]. At the community level, neighborhoods perceived as unsafe, hostile, isolating socially or culturally, or that are extremely polluted have been linked to poor self-rated health and higher mortality [17,18]. Greater levels of stress [19] and poorer sleep quality [20] occur among people who perceive their neighborhoods as unsafe and esthetically unpleasing. High levels of reported stress are also related to being less likely to engage in healthy behaviors [21], and the Centers for Disease Control and Prevention reported that individuals of low SES may also be more likely to smoke cigarettes, to be obese, to develop diabetes, and to experience preventable hospitalizations [22]. Therefore, this study will focus on a low SES community where the risk of chronic disease is higher and there is greater potential to make an impact on these health disparities.

Finally, this study will focus on co-designing and implementing the intervention with mothers, given their ability to influence the health behaviors of their households. According to Yuma-Guerrero and colleagues [23], social cohesion may improve mothers' engagement in physical activity, and thus directly impact individuals in that family because mothers make decisions that affect family health and model behavior for their children. Accumulating evidence [24] suggests that, ideally, cultivating risk-reduction behaviors begins in childhood, modeled by trusted caregivers and communities. We also selected mothers as the target population as they are more likely to have common interests and experiences that could facilitate building social cohesion, as opposed to a more heterogenous group. Therefore, this study will focus on cultivating social cohesion to promote healthy behaviors among mothers living in an urban, low-income community.

We hypothesize that an intervention using neighborhood-level social media to encourage behavioral activation and accountability to others will help to increase healthy behaviors among mothers living in an urban, low-income community.

Methods

Purpose

The purpose of this study is to co-design and assess the feasibility of the FT4W intervention. FT4W uses a social networking platform, Nextdoor, to improve social cohesion among mothers in a low-income, urban community (Washington Heights, NYC), with the ultimate goal of improving health behaviors that prevent chronic disease, such as physical activity. By focusing on building social cohesion, rather than explicitly discussing disease prevention or healthy behaviors, this intervention will employ a "stealth approach" to health promotion and will focus on addressing process motivation rather than on an explicit health outcome [25]. To our knowledge, no interventions using this approach to promote healthy behavior while building social cohesion have been performed in this target population with this social media platform.

This pilot study has two aims. Aim 1 is to identify the barriers and facilitators to free time for wellness activities, and to co-design an intervention with mothers from an urban, low-income community. Aim 2 is to assess the feasibility of the intervention, leveraging social cohesion to promote healthy behaviors using Nextdoor among mothers in Washington Heights.

Premise of the Study

Although the exact intervention activities will be designed together with mothers from the target community, the research team has developed initial ideas for the intervention based on evidence, theory, and personal experience, and will seek feedback from mothers on these ideas. These initial ideas relate to the communication mode, program leadership, and intervention activities.

Communication Mode: Nextdoor

In our initial conceptualization, mothers would enroll in a Nextdoor group with others from their neighborhood. As outlined above, social media interventions show promise for improving social support and healthier behaviors, and Nextdoor was selected as the platform of interest by the research team because of its focus on physical proximity and safety through address verification. The relevant features of Nextdoor that will be considered for utilization in this intervention are: (i) connecting participants to others living in their neighborhood, (ii) creating a group of study participants where plans for group wellness activities in their neighborhood (and other topics of interest) can be discussed among participants, and (iii) group moderators can post information or reminders about upcoming events or activities. It is anticipated that the Nextdoor platform will be used for communication, whereas the wellness activities themselves will take place in person in the participants' neighborhood.

Program Leadership: Community Champion

We plan to engage a community champion to promote enrollment and participation in the intervention. We plan that their role will include sharing information about activities with the group, facilitating conversations among group members in the online platform, participating in activities, and generally promoting interest and engagement. The idea to utilize a community champion to facilitate the intervention stems from Rogers' diffusion of innovation theory, and subsequent evidence that suggests champions may be able to best influence others to enroll and maintain engagement in the program [26,27]. We plan to identify interested community champions during the activities of Aim 1 (interviews and workshop) and to offer a stipend as a gesture of appreciation for their time.

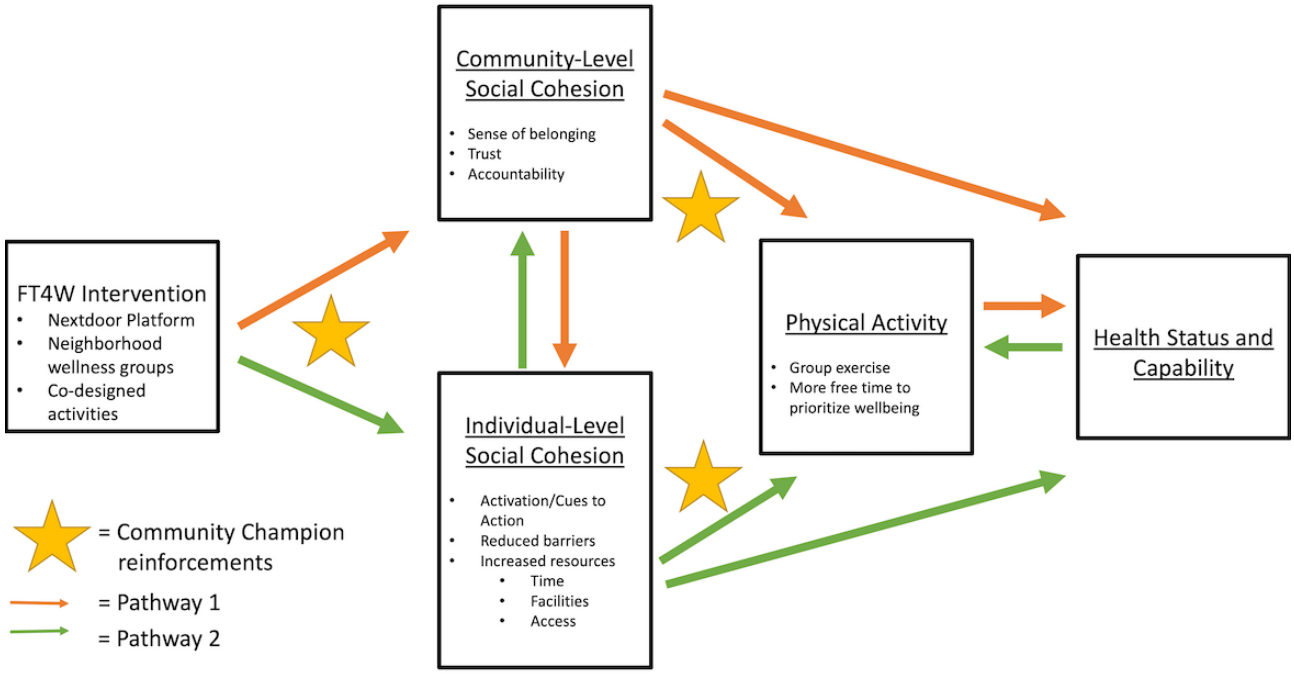
Intervention Activities: Alternating Childcare and Exercise

A potential intervention activity could include taking turns to watch children in a small group while other mothers go for a group walk, and then alternating roles so that all mothers have the opportunity to be active. This idea was inspired by personal experiences of the researchers, who had used Nextdoor in their own neighborhoods to arrange their own childcare and fitness activities.

Although these ideas are included here to illustrate the potential of this intervention, obtaining input from mothers during the co-design workshop is essential to ensure that the intervention fits their needs, and that they will be interested and motivated to participate.

We hypothesize that the co-design FT4W intervention can lead to behavior change through the framework outlined in Figure 1. Specifically, we hypothesize that the co-designed FT4W intervention will promote social cohesion, both at a community and individual level. A community champion will be used to facilitate the Nextdoor group intervention and to reinforce positive group dynamics. We expect that increases in social cohesion will result in greater community-level trust and accountability, as well as individual-level resources and activation (or cues to action). In turn, mothers will adopt healthier behaviors such as higher levels of physical activity, and will experience better health and greater capability.

Figure 1. Hypothesized framework of behavior change. FT4W: Free Time For Wellness.



Approach

Aim 1

To achieve Aim 1, the researchers will perform qualitative interviews and a co-design workshop with mothers from the low-income, urban community of Washington Heights, NYC.

First, semistructured, open-ended interviews will be performed with mothers to understand the barriers and facilitators to free time for wellness. These interviews will also explore mothers' ability and willingness to use the social media platform Nextdoor. Approximately 12 mothers will be recruited for interviews from the Washington Heights community, although the final number will depend on when data saturation is met. Data saturation will be defined as "the degree to which new data repeat what was expressed in the previous data" [28]. In practice, this means that when the interviewers begin to hear the same comments being repeated in interviews, we will stop collecting new data and will begin analysis [28]. Recruiting will be performed through community groups, newsletters, Facebook groups, and listservs for mothers in the Washington Heights neighborhood, resulting in a convenience sample. The interviews will be recorded and transcribed, and the data will be inductively coded following grounded theory [29].

Second, a co-design workshop will be held with mothers in Washington Heights to design the content of the intervention. The workshop will include rotating, small group discussions at four "stations" to elicit ideas and feedback from mothers on four topics: (i) use of the Nextdoor platform and other communication technologies, (ii) ways to create additional free time in their schedules for wellness activities, (iii) the types of wellness activities they would like to participate in, and (iv) the characteristics they would like the community leader/facilitator to have. These topics were prioritized by the researchers as the main areas where feedback and input from participants were needed. The format of rotating small group discussions was chosen to facilitate easier conversation, where all participants would have the chance to speak and to give input on multiple topics.

A total of 20 mothers will be recruited to participate in the co-design workshop, starting with extending invitations to the mothers who participated in the interviews and asking them to invite other mothers from their community as well. In addition to this snowball sampling, flyers will be posted in the neighborhood to recruit additional mothers. Mothers' input will be audio-recorded and collected through notes taken by the research team during the workshop. Analysis of these qualitative data will be performed immediately following the workshop by reviewing the audio recordings and notes as a research team, discussing common themes emerging from the results, and deciding on the final components of the intervention through consensus. Using the design input from the mothers at the co-design session, the research team will decide on: (i) *what* the intervention wellness activities will be, (ii) *how* intervention group communication will take place, (iii) *who* will facilitate group communication and wellness activities, (iv) *where* the wellness activities will take place, and (v) *when* the wellness activities will take place (frequency).

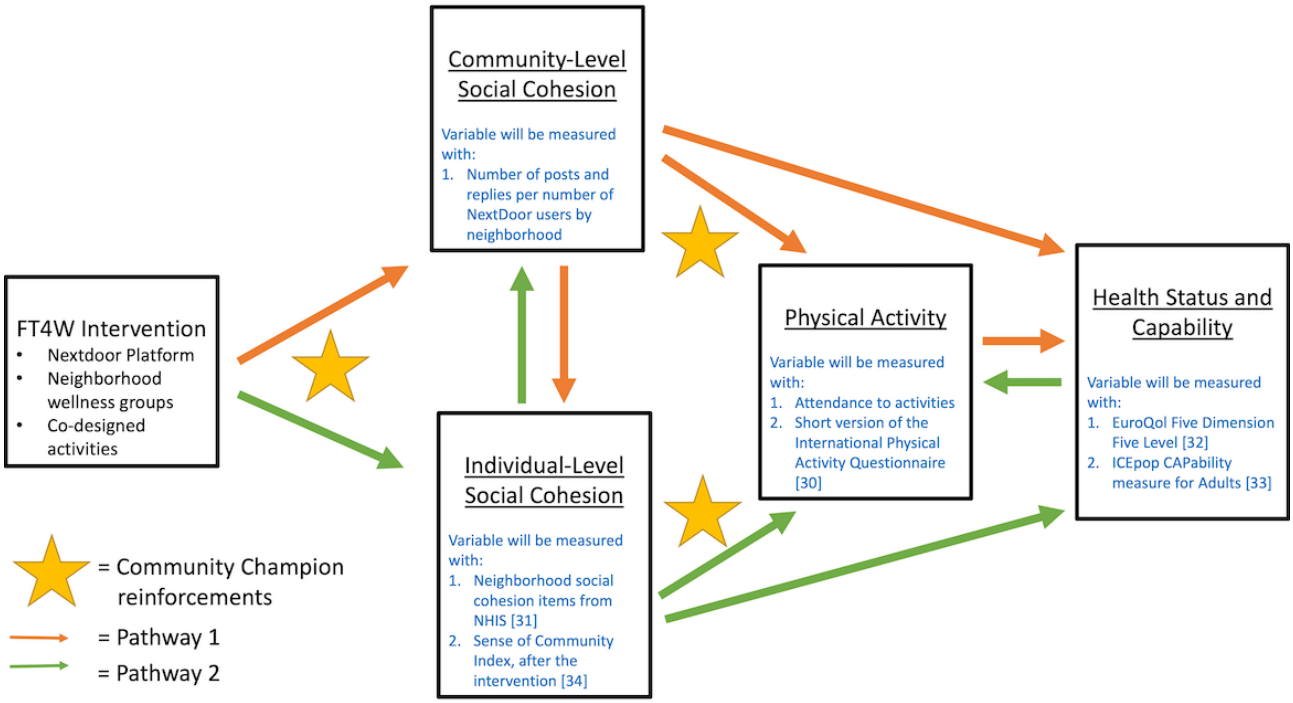
Aim 2

To achieve Aim 2, the research team will aim to enroll 30 mothers in the intervention group and will administer a baseline survey before the intervention begins and a follow-up survey after the intervention ends (4 months later). Mothers who attend the co-design workshop will be asked if they would like to participate in the intervention, and snowball sampling and neighborhood flyers will be used to recruit additional mothers until the target number is reached.

The baseline and follow-up survey will measure: physical activity (using the short version of the International Physical Activity Questionnaire [30]), individual-level perceptions of

neighborhood social cohesion (using 4 questions from the National Health Interview Survey [31]), health status (using the EuroQol Five Dimension Five Level [32]), and capability (using the ICEpop CAPability measure for Adults [33]). The follow-up survey will also measure acceptability of the FT4W intervention (using questions to measure mothers' perceptions on whether the intervention is effective at freeing up their time to participate in wellness activities), perceptions of community among FT4W participants (through the Sense of Community Index [34]), and self-reported attendance to activities. In addition to the survey, data will also be collected on study retention (through attendance to intervention activities and participation in group communications), community-level interactions on Nextdoor (number of posts and replies among all Nextdoor members in Washington Heights neighborhoods during the study period), and the cost of the intervention. The relationships of these measured variables to our hypothesized framework of behavior change are outlined in Figure 2, showing how each variable will be measured through the Aim 2 data collection.

Figure 2. Hypothesized framework of behavior change with details on how each variable will be measured in Aim 2. NHIS: National Health Interview Survey; FT4W: Free Time For Wellness.



A descriptive analysis will be performed for each quantitative outcome measure described above. Given the small sample size, it will not be possible to make statistical inferences of the effectiveness of the intervention; however, the instruments used to collect the data will be assessed for their sensitivity and relevance for use in a future larger-scale trial. We will also perform an economic cost-benefit analysis because the introduction of a new intervention requires efficient resource allocation to achieve the greatest outcome. Economic evaluation is a tool that is used to compare the costs and benefits of two or more interventions [35]. To fully assess the cost and benefits of a new intervention, a trial with a sufficiently large sample size is required. However, it is important to consider the design of a cost-benefit (effectiveness) analysis from the inception of a new intervention. The purpose of the economic analysis for this study will be to test data collection methods (eg, baseline and follow-up surveys) to ascertain the most relevant and sensitive outcome measures that can be used to capture changes. Cost data will be estimated by collecting costs for services that would need to be funded for the intervention to succeed/function, including the cost of renting a community space for an intervention activity.

Results

As of March 2021, recruitment and data collection for this study is complete. This protocol outlines our original study plan, although final enrollment numbers and intervention implementation deviated from our initial planned methodology that is outlined in this protocol. These implementation learnings will be shared in subsequent publications of our study results.

Discussion

This protocol outlines the study methodology for a multilevel participatory community intervention to promote healthier behaviors among mothers in a low-income neighborhood. Unhealthy lifestyles and low rates of physical activity are potentially modifiable risk factors for many chronic diseases. Low SES communities are at especially elevated risk for developing chronic diseases, and they experience many barriers to better health. Low-cost, scalable programs that could be implemented regardless of geography, but tailored to the needs of neighborhoods, could result in a significant positive impact on national and potentially international health outcomes.

This study involves a multidisciplinary research team with expertise in behavioral science and interventions, implementation science, health education, digital health, epidemiology, anthropology, psychology, health economics, and health communication. This study will also employ a multilevel approach to address barriers to healthy behavior at both the community and individual levels. Further, this study employs co-design methodology to engage the target community in the planning of the intervention, to ensure it meets their needs and is desirable and engaging. Finally, we have cultivated an informal partnership with the social media platform Nextdoor. Similarly, we plan to engage with community services in Washington Heights to ensure that the intervention is local and accessible for mothers in the community.

The proposed multilevel mixed methods study will harness neighborhood-based social networking to improve social cohesion and ultimately chronic disease prevention through enhanced healthy behaviors among mothers in Washington Heights. If successful, this work could help reduce persistent disparities in chronic disease incidence and outcomes among communities with low SES.

Acknowledgments

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Authors' Contributions

All authors developed this study’s aims and methodology. KC performed the background literature review. IG and KC drafted the manuscript. All authors provided feedback. JW added literature to the background section and revised the manuscript. All authors approved the final manuscript.

Conflicts of Interest

LCH is married to the Executive Director of one of the community service organizations where the intervention took place. Participants of the intervention received services that any member of New York City is eligible to receive. No money was exchanged. The remaining authors declare no conflict of interest.

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Abbreviations

FT4W: Free Time for Wellness
NYC: New York City
SES: socioeconomic status

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Protocol

The VICTORY (Investigation of Inflammacheck to Measure Exhaled Breath Condensate Hydrogen Peroxide in Respiratory Conditions) Study: Protocol for a Cross-sectional Observational Study

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Abstract

Background: More than 7% of the world's population is living with a chronic respiratory condition. In the United Kingdom, lung disease affects approximately 1 in 5 people, resulting in over 700,000 hospital admissions each year. People with respiratory conditions have several symptoms and can require multiple health care visits and investigations before a diagnosis is made. The tests available can be difficult to perform, especially if a person is symptomatic, leading to poor quality results. A new, easy-to-perform, point-of-care test that can be performed in any health care setting and that can differentiate between various respiratory conditions would have a significant, beneficial impact on the ability to diagnose respiratory diseases.

Objective: The objective of this study is to use a new handheld device (Inflammacheck) in different respiratory conditions to measure the exhaled breath condensate hydrogen peroxide (EBC H_2O_2) and compare these results with those of healthy controls and with each other. This study also aims to determine whether the device can measure other parameters, including breath humidity, breath temperature, breath flow dynamics, and end tidal carbon dioxide.

Methods: We will perform a single-visit, cross-sectional observational study of EBC H_2O_2 levels, as measured by Inflammacheck, in people with respiratory disease and volunteers with no known lung disease. Participants with a confirmed diagnosis of asthma, chronic obstructive pulmonary disease, lung cancer, bronchiectasis, pneumonia, breathing pattern disorder, and interstitial lung disease as well as volunteers with no history of lung disease will be asked to breathe into the Inflammacheck device to record their breath sample.

Results: The results from this study will be available in 2022, in anticipation of COVID-19–related delays.

Conclusions: This study will investigate the EBC H_2O_2, as well as other exhaled breath parameters, for use as a future diagnostic tool.

(JMIR Res Protoc 2021;10(7):e23831) doi:10.2196/23831

KEYWORDS

medical device; diagnosis; hydrogen peroxide; lung diseases; exhalation; asthma; COPD; bronchiectasis; interstitial lung disease; lung cancer; breathing pattern disorder; pneumonia

Introduction

Respiratory Diseases

Globally, respiratory disease is a leading cause of morbidity and mortality, with over 7% of the world's population living with a chronic respiratory disease [1], including a significant burden on children. Respiratory diseases account for more than 10% of all disability-adjusted life years worldwide [2]. Diagnosing respiratory conditions at an earlier stage affords patients the opportunity to receive appropriate treatment, along with reducing symptoms and improving quality of life and reducing the impact of frequent visits to health care services due to misdiagnosis or exacerbations. A rapid point-of-care test may be more useful in low-resource settings.

Within the United Kingdom, approximately 1 in 5 people have ever developed asthma, chronic obstructive pulmonary disease (COPD), or other long-term respiratory illness [3]. In addition, lung diseases are responsible for more than 700,000 hospital admissions and over 6 million inpatient bed days each year [3]. It is estimated that each week, 10,000 people are given a new diagnosis of lung disease, but there are thousands of more people living with the symptoms of lung conditions without a diagnosis.

Table 1 presents the respiratory conditions that are under investigation in this study. As the table shows, there is no one gold standard diagnostic investigation to support the diagnosis of these different conditions. As a consequence, patients can undergo multiple investigations, leading to a delay in diagnosis and a prolonged period of struggling with untreated symptoms.

Table 1. Disease group summaries and diagnostic investigations.

Respiratory disease	Background (key facts)	Diagnostic investigations
COPD[a]	In the United Kingdom, there are an estimated 3 million people affected by COPD, with a third of those having a diagnosis and two-thirds who remain undiagnosed [4]. COPD is common and treatable but is a leading cause of morbidity and mortality worldwide, and its prevalence is likely to increase in the next decade [5]. COPD is responsible for a significant financial burden on the NHS[b], with the total annual cost of COPD reaching £982 million (US $1.3 billion), as well as the personal burden, causing almost 22 million lost working days per year [6].	Spirometry, chest x-ray, and CT[c] scan
Asthma	Asthma affects over 5.4 million people in the United Kingdom, with 200,000 experiencing severe disease with frequent exacerbations [7]. The National Review of Asthma Deaths in 2014 found that there were 900 deaths due to asthma, highlighting that more needs to be done regarding the diagnosis and management of this disease [8]. Treating asthma costs the NHS over £1 billion (US $1.42 billion) per year, and it is a burden for the person living with asthma, with significant psychological and physical morbidity [9,10]. Delays in diagnosing asthma and achieving good disease control cause an increase in emergency health care use and inappropriate treatment.	Peak expiratory flow, spirometry, bronchial provocation, exhaled nitric oxide, and eosinophilic markers
Bronchiectasis	The prevalence of bronchiectasis in the United Kingdom is rising, and it is estimated that the number of people living with this disease exceeds 300,000 [11,12]. People with bronchiectasis experience symptoms of excessive sputum production and recurrent respiratory infections, sometimes requiring hospital admission.	Chest x-ray, CT scan, and sputum microbiology
ILD[d]	ILDs are a group of diffuse parenchymal lung disorders associated with substantial morbidity and mortality. ILD can be difficult to diagnose and often requires collaborative expertise from multiple specialties to reach a consensus. As a consequence, ILD is often diagnosed late in the course of the disease, impacting patients' quality of life, and can even limit access to novel treatments [13,14]. For example, idiopathic pulmonary fibrosis, one of the more common ILDs, is a chronic, progressive disease with a median survival of only 3 years from the time of diagnosis [15]. As such, developing a test that could confirm ILD at an earlier stage is urgently required.	CT scan or lung biopsy
Lung cancer	Lung cancer is a leading cause of global cancer death [16]. Even with recent advances in treatment options, approximately 86% of lung cancer patients die within 5 years of diagnosis. However, with early detection and treatment, 5-year survival rates improve to 70% in patients with stage 1 disease [17]. Consequently, new, accurate diagnostic tests that can detect lung cancer at the earliest stage possible are urgently needed.	CT scan and lung biopsy
Pneumonia	Pneumonia is the most common cause of respiratory hospital admissions. It is the inflammation of one or both lungs, normally caused by an infection. It is estimated that approximately 220,000 people receive a diagnosis of pneumonia each year [3]. Pneumonia is responsible for over 5% of all deaths and over 25% of all respiratory deaths [3]. It can be difficult to diagnose, and diagnosis can depend upon the quality of the chest x-ray or the ability of the person to mount an immune response.	Chest x-ray and CT scan
BPD[e]	BPD is a very common, potentially debilitating, and easily treatable condition. Unfortunately, it is rarely considered as a common cause of breathlessness, and besides the Nijmegen questionnaire, there is no quick and easy way of diagnosis [18].	Clinical assessment

[a]COPD: chronic obstructive pulmonary disease.

[b]NHS: National Health Service.

[c]CT: computed tomography.

[d]ILD: interstitial lung disease.

[e]BPD: breathing pattern disorder.

Airway and Lung Inflammation

A common feature of most of these lung conditions is airway inflammation. The current breathing devices to measure the levels of inflammation focus on eosinophilic rather than neutrophilic inflammation, which is the predominant phenotype in COPD, bronchiectasis, steroid-resistant asthma, and pneumonia. Prolonged exposure to toxic irritants has been implicated in airway inflammation in lung cancer [19]. Interstitial lung disease (ILD) is an umbrella term for lung diseases characterized by fibrosis, which can occur as a result of chronic inflammation, remodeling, and repair [20].

Airway inflammation leads to an imbalance between the production of reactive oxygen species (ROS) and the ability of the body to counteract their harmful effects through neutralization by antioxidants. This results in oxidative stress [21,22]. Increased expression of ROS by activated inflammatory cells, including neutrophils, macrophages, and eosinophils, can lead to further generation of inflammatory mediators, causing damage to epithelial cells and increased bronchial hyperreactivity. ROS are metabolized in cells to produce highly reactive oxidants such as hydrogen peroxide (H_2O_2), which is fat soluble and can move across cell membranes. As H_2O_2 is

volatile and readily equilibrates with air, its presence is detected in exhaled breath condensate (EBC). Therefore, measurement of exhaled breath condensate hydrogen peroxide (EBC H_2O_2) provides a quantitative measure of oxidative stress and airway or lung inflammation [23,24].

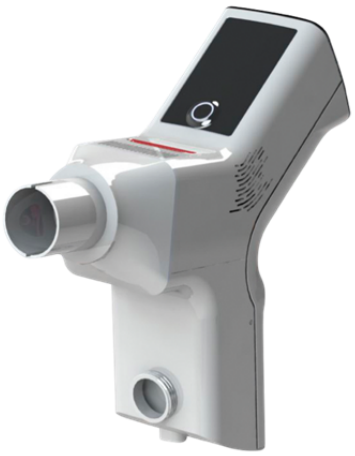
Breathing pattern disorder (BPD) is a noninflammatory condition but is a common comorbidity with other respiratory disorders. Preliminary data have shown that breath flow dynamics in a person with BPD is unique (D. Neville, unpublished data, 2018); therefore, by studying those with BPD only, we may be able to identify specific features and use the device to assess when dual pathology is present.

Inflammacheck

In contrast to the current measures of airway inflammation, the collection of EBC H_2O_2 is performed during tidal breathing, making it noninvasive and easy to perform. It can be repeated quickly and is well tolerated even in patients with severe airway disease. It is widely appreciated that EBC H_2O_2 measurement has the potential to improve clinical practice by safely providing vital information on aspects of disease that are currently inaccessible [25]. To date, measurement of H_2O_2 in EBC requires complex, multistep processing of the collected breath samples to produce a result, and consequently, it has largely been used as a research tool.

Exhalation Technology Ltd developed a table-top device for point-of-care H_2O_2 measurement in exhaled breath—the *Inflammacheck* device. Previous studies including EXHALE 1A (Exhaled Hydrogen Peroxide as a Marker of Lung Disease Study 1–Airways; A. Chauhan, unpublished data, 2019) and EXHALE 1B (Exhaled Hydrogen Peroxide as a Marker of Lung Disease Study 1–Breathlessness; [26]) have shown that it accurately measures the level of H_2O_2 in EBC and that levels of H_2O_2 are significantly higher in patients with asthma, COPD, ILD, and lung cancer than in healthy controls. The EXHALE 1V (Exhaled Hydrogen Peroxide as a Marker of Lung Disease Study 1–Validation) COPD validation study was terminated early as significant changes were made in the sensor processing and device housing, which made the results unreliable. Participant feedback from these studies helped refine the device further, and now, Exhalation Technology Ltd has produced a handheld device (Figure 1), which can accurately and reliably measure the H_2O_2 level in a single test. This new device can also measure additional parameters, including breath humidity, breath temperature, breath flow dynamics, and carbon dioxide (CO_2) waveform. Previous studies have demonstrated significant differences in H_2O_2 levels between healthy controls and some respiratory diseases including asthma, COPD, and ILD. We now want to expand upon these results to determine whether these differences are seen across a wider spectrum of respiratory diseases and whether the additional parameters measured by the Inflammacheck device (Exhalation Technology Ltd) also reflect differences between conditions. This could potentially provide a unique test that measures common biological and physiological parameters in a point-of-care device to aid earlier diagnosis and support personalized management plans. This simple, noninvasive technique may also make repeat sampling and longitudinal monitoring of global airway inflammation a realistic possibility. The Inflammacheck device is currently Conformité Européenne marked for adults only, which is the subject of this protocol.

Figure 1. The Inflammacheck device.



Objectives

Primary Objective

The primary objective is to measure and compare the levels of H_2O_2 in EBC in patients with a range of commonly occurring respiratory conditions and compare these results with those of healthy controls, and with each other.

Secondary Objectives

The secondary objectives are as follows:

- To assess whether the device can measure EBC H_2O_2 consistently (pilot phase only) and ensure that there are no safety issues or participant issues when using the device
- To determine whether EBC H_2O_2, as measured by Inflammacheck, can differentiate between patients with asthma, COPD, lung cancer, ILD, BPD, bronchiectasis, and pneumonia and healthy controls
- To measure and compare the levels of the following parameters using Inflammacheck in patients with a range

of commonly occurring respiratory conditions and compare with healthy controls:
  - Breath humidity
  - Breath temperature
  - Exhaled CO_2 waveform
  - Breath flow dynamics
- To determine whether H_2O_2, breath humidity, breath temperature, exhaled CO_2 waveform, and breath flow dynamics, as measured by Inflammacheck, can either alone or in combination differentiate patients with asthma, COPD, lung cancer, ILD, BPD, bronchiectasis, and pneumonia from each other and from healthy controls
- To assess the experience of a small group of participants and health care professionals in using the Inflammacheck device using a questionnaire methodology

Methods

Overview

This is a cross-sectional observational study of EBC H_2O_2 levels, as measured by Inflammacheck, in people with asthma, COPD, bronchiectasis, ILD, lung cancer, pneumonia, and BPD and in healthy volunteers. The participants were screened for the absence of COVID-19 symptoms before testing.

Outcome Measures

Respiratory Outcomes

Respiratory outcomes will include the following:

- EBC H_2O_2 measured by Inflammacheck
- Breath humidity
- Breath temperature
- Exhaled CO_2 waveform
- Breath flow dynamics
- Forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and expiratory ratio as appropriate.

Experience Outcomes (by Questionnaire)

Experience outcomes will include the following:

- Rating of *ease of use* of the test
- Rating of whether the test is acceptable to the participant
- The participant's perception of the device
- The health care professional's experience of the device

Eligibility Criteria

Study Participants

Participants with the abovementioned respiratory conditions and healthy volunteers will be recruited. There are some overarching inclusion and exclusion criteria, along with some specific respiratory condition criteria to ensure that each disease is well defined.

Inclusion Criteria

The participants must meet all the following criteria to be considered eligible for the study:

- Male or female aged ≥16 years
- Asthma (confirmed by spirometry or airway inflammation and function tests) with a smoking history of ≤10 pack-years
- COPD (confirmed by spirometry)
- Bronchiectasis (confirmed by computed tomography scan)
- ILD (confirmed by computed tomography scan and multidisciplinary team or specialist consensus)
- Primary lung cancer (confirmed diagnosis by histology or radiology) and not yet started significant treatment
- Current pneumonia (confirmed by chest imaging)
- BPD (specialist confirmed) with no other significant respiratory comorbidity
- Healthy controls (defined as no current clinical diagnosis of, or receiving treatment for, a lung disorder or other significant medical disorder)
- Willing and able to give informed consent for participation in the study
- In a stable state (at least 4 weeks after treatment of an exacerbation of their respiratory disease)

Exclusion Criteria

The participants may not enter the study if any of the following apply:

- Existing comorbidities that may prevent them from performing spirometry (for those with asthma and COPD or healthy controls) and no spirometry in the previous 12 months (at the discretion of the clinical investigator)
- Unable to comprehend the study, unable to provide informed consent, and unable to perform any of the study procedures
- Requirement of supplemental oxygen (participants with pneumonia only)

Sampling and Sample Size

The sample size was based on the primary objective of comparing EBC H_2O_2 values between each of the study groups (patients with asthma, COPD, ILD, and lung cancer and controls) based on the results from previous studies (EXHALE 1A and EXHALE 1B), using an older version of the device. Sample sizes were calculated based on 5% significance and 80% power using a comparison of 2 means (two-tailed *t* test across independent groups) and using effect sizes based on the results of the previous studies.

Using these calculations, we will recruit the following:

- 30 people with COPD
- 35 people with asthma
- 25 people with ILD
- 40 people with lung cancer
- 50 healthy controls

The BPD, bronchiectasis, and pneumonia groups are exploratory, and no information exists to base their sample size on. Therefore, we will aim to recruit 25 people in each of these groups.

Study Procedures

Recruitment

This is a multicenter study in which the identification of potential participants are being performed in respiratory

outpatient clinics, inpatient wards across the hospital, and integrated specialist community clinics in primary care. Participants in our research database who have previously provided their consent to participate in future studies that adhere to the general data protection regulations will also be offered the opportunity to participate in this study. People with suspected lung cancer can be recruited before a confirmed diagnosis. If tests confirm that the participant does not have cancer, they can be entered into any other category if appropriate; otherwise, they will be considered a screen fail. Healthy volunteers will be recruited from National Health Service staff, our research database, friends and family of participants with respiratory disease, and students or staff at the University of Portsmouth.

Participants will be approached by their clinical care team, and those who express an interest will be provided with a participant information sheet (PIS), an opportunity to ask any questions, and a review with the research team either at that point in time or at a future convenient date and time.

Pilot Phase

Before starting full recruitment, we will run a pilot phase to ensure that the device can produce consistent and reliable results. Participants will be recruited as detailed above, and the study procedures will be identical. These data will be analyzed as soon as possible after collection to assess the quality and accuracy of the results. The criteria for termination of the pilot phase will be determined by the clinical, engineering, and manufacturing teams based on the quality of data, safety information, clinical training, and ease of use.

Study Assessments

Participant Characteristics

Before other study procedures, the characteristics of participants, which are known to have a potential influence on respiratory test results, will be documented. These will include the following:

- Demographics (age, gender, and ethnicity)
- Categories of disease-specific medications that participants are taking
- Categories of other medical comorbidities

Respiratory Tests

The participants will then perform the EBC H_2O_2 level measurement performed by the Inflammacheck device, followed by spirometry if the participant has asthma or COPD or is a healthy control, unless this has been done in secondary care or by the research team within the last 12 months. Following this, a small subgroup of participants will answer a brief Likert-type questionnaire regarding their experience. For every Inflammacheck test, the following will be recorded:

- Whether the test was completed, and if not, the reason for this
- Any adverse events (AEs) related to the test that are reported by the participant or noted by the clinical staff during the test procedures.

Hydrogen Peroxide in Exhaled Breath Condensate

EBC H_2O_2 will be measured using the Inflammacheck device according to the manufacturer's instructions. This involves simple relaxed tidal breathing for up to 6 minutes into a disposable mouthpiece attached to the handheld device, while wearing a nose clip. The Inflammacheck device then provides a reading of the EBC H_2O_2. The results will not be recorded in any clinical notes, as they are not intended to inform patient management decisions in this study. As this is a point-of-care test, this investigation can be performed in any clinical environment. Understandably, preventing cross-contamination in any era, but especially in this global coronavirus pandemic, is paramount, and this investigation is performed using a bacterial viral filter within the mouthpiece, with single-use disposable valve houses and sensors. The device itself is cleaned between each participant's use according to the local cleaning guidelines for medical devices.

Spirometry

Spirometry (performed conforming to the American Thoracic Society and European Respiratory Society standards) will only be performed in patients with asthma and COPD or in healthy controls who have not undergone spirometry in the last year in secondary care or by the respiratory research team. Participants will inhale rapidly and completely from functional residual capacity, then exhale in an initial forced exhalation, and then continue exhalation until the end of the breath. FEV_1 (measured in liters), FVC (measured in liters), and FEV_1/FVC ratio will be recorded. FEV_1 and FVC will be documented as absolute values and as a percentage of the predicted value (25). A minimum of 3 blows will be performed, with 2 blows within 100 milliliters or 5% of each other. Given the current coronavirus pandemic, spirometry is only being performed if it will impact clinical decisions.

Self-Completion Questionnaire

A brief self-completion questionnaire will be used in 20 randomly selected participants to evaluate their opinions on the Inflammacheck device on a Likert-type scale. Participants will be asked about ease of use, comfort during testing, and perception and satisfaction of Inflammacheck.

Health Care Professionals' Self-Completion Questionnaire

A brief self-completed questionnaire will be used by 5 randomly selected health care professionals to evaluate their opinions on the Inflammacheck device on a Likert-type scale, as described above.

Participant Withdrawal

Withdrawal Rules

Participants who are unable to perform the EBC H_2O_2 measurement with Inflammacheck or spirometry will not be withdrawn. The reason for failing to perform these tests will be documented in the case report form (CRF).

Safety Assessments: AE

Overview

An AE is any untoward medical occurrence in a participant taking part in a clinical trial, which does not necessarily have to have a causal relationship with the device under investigation. An AE can, therefore, be any unfavorable or unintended sign, symptom, or disease temporarily associated with the use of the device, whether or not this has a causal relationship with the device under investigation.

Recording and Reporting of AEs

There are not expected to be any AEs associated with the use of the Inflammacheck device, and no AEs were noted during any of the previous studies that involved this device. Only AEs that have a reasonable possibility of being attributable to the device and any other AE considered to be of clinical significance by the principal investigator (PI; eg, causing harm to the patient) will be recorded in the CRF and reported to the sponsor as per their guidelines. We will record all AEs that are observed during all respiratory test procedures as a study outcome. Any AEs that do occur and are considered by the PI to be related to the device will be expedited to the sponsor, research ethics committee (REC), and the device manufacturer within 7 days. Lists of the AEs will be provided to the sponsor when requested.

Data Collection and Management

Data collection will be performed by the research team comprising research doctors, nurses, and clinical research associates, all of whom have received appropriate training. Enrollment in the study will be documented in each participant's medical notes if they are an inpatient. The data collection forms are as follows:

- CRF, including participant characteristics and respiratory test results confirming the underlying diagnosis
- Self-completed questionnaire for participants

The data will be entered into a secure electronic platform. Anonymized data will be shared electronically with Exhalation Technology Ltd for analysis and interpretation of the breath humidity, temperature, breath flow dynamics, and CO_2 waveform data. The Inflammacheck results will be uploaded to a secure shared database to allow analysis and review of the collected data. Participants will consent to this, and no identifiable data will be shared.

Data Analysis

All participants with an EBC H_2O_2 result, as measured by Inflammacheck, will be analyzed. Subgroup analyses may be carried out if there are sufficient number of patients with particular characteristics, such as smokers and nonsmokers.

Analysis of End Points

Summary Statistics

Demographics or baseline characteristics of each study group will be produced, as well as an overall summary for all groups combined. Normally distributed continuous variables will be summarized by the mean and SD, whereas the median and IQR will be preferred for nonnormally distributed continuous variables. The number and percentage of subjects in each category will be recorded for categorical variables.

Primary Analysis

The primary analysis will be a comparison of EBC H_2O_2 values, as measured by the Inflammacheck device, between participants with the index disease and controls and with each other. It is expected that the EBC H_2O_2 will have a positively skewed distribution. To allow for the skewed distribution, one approach would be to analyze the data on a log-transformed scale and to compare between groups using analysis of variance, with post hoc tests performed to compare between pairs of groups. It is possible that there may be EBC H_2O_2 measurements below the lower detection limit, and thus, the previous approach may not be practical. If measurements are below the detection limit, nonparametric methods will be used. The Kruskal-Wallis test will be used to evaluate if differences exist between the 3 groups, with post hoc Mann-Whitney *U* analyses used to compare differences between pairs of groups. When comparing pairs of groups, a Bonferroni correction will be applied to allow for multiple testing.

Secondary Analyses

The association between the EBC H_2O_2 measurements and other parameters (breath temperature, breath humidity, breath flow dynamics, and CO_2 waveforms) will be examined. Associations between EBC H_2O_2 and the continuous variables listed above will be examined using either Pearson or Spearman rank correlation (as appropriate).

The percentage of attempted tests that failed for each test will be recorded. The association between patient characteristics and this outcome will be examined. Assuming that patient characteristics are categorical in nature, the chi-square test or Fisher exact test will be used to examine associations with this outcome. Secondary analyses will be performed for all subjects combined and for each study group separately.

Exploratory Analysis

The relationship between EBC H_2O_2 and other lung function parameters with respiratory disease type will be further examined, assuming that EBC H_2O_2 and other factors are possible predictors of respiratory disease. Respiratory disease type, using the patient groups included in the study, will be considered as a binary outcome: healthy versus disease type, and the analysis will be performed using multivariable logistic regression. Receiver operator curve characteristic analyses will also be undertaken to assess the predictability of EBC H_2O_2 levels to differentiate between healthy volunteers and patients with respiratory disease. Further analyses will be performed to assess whether H_2O_2 alone or in combination with temperature, humidity, breath flow dynamics, and CO_2 waveform characteristics can discriminate between healthy controls and those with a lung disorder using sensitivity, specificity, and receiver operating characteristic curves as well as using generalized linear models with post hoc least significant difference testing.

Procedure for Dealing With Missing, Unused, and Spurious Data

The analysis will include any measured data values, with missing values omitted from the analysis. No imputation of the missing data will be performed. These data will be examined for outlying values. Where possible, these will be retained in the data analysis, and their influence will be minimized by a data transformation or a nonparametric approach. If such approaches are not practical, the analysis of the primary outcome will be performed twice, with and without the outlying values.

Ethics

Participant Confidentiality

The study staff will ensure that participants' anonymity is maintained. The participants will be identified only by initials and a participant's ID number on the CRF and any electronic database. All documents will be stored securely and will only be accessible by the study staff and authorized personnel. The study will comply with the Data Protection Act 2018, which requires data to be anonymized as soon as it is practicable to do so.

Other Ethical Considerations

The study was approved by the Berkshire REC (reference 19/SC/0462) in August 2019. They reviewed and approved the protocol and all study-relevant material. Any changes to the protocol or relevant study documents will be approved by the sponsor. If an amendment is made that requires REC approval, as defined by the REC as a substantial amendment, the changes will not be instituted until the amendment has been reviewed and received approval or favorable opinion from the REC and research and development departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately, providing that the REC is notified as soon as possible, and an approval is requested. Minor amendments as defined by REC as a nonsubstantial amendment may be implemented immediately, and the REC will be informed. All participants will have adequate time to consider participation in the study, as per the Good Clinical Practice guidelines.

Patients who are already enrolled in other research trials will be invited and allowed to participate in the study if they wish to do so. This was discussed with our patient and public involvement (PPI) representatives who felt that these patients should have the opportunity to participate in this study and should not be excluded. There is a possibility that this study reveals potential new, previously unknown disease pathology. This would be more likely to occur in *healthy controls*. If such a circumstance occurs, then the participant will be told about the results and immediately referred to the most appropriate National Health Service department for further review. With the participant's consent, a letter will be written to their general practitioner explaining the findings.

Where possible, this study will be performed alongside an existing appointment to limit any extra burden to the participant, and all participants will receive a small compensation for travel costs. Participants in the pneumonia arm will be recruited while an inpatient and will not require any additional visits.

Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulations), to obtain written informed consent from each person participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study using the PIS.

Electronic consent will be obtained using the REDCap (Research Electronic Data Capture; Vanderbilt University) platform. Once participants have read the PIS, they will be asked to enter their signature (using their cursor or finger if on a tablet device). Participants will have the opportunity to download or print a copy of their consent form and the PIS. If a participant is unable to complete e-consent, they will have the opportunity to sign a paper consent form when they attend to complete the study visit.

The process for obtaining informed consent will be in accordance with REC guidance, Good Clinical Practice guidelines, and any other regulatory requirements that might be introduced. The PI or delegate and the participant shall both sign and date the informed consent form before the person can participate in the study.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or without affecting the quality or quantity of their future medical care or without loss of benefits to which the participant is otherwise entitled.

PPI Details

PPI in this study has been sought from patients with firsthand experience of living with a respiratory disease. Through face-to-face meetings, email, and telephone contact, we have discussed the concept, impact, and details of the study with our patient representatives from local groups. They have contributed to developing the key questions and setting our study objectives, ensuring that we answer questions relevant to people with respiratory diseases. They have helped design the questionnaire that will be used to record the participant experience of the device and the PIS.

Results

This study has been receiving funding since 2019 and was approved by a REC in August 2019. As of May 2020, the pilot phase has been completed, and 78 participants enrolled into the VICTORY (Investigation of Inflammacheck to Measure Exhaled Breath Condensate Hydrogen Peroxide in Respiratory Conditions) study. The results from this study will be available in 2022, in anticipation of COVID-19–related delays.

Discussion

An easy-to-use point-of-care device that can be used in any health care setting and can differentiate between a range of respiratory conditions would revolutionize the diagnosis of respiratory conditions. By improving our ability to confirm a correct diagnosis, we could initiate earlier treatments, reduce the burden of frequent health care visits, and improve patients'

quality of life. The Inflammacheck device is noninvasive, repeatable, and requires minimal participant effort, which are beneficial attributes for patients with respiratory conditions who often struggle with breathlessness. The VICTORY study will evaluate the Inflammacheck device, using EBC H_2O_2 alongside further exhaled breath parameters as a diagnostic tool in respiratory conditions.

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Conflicts of Interest

HR reports honoraria and lecture fees from Astra Zeneca, Teva Pharmaceutical Industries, Novartis, Glaxo Smith Kline, and Chiesi, of which all are outside the submitted work. TB reports personal fees from Astra Zeneca; grants, personal fees, and nonfinancial support from Glaxo Smith Kline; personal fees and nonfinancial support from Teva Pharmaceutical Industries; nonfinancial support from Napp Pharmaceuticals; and personal fees and nonfinancial support from Novartis, of which all are outside the submitted work. AJC reports honoraria and lecture fees from Teva Pharmaceutical Industries, Astra Zeneca, and Sanofi and research grants from Airsonett, Novartis, and Glaxo Smith Kline, of which all are outside the submitted work. All other authors have no conflicts of interest to declare.

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Abbreviations

AE: adverse event
BPD: breathing pattern disorder
CO2: carbon dioxide
COPD: chronic obstructive pulmonary disease
CRF: case report form
EBC H_20_2: exhaled breath condensate hydrogen peroxide
EBC: exhaled breath condensate
EXHALE 1A: Exhaled Hydrogen Peroxide as a Marker of Lung Disease Study 1–Airways
EXHALE 1B: Exhaled Hydrogen Peroxide as a Marker of Lung Disease Study 1–Breathlessness
EXHALE 1V: Exhaled Hydrogen Peroxide as a Marker of Lung Disease Study 1–Validation
FEV1: forced expiratory volume in 1 second
FVC: forced vital capacity
H_20_2: hydrogen peroxide
ILD: interstitial lung disease
PI: principal investigator
PIS: participant information sheet
PPI: patient and public involvement
REC: research ethics committee
REDCap: Research Electronic Data Capture
ROS: reactive oxygen species
VICTORY: Investigation of Inflammacheck to Measure Exhaled Breath Condensate Hydrogen Peroxide in Respiratory Conditions

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Protocol

Examining the Relationship Between Environmental Factors and Inpatient Hospital Falls: Protocol for a Mixed Methods Study

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Abstract

Background: Patient falls are the most common adverse events reported in hospitals. Although it is well understood that the physical hospital environment contributes to nearly 40% of severe or fatal hospital falls, there are significant gaps in the knowledge about the relationship between inpatient unit design and fall rates. The few studies that have examined unit design have been conducted in a single hospital (non-Veterans Health Administration [VHA]) or a small number of inpatient units, limiting generalizability. The goal of this study is to identify unit design factors contributing to inpatient falls in the VHA.

Objective: The first aim of the study is to investigate frontline and management perceptions of and experiences with veteran falls as they pertain to inpatient environmental factors. An iterative rapid assessment process will be used to analyze the data. Interview findings will directly inform the development of an environmental assessment survey to be conducted as part of aim 2 and to contribute to interpretation of aim 2. The second aim of this study is to quantify unit design factors and compare spatial and environmental factors of units with higher- versus lower-than-expected fall rates.

Methods: We will first conduct walk-through interviews with facility personnel in 10 medical/surgical units at 3 VHA medical centers to identify environmental fall risk factors. Data will be used to finalize an environmental assessment survey for nurse managers and facilities managers. We will then use fall data from the VA Inpatient Evaluation Center and patient data from additional sources to identify 50 medical/surgical nursing units with higher- and lower-than-expected fall rates. We will measure spatial factors by analyzing computer-aided design files of unit floorplans and environmental factors from the environmental assessment survey. Statistical tests will be performed to identify design factors that distinguish high and low outliers.

Results: The VA Health Services Research and Development Service approved funding for the study. The research protocol was approved by institutional review boards and VA research committees at both sites. Data collection started in February 2018. Results of the data analysis are expected by February 2022. Data collection and analysis was completed for aim 1 with a manuscript of results in progress. For aim 2, the medical/surgical units were categorized into higher- and lower-than-expected fall categories, the environmental assessment surveys were distributed to facility managers and nurse managers. Data to measure spatial characteristics are being compiled.

Conclusions: To our knowledge, this study is the first to objectively identify spatial risks for falls in hospitals within in a large multihospital system. Findings can contribute to evidence-based design guidelines for hospitals such as those of the Facility Guidelines Institute and the Department of Veterans Affairs. The metrics for characterizing spatial features are quantitative indices that could be incorporated in larger scale contextual studies examining contributors to falls, which to date often exclude physical environmental factors at the unit level. Space syntax measures could be used as physical environmental factors in future research examining a range of contextual factors—social, personal, organizational, and environmental—that contribute to patient falls.

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KEYWORDS

falls; accidental falls; hospital design and construction; health facility environment; hospital units; evidence-based facility design; nursing; environmental factors; well-being; accident

Introduction

Background

According to the Joint Commission, patient falls are hospital-acquired conditions, and falls with serious injury were the most reported sentinel event in 2018 [1]. Inpatient falls result in a financial burden to US medical organizations, contributing to a 61% increase in patient care costs [2] and decreased quality of life for the injured patients. In 2015, the total medical costs for falls totaled more than $50 billion, and Medicare and Medicaid shouldered 75% of these costs [3]. Thus, decreasing the rate of patient falls is a main focus for improving the quality of health care. According to the Joint Commission, physical environment was a common factor contributing to a fall with injury [4]. Although programs that address multiple risk factors have been implemented to reduce hospital falls, none of the commonly used fall risk assessment tools include built environment factors [5]. Retrospective research studies examining the association between the physical environment of the hospital unit and patient falls are few [6], and many of these rely on Likert-type scales of perceived intensity (eg, excellent to poor lighting or sight lines) rather than physical measurement of environmental factors (eg, lumens, distance in linear feet). Many of these studies narrowly focus on design factors immediately impinging on the patient (eg, bedrails) [7] and overlook how physical design affects workflow and care delivery, which in turn affects patient outcomes such as falls [5,8].

Factors in the facility environment that affect social organization and behavior include spatial organization, environmental systems, communication cues, ambient qualities, and architectural details [9]. Of these, spatial organization factors play a prominent role in supporting or hindering behaviors of staff and patients in health care settings. Corridor layout, the location of nursing stations, and placement of interior doors and windows can facilitate or impede staff oversight of patient movement and activities. In one hospital case study, Choi [6] examined the locations of patient falls in relation to physical accessibility and visibility from nurse to patient bed using key locations (nursing station, medications, and a corridor's circulation path). Using digitized floor plans and spatial analysis software, Choi numerically and graphically analyzed physical accessibility and visibility (ie, sight lines) from key locations to inside patients' rooms. Findings showed that patient bed visibility from decentralized nurses' stations and from corridors was significantly associated with the incidence of patient falls. As part of our mixed methods study, we propose a similar approach to physically measure environmental design factors within Department of Veterans Affairs (VA) hospitals that may contribute to patient falls via the manner in which design affects accessibility and visibility. It should be noted that this does not include video monitoring as it may not be not allowed in medical/surgical units. The physical design of a unit can facilitate or impede nursing care, affecting efficiency, stress, and patient care [10]. Hospital unit design experts often ask if the design is (1) flexible, allowing for changes over time, (2) efficient, allowing for quick and easy access to patients, families, computers, and supplies, (3) permitting the most optimal use of the space while increasing unimpeded sight lines, and (4) welcoming to patients and their families.

Data on falls and fall-related injuries have been systematically collected and analyzed for all nonfederal hospital units since 2011. Although the complementary data sources exist for Veterans Health Administration (VHA) hospitals, there are only a few published studies describing the system-wide burden of hospital falls in the VHA system of care [11,12]. In the past decade, hospital and health care design is increasingly guided by evidence-based design and rigorous research to link the spatial design and built characteristics of hospitals to health care outcomes [5,13].

Study Objectives

This mixed methods study will explore the relationship between unit design and patient falls in VHA medical/surgical units. The goal of aim 1 is to investigate frontline staff and management perceptions of and experiences with veteran falls as they pertain to inpatient environmental factors including patient rooms, bathrooms, nurses' stations, and hallway design features. We will conduct walk-through interviews in medical/surgical units at 3 VHA medical centers with unit and facility personnel to identify environment-related fall risk factors for patient falls. Interview findings will be used to develop an environmental assessment survey to be conducted as part of aim 2. The goal of aim 2 is to quantify unit design factors and compare spatial and environmental factors of units with higher- versus lower-than-expected fall rates. We will use fall data from the VA Inpatient Evaluation Center and patient data from additional data sources to identify units with higher- and lower-than-expected risk-adjusted fall rates. Predicted values

for hospital fall rates will be based on a regression model by using the SAS Proc Mixed procedure employing residual (restricted) maximum likelihood covariance structure and accounting for nesting within Veterans Integrated Service Networks (VHA region) and facility [14]. Differences between predicted and observed values will be based on studentized residuals. We will measure spatial factors by analyzing computer-aided design (AutoCAD) files of unit floorplans and environmental factors based on the environmental assessment survey.

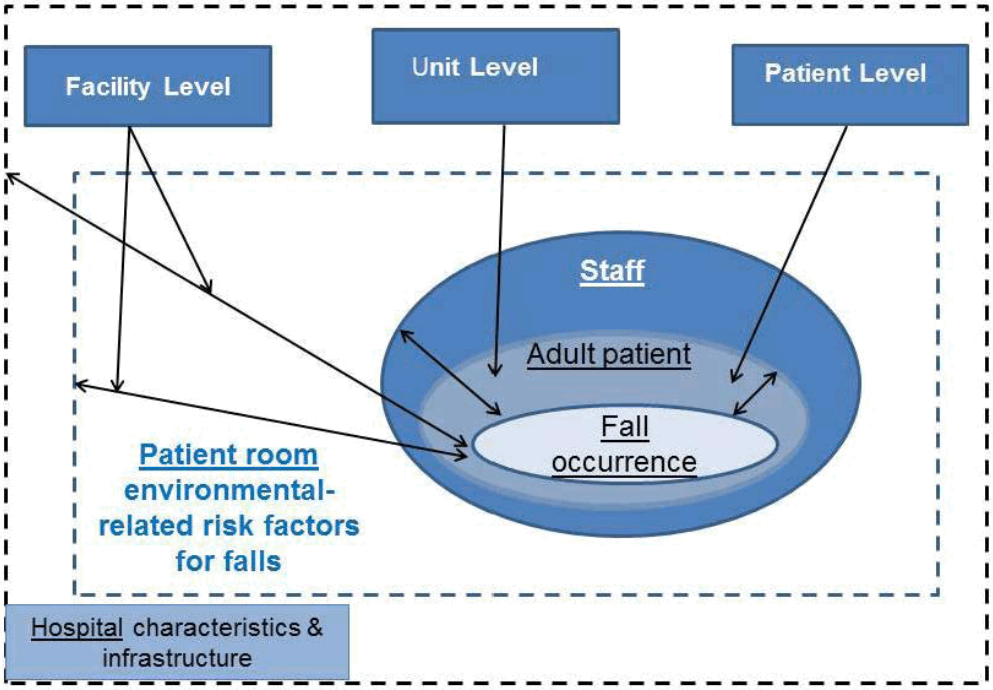
Methods

Design

We propose a mixed methods descriptive study to explore the relationship between unit design and patient falls in VHA medical/surgical units. We will use a qualitative approach of participant observation with walk-through interviews to investigate staff and management perceptions of environmental factors that contribute to patient falls (aim 1). We will use quantitative approaches to identify medical/surgical units with higher- or lower-than-expected fall rates and identify spatial and environmental factors that distinguish them (aim 2).

The study conceptual framework is based on the box model proposed by Tzeng [15], which acknowledges that fall prevention encompasses patient-, unit-, and facility-level system risk factors (Figure 1). Patient-level characteristics include factors like age, gender, severity of illness/comorbidities, surgical procedures, psychotropic drugs, and altered mental status. Unit-level characteristics include nurse staffing, type of additional unit level and patient room characteristics such as unit accessibility, unit visibility, corridor path length, distance from bed to bathroom, and patient room type. Facility-level characteristics include facility complexity and geographic location.

Figure 1. Conceptual model.



Setting and Study Population

The VA is the largest integrated health care system in the United States, consisting of 150 medical centers, nearly 1400 community-based outpatient clinics, community living centers, Vet Centers and domiciliaries. Together, these health care facilities and the more than 53,000 independent licensed health care practitioners who work in them provide comprehensive care to more than 9 million veterans each year [16].

Inclusion Criteria

Within each facility, personnel at 4 different organizational levels and in different roles will be invited to participate. Participants will be nurse managers, staff nurses, patient care technicians, occupational and physical therapists, and Patient Safety Committee members currently working in medical/surgical units at the facilities. Participants should have at least 1 year of hospital experience at the hospital where they are currently employed. Both day and night shift staff will be recruited.

From all medical/surgical units in the VHA system, we will identify nursing units reporting unusually high and low patient fall rates over time (ie, nursing units showing highest deviation from the rates predicted by an appropriately fitted regression model that includes the known standard predictors of patient falls) [17]. To simplify modeling, we will use aggregated measures of 48 months of observation. Nursing units that report extreme risk-adjusted fall rates may constitute interesting outliers that are not statistical nuisances but which can be used to gain a deeper understanding of the underlying processes leading to patient falls [12].

Study Procedure Aim 1: Participant Observation

Recruitment and Enrollment

We will recruit a purposive [18] sample of clinical staff. We will ask the nursing service administrator at each facility to identify nurse managers of the chosen units and work with the nurse managers to identify individual staff. While identifying staff through administrators and managers may introduce bias, we have used this method successfully in VHA hospitals and have found staff to be forthcoming in responses to interview questions and questionnaires. The unions at each facility endorsed this recruitment method. Once potential interview participants have been identified, project team members will contact each in person or by email or telephone and explain the project. The project manager will explain the informed consent with audio addendum process to each potential participant and, if agreeable, send them the informed consent form. Walk-through interviews will be scheduled in accordance with facility and union standard operating procedures and regulations. We will schedule the interviews at times that are convenient for participants and hospital unit workflow.

Interview Procedures

We will conduct 10 walk throughs in 3 facilities yielding 10 group interviews with a total of up to 35 participants. Walk-through interviews are a data gathering technique frequently used in architectural programming to build postoccupancy evaluation. In the walk-through interview, observation and interviewing take place simultaneously. The interviewer walks through designated areas of the building under study with a small group of building occupants. As they walk from area to area, questions are posed by the interviewer, eliciting discussion of key issues, problems, and benefits as perceived by occupants. By coupling the interview with observation of the setting, the walk through triggers detailed recalls of experiences and reactions as related to building factors. This approach allows investigators to triangulate direct observation of the physical factors of the hospital unit with the subjective perspective of the occupant regarding situations associated with it.

The interview team will include (1) a facilitator skilled in qualitative methods who will lead discussions using an interview guide, (2) an assistant facilitator who will take photographs of environmental conditions, and (3) subject matter experts from the study team who will be primarily nonparticipant observers. Interviews will be audiorecorded on password-protected and encryption-capable digital recorders with high-quality audio. Participants will complete an anonymous questionnaire to summarize demographics of the group. At the start of the walk-through interview, the purpose will be explained and any questions from participants will be answered. Participants will be told that their responses will be presented in aggregate or an otherwise deidentified manner and that the interview discussions will remain confidential. Standard response-eliciting techniques will facilitate discussion using generic prompts (eg, “tell me more”), summarizing statements, asking for similar and contrasting opinions, controlling overtalkers, and including all participants in the discussion. The facilitator will use a flexible approach that provides an opportunity to uncover participants’ perspectives using a conversational style.

Interview Guide

We developed a semistructured interview guide to elicit responses from all staff participants regarding hospital falls (Multimedia Appendix 1). The interview guide was designed to elicit perceptions and ideas related to unit design factors and their interactions with facility and patient factors that increase the risk of falls. Examples of interview questions include the following:

- What factors at this hospital influence the risk of inpatient falls?
- What efforts are being made at the leadership level to change these factors?
- Do you think unit design has an impact on how staff are able to see patients as they ambulate or get out of their beds?
- As we walk through the unit, please describe where a patient fall occurred and whether you thought the layout of the unit or patient room influenced the fall or its outcome.

Data Management

To ensure data quality of walk-through interviews, (1) experienced facilitators will conduct the interviews; (2) data analysis will be concurrent with data collection, and participant feedback will be assessed and compiled; (3) interviews will be audiorecorded to ensure that no information is missed; (4) photographs will be labeled with interview time, location, and corresponding statements referencing design factors of interest; and (5) data analysis will be conducted by one investigator and the qualitative data manager. Additionally, an assistant facilitator will take notes and debrief with the facilitator after the interviews to record shared or unique perspectives. The qualitative data manager will manage data files and organize and assist with data coding. Interview recordings will be reviewed by both facilitators to verify accuracy of field notes and add missing data. Data will be secured and backed up behind the password-protected VA firewall with access limited to team members. Investigators will meet regularly to debrief on data methodologies, data integrity, and data security.

Data Analysis Plan

Analysis of interview data will begin following the first interview and will be performed concurrently with ongoing interviews as transcripts are obtained. Insights obtained from continuous analysis will be used to guide further data collection by modifying the interview guide, understanding feedback from participants, and conceptualizing provisional results. A rapid assessment process, an “intensive, team-based, qualitative inquiry using triangulation, iterative data analysis, and additional data collection to quickly develop a preliminary understanding of a situation from the insider’s perspective” [19], will be used to analyze the data. This analysis [20] emphasizes speed of data collection and analysis to focus on programmatic questions or problems encountered by health services researchers. Triangulation of data will be facilitated by including staff who hold different roles, using photographs to validate interviewee responses and collecting data on different units in different hospitals. Interview notes and transcripts will be reviewed by

the data team for inductive data reduction to sort, focus, and organize data so themes can be identified and conclusions obtained [20]. Domain names will be developed to correspond with interview questions, and a summary template will be created. Prior to analysis, the template will be internally tested by the team for usability and reliability. Several team members will summarize transcripts and transfer the themes into a matrix to synthesize important findings.

Study Procedure Aim 2: Modeling Falls Data

Procedures

We will obtain the studentized residuals, the difference between the observed data and the predicted value of the observation, based on the model fitted as described below. The top and bottom 25 units (n=50) according to the ranked studentized residuals will be selected to form high and low comparison groups in the second phase. The use of residuals to classify units as high versus low fall rates implies that the amount of unexplained variance is higher or lower than expected after adjusting for available known factors. For example, a unit with the highest predicted adjusted rate may not qualify to be in the unusually high group because it was accurately predicted by the multivariable model; the difference between predicted and observed rates would be relatively small. Alternately, if a medium rate is predicted for a unit but the observed rate is unexpectedly high, this would be regarded as an unusually high value.

To develop the models, we will use the most recent national VHA falls data based on the start date of the study, fiscal years 2013-2017. To provide an estimate of available data for the study, we accessed unit-level fall data for all medical/surgical units through the VHA Support Service Center (317 units and 12,531 unit months). After excluding units with fewer than 3 or more than 200 patient days per month, 11,532 patient months were available for analysis. Multimedia Appendix 2 summarizes the definitions and sources for each of these variables, grouped by model domains.

Data Analysis Plan

To develop models, we will investigate the patterns of fall rates per unit per month across 60 months. The degree of variability or stability in rates will guide how to aggregate the falls data. Mean fall rates and risk measure scores will be included in a linear mixed model using SAS (SAS Institute Inc) statistical software. The facility identifier will be treated as a random effect (to adjust for nesting of data within facilities), with all other predictors as fixed effects. We will review regression statistics on the basis of how well the regression model predicts the dependent variable of fall rates.

Power Analysis

Statistical testing will be conducted to compare unit design variables between units identified with risk-adjusted high-fall and low-fall rates. Estimated sample sizes (number of nursing units) required to achieve 80% statistical power and the corresponding minimum detectable effect sizes range from a low of 40 (20 high-fall and 20 low-fall) to a high of 50 (25 high-fall and 25 low-fall). In the sample size calculation for the *t* test, the standard deviations were assumed to be unknown and equal. The second sample size calculation was based on a 1-degree of freedom chi-square test. A 2-sided alpha level of .50 was used in both calculations.

Study Procedure Aim 2: Linking Unit Design and Falls

Procedures

To gather data on spatial and environmental characteristics of the units and patient rooms, we will contact facility managers of the sampled hospitals to request AutoCAD digitized documents of floor plans and interior sections of the designated unit and completion of the environmental assessment survey by nurses and facilities management staff developed during aim 1 that includes design features not available on AutoCAD documents (Multimedia Appendix 3). Efforts to maximize cooperation and participation by nurse managers and facilities management will include (1) an email request explaining the study and study findings as highly relevant because they reflect evidence-based design objectives called for by the VA Office of Construction and Facilities Management, (2) request cosigned by the principal investigator and VA Senior Healthcare Architect, (3) follow-up email requests, (4) collaboration with the VHA Office of Nursing Service, and (5) follow-up for nonresponders.

AutoCAD documents are digitized files of floor plans and interior sections of the hospital units. Many spatial features (eg, walls, doors, interior and exterior windows, counter heights) and functional locations (eg, nurses' stations, medication rooms) are contained in these documents. Project team members will be blinded to whether the floor plans come from high-fall or low-fall units.

Spatial Analysis

Space syntax metrics will be computed indirectly by Depthmap software analysis using spatial data entered directly from AutoCAD files. Depthmap is a single software platform that performs spatial network analyses (ie, space syntax) [21,22] using maps of the spatial layout of the hospital unit based on user-designated points within units. Depthmap operates by performing a set of spatial network analyses. One set uses visibility graph analysis [22]. A grid of points is overlaid on a floor plan where each point is connected to every other point that it can see. The visual integration of a point is based on the number of steps it takes to get from that point to any other point within the network. Various graph measures and ratio-level metrics can be calculated, depending upon the research hypotheses [23,24].

Physical and design characteristics data will be extracted directly from AutoCAD files and environmental surveys. Some physical and design characteristics (eg, distance from patient bed to patient bathroom) will be calculated within the AutoCAD program itself (Multimedia Appendix 4). Use of AutoCAD files, environmental surveys, and Depthmap reduces the need for extensive on-site measurement by hospital staff or researchers. This methodology ensures reliability of data collection across sites and minimizes measurement error that occurs by direct measurement.

Statistical Analysis

Statistical and graphic comparisons will be made between high-fall and low-fall units for the variables in Multimedia Appendix 4. The presence of statistically significant associations between hospital unit fall category (high, low) and each unit design measure will be tested separately as follows: a 2-sample *t* test for continuous measures (accessibility, visibility, corridor length) and a chi-square test for categorical measures (ie, single versus multioccupancy patient rooms).

Ethical Approval and Consent to Participate

The research protocol was approved by the University of Florida and University of South Florida institutional review boards and VA Research Committees at both sites. Local union approval was obtained to conduct the walk-through interviews, and written informed consent was obtained before the interviews. VHA Labor Relations and the National Nurses Union reviewed the protocol and instruments and provided concurrence to conduct the nurse environmental assessment survey. The environmental assessment surveys were emailed; a waiver of documentation of informed consent was approved as the completion of the survey implied consent. Approved informed consent language was included on the first page of the environmental assessments.

Results

All study approvals were obtained by January 2018. From January to March 2019, we conducted walk-through interviews and finalized the environmental assessment survey. By November 2019, we identified 25 units with higher-than-expected fall rates and 25 units with lower-than-expected rates. In January 2020, we began to request AutoCad files from these units. In January and August 2020, we surveyed facilities managers and nurse managers, respectively. We expect to complete data analysis by February 2022. Dissemination will occur during the following year.

Discussion

Principal Findings

Patient falls are the most common adverse events reported in hospitals [1,25]. Although it is well understood that the physical hospital environment is a common contributing factor to falls with injuries [26], there are significant gaps in our knowledge about the relationship between inpatient unit design and fall rates. The few studies that have examined unit design have been conducted in a single hospital or a small number of inpatient units, limiting generalizability [27,28]. Furthermore, no studies have focused on unit design and falls in VHA medical centers. Thus, the overarching goal of this study is to identify unit design factors contributing to inpatient falls within the VHA.

Study Strengths

To our knowledge, this study represents the first attempt to study hospital falls in a large multihospital system. Hospitals employ numerous approaches to develop fall prevention policies. In general, the procedures are largely directed at nursing techniques and include identifying patients who are at high risk of falling and using clinical judgment to decide which of a myriad of strategies will reduce fall risk [29]. A quantitative review found no evidence of benefit among published nursing-oriented hospital fall prevention studies using concurrent controls (incidence rate ratio 0.92; 95% CI 0.65-1.30) [30,31]. Even though tremendous resources have been dedicated to reduce falls in VHA hospital units, a wide variation in fall rates still occurs. The advantages of the proposed research design are that it leverages the power of large VA administrative databases to identify nursing units that have the highest and lowest risk-adjusted fall rates and conducts in-depth analyses using physical measurements of environmental factors to identify factors contributing to fall rates. We will employ a novel analysis of floor plans using Depthmap spatial software to investigate unit design factors between the units with high and low fall rates. These space syntax measures could be used as physical environmental factors in future research examining a range of contextual factors—social, personal, organizational, and environmental—contributing to patient falls. In addition, the findings from this study can contribute to development and refinement of evidence-based design guidelines for hospitals and health care settings such as those of the Facility Guidelines Institute and the VA.

Study Limitations

The walk-though portion of the study had 3 limitations we attempted to minimize through design of the study. First, the facilities selected for walk-through interviews formed a convenience sample, so they may not be representative of all VHA medical/surgical units. Given that the facilities available were built or renovated during different time periods, they provided for variations that may exist across the VHA. Second, because units are very busy places with high demands on staff, we included multiple staff so that if one was called away the walk throughs could be completed without them. Staff not in the walk throughs covered their absences as they were able. Third, because walk-through interviews included managers and frontline staff, we were aware of the potential for group dynamics being influenced by power differentials. The research team used validated focus group techniques to elicit feedback from all participant such as calling on individuals who were not as likely to offer responses as others.

Three limitations were noted for aim 2. First, each unit had only one participant per unit completing the environmental assessment survey, increasing the possibility of bias responses. To minimize this bias, we asked nurse managers, who are highly knowledgeable decision makers, to complete the surveys. Second, the risk adjustment models were complex and built on data from multiple data sources. While the VHA is an integrated health care system, we were faced with linking data that have no formal common identifying codes. All information available in each data source was used to match the units, and we conducted validity checks across datasets. Third, use of space syntax analysis requires some assumptions (eg, height of the agent line of sight). In this study, we considered that nurses are sitting in the nursing station and have a 360° view of their surroundings. However, they may be in the nursing station performing administrative tasks and not observing patients. Also, nurses are not always sitting in the nursing station; they

might be walking in the corridor, which requires the assumption of standing height for the line of sight.

Conclusions

To our knowledge, this study is the first to objectively identify spatial risks for falls in hospitals within a large multihospital system. Findings can contribute to evidence-based design guidelines for hospitals such as those of the Facility Guidelines Institute and the VA. The metrics for characterizing spatial features are quantitative indices that could be incorporated in larger scale contextual studies examining contributors to falls, which to date often exclude physical environmental factors at the unit level. Space syntax measures could be used as physical environmental factors in future research examining a range of contextual factors—social, personal, organizational, and environmental—that contribute to patient falls.

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Authors' Contributions

All authors were involved in the design of the study. GPC was responsible for drafting and editing the manuscript. All authors provided significant edits and comments, read drafts, and approved the final version of the manuscript.

Conflicts of Interest

RIS serves as an expert witness in cases of hospital falls. All other authors declare no conflicts of interest.

Multimedia Appendix 1
Walk-through interview guide.
[PDF File (Adobe PDF File), 117 KB - resprot_v10i7e24974_app1.pdf]

Multimedia Appendix 2
Variables for creating models to identify fall rates that are higher and lower than expected.
[DOCX File , 15 KB - resprot_v10i7e24974_app2.docx]

Multimedia Appendix 3
Nurse environmental assessment survey.
[PDF File (Adobe PDF File), 680 KB - resprot_v10i7e24974_app3.pdf]

Multimedia Appendix 4
Spatial and environmental variables.
[DOCX File , 14 KB - resprot_v10i7e24974_app4.docx]

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Abbreviations

AutoCAD: computer-aided design
VHA: Veterans Health Administration
VA: Department of Veterans Affairs

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Protocol

Adolescent Levers for a Diet and Physical Activity Intervention Across Socioecological Levels in Kenya, South Africa, Cameroon, and Jamaica: Mixed Methods Study Protocol

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Abstract

Background: The increasing burden of noncommunicable diseases that are prevalent in low- and middle-income countries (LMICs) is largely attributed to modifiable behavioral risk factors such as unhealthy diets and insufficient physical activity (PA). The adolescent stage, defined as 10 to 24 years of age, is an important formative phase of life and offers an opportunity to reduce the risk of noncommunicable diseases across the life course and for future generations.

Objective: The aim of this paper is to describe a protocol for a study using a convergent mixed methods design to explore exposures in the household, neighborhood, school, and the journey from home to school that may influence diet and PA behaviors in adolescents from LMICs.

Methods: Male and female adolescents (n≥150) aged between 13 and 24 years will be recruited from selected high schools or households in project site countries to ensure the socioeconomic diversity of perspectives and experiences at the individual, home, and neighborhood levels. The project will be conducted at 5 sites in 4 countries: Kenya, Cameroon, Jamaica, and South Africa (Cape Town and Johannesburg). Data on anthropometric measures, food intake, and PA knowledge and behavior will be collected using self-report questionnaires. In addition, a small number of learners (n=30-45) from each site will be selected as citizen

scientists to capture data (photographs, audio notes, text, and geolocations) on their *lived experiences* in relation to food and PA in their homes, the journey to and from school, and the school and neighborhood environments using a mobile app, and for objective PA measurements. In-depth interviews will be conducted with the citizen scientists and their caregivers to explore household experiences and determinants of food intake and foodways, as well as the PA of household members.

Results: The study described in this protocol paper was primarily funded through a UK National Institute for Health Research grant in 2017 and approved by the relevant institutional ethics review boards in the country sites (South Africa, Cameroun, and Jamaica in 2019, and Kenya in 2020). As of December 23, 2020, we had completed data collection from adolescents (n≥150) in all the country sites, except Kenya, and data collection for the subgroup (n=30-45) is ongoing. Data analysis is ongoing and the output of findings from the study described in this protocol is expected to be published by 2022.

Conclusions: This project protocol contributes to research that focuses on adolescents and the socioecological determinants of food intake and PA in LMIC settings. It includes innovative methodologies to interrogate and map the contexts of these determinants and will generate much-needed data to understand the multilevel system of factors that can be leveraged through upstream and downstream strategies and interventions to improve health outcomes.

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KEYWORDS

adolescent; food intake; foodways; physical activity; noncommunicable diseases; socioecological levers; low and middle income countries; health outcomes

Introduction

Background

There is a rising global burden of noncommunicable diseases (NCDs), resulting in approximately 70% of the deaths, of which more than three-quarters are from low- and middle-income countries (LMICs) [1,2]. A significant proportion of these deaths is attributable to modifiable behavioral risk factors such as poor or unhealthy diets (high consumption of sugar, fats, and salt and low consumption of fruits and vegetables) and insufficient physical activity (PA), both of which are associated with obesity, a metabolic risk factor for NCDs [3]. Of note, the global prevalence of overweight or obesity and physical inactivity is on the rise [1,4,5].

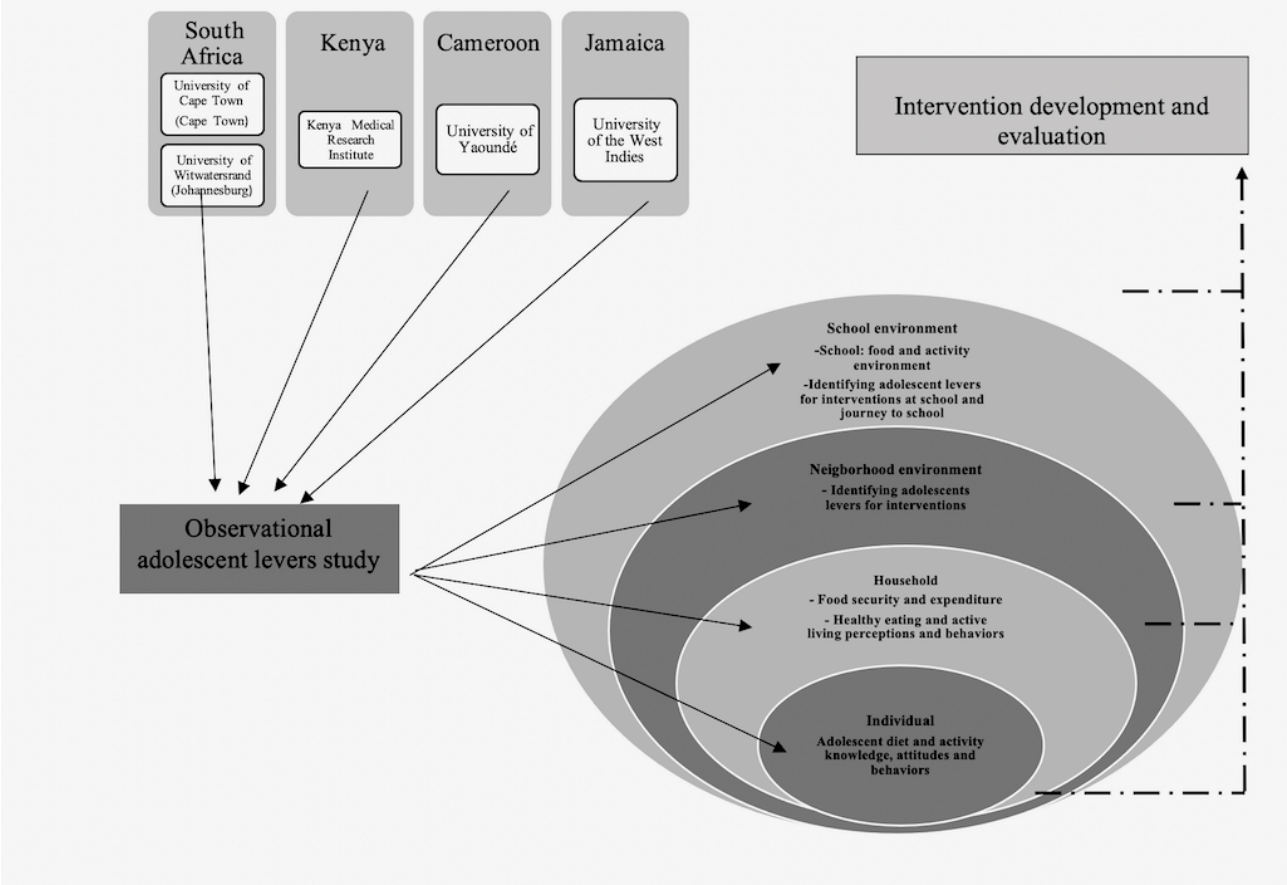
Adolescence, recently defined as 10-24 years of age by Sawyer et al [6] is a *transitory period* accompanied by physical, psychological, and social development and by increasing socialization with peers and independence outside of the family [6,7]. The adolescent period offers an opportunity to reduce intergenerational NCD risk because the increasing independence that characterizes this period of life makes it an important entry point for interventions to promote health across the life course [8]. This age group comprises approximately one-quarter of the world's population, with most of the adolescents living in LMICs [9]. The global prevalence of obese adolescents in 2016 was more than double the prevalence in 2000 [10] and underscores the current global epidemic of risk factors for NCDs in LMICs [7,11].

Factors such as poverty and the uneven distribution of wealth, lack of education, and urban migration—often into informal settlements—are known contributors to the rising incidence and prevalence of NCDs, especially in LMICs [12]. Consequently, addressing the growing burden of obesity and NCDs effectively requires a focus on different individual and contextual social and environmental exposures and on the interplay among micro-, meso-, and macrolevel factors that influence obesogenic health behaviors [13]. However, it is difficult to intervene in complex urban health realities without taking into consideration the factors that also influence health behavior decisions, many of which go beyond personal choice and include factors at the community, economic, and cultural levels.

Despite these concerns, there is a dearth of research from LMICs on the interplay among the factors at different socioecological levels that influence behavior, especially in adolescents, despite the consensus that this knowledge is important. Consequently, there is an apparent *disconnect* between *lived experiences* and evidence generated to support public health recommendations and policies, with a lack of contextually relevant interventions in these settings [14] and little to no evidence for scalability and sustainability.

The proposed study described in this protocol paper will use a convergent mixed methods design including survey, observational data, and ethnographic research to identify socioecological influencers of diet and PA in adolescents living in various LMIC settings (Figure 1). This project is 1 work package in a portfolio of projects of the Global Diet and Activity Research (GDAR) network. This network aims to address the previously detailed knowledge gaps, with the overall goal of contributing to the prevention of NCDs in LMICs, with a specific focus on Kenya, Cameroon, South Africa, and Jamaica—countries with moderate to high levels of income disparity [15].

Figure 1. Socioecological framework of the project.



Objectives

The specific objectives of this project on NCD prevention in LMICs are as follows:

1. To measure dietary behavior (dietary patterns, nutrition knowledge, and nutritional status) and PA behavior (total and domain-specific) in adolescents from low- and middle- to high-income communities.
2. To explore household exposures that may influence dietary and PA behavior in adolescents from low- and middle- to high-income communities.
3. To identify neighborhood-based exposures that may influence dietary and PA behavior in adolescents from low- and middle- to high-income communities.
4. To identify school-based exposures that may influence dietary and PA behavior in adolescents from low- and middle- to high-income communities.
5. To identify exposures that may influence dietary and PA behavior in adolescents on the journey between home and school.
6. To explore the relationships between the socioecological factors that may influence dietary and PA behavior and individual-level factors in adolescents.
7. To explore the similarities and differences among various LMIC settings and across socioecological domains.

Methods

Overview

The GDAR network was launched in 2017 with the overall goal of contributing to the prevention of NCDs such as type 2 diabetes, cardiovascular disease, and cancers in LMICs. The GDAR network is funded through a UK National Institute for Health Research (NIHR) grant.

In this paper, we present our original field protocol and describe modifications made following the COVID-19 pandemic, which interrupted data collection at the home-, neighborhood-, and school-environment levels. We describe new approaches that are being taken to meet our study objectives and improve our understanding of the determinants of diet and PA in adolescents.

Ethical Considerations

We have obtained approval for the study protocol and amendments made because of the COVID-19 pandemic from the University of Cambridge Research Ethics Committee (PRE.2019.105) and local and university ethics committees at the different sites (Cape Town: University of Cape Town Human Research Ethics Committee: 088/2019; Johannesburg: University of the Witwatersrand Human Research Ethics Committee [Medical]: M171137 and M190523; Kenya Medical Research Institute: KEMRI/SERU 4040; Cameroon: Centre Regional Ethics Committee for Human Health Research CE No. 1836 CRERSHC/2020; and the University of the West Indies: ECP 87, 18/19), as well as from relevant educational authorities such as school district management authorities and

school principals of selected schools. The study will be conducted in accordance with the Declaration of Helsinki, applying the Society of Adolescent Health Guidelines for Adolescent Health Research pertaining to specific ethical considerations relevant to the protection of minors participating in research [16]. As such, the assent of each adolescent and consent from an adult parent or guardian (for those volunteers under the age of 18 years) will be sought before data collection.

Participant information sheets and consent and assent forms will be translated into the local languages of each country to ensure adequate understanding. All source data will be collected electronically and will be encrypted and password protected. Data-capturing devices will also be password protected, with access limited to the study team. With the exception of the University of the Witwatersrand in Johannesburg, we will recruit participants aged 13 years or older from secondary schools. The University of the Witwatersrand will recruit older adolescents (aged 18-24 years) who have transitioned from high school and will be recruited from an ongoing study in Johannesburg.

Adolescents who participate will be provided with a small noncash reimbursement (such as school stationery or similar items) in remuneration for the time taken to participate. We have provided an option for varying reimbursements to ensure that they could be tailored to each site based on the participating study teams' knowledge of their country contexts.

Participant Selection

Overview

This protocol paper describes a pilot study; no sample size calculation was conducted because of the lack of baseline data to inform such calculations. It is intended that the collection of several health behavior outcomes across a wide range of settings (and among country sites) will provide information on the variation among groups that will facilitate more accurate sample size calculations for future large-scale research. As such, the sampling size of 150 adolescents from each site allowed us to generate findings across the sites.

Cameroon, Jamaica, South Africa (Cape Town)

Adolescents attending school will be categorized using a general sampling guide that defines three categories based on the socioeconomic status of the neighborhood in which their school is located and that of the area where they reside. This is to ensure a diversity of perspectives and experiences. The two socioeconomic categories of the participants' neighborhoods and schools into low, middle, and high will be determined using a combination of land and property value indices and socioeconomic index map of the locations of their residential areas and schools, respectively, or household assets. The three categories are low-income home neighborhood and low-income school neighborhood (L-L), low-income home neighborhoods and middle- to high-income school neighborhood (L-H), and middle- to high-income home neighborhoods and middle- to high-school neighborhood (H-H), and they are described as follows:

- Adolescents from low-income households attending schools in nearby predominantly low-income neighborhoods (L-L), n≥50 at each site.
- Adolescents from low-income households attending schools farther away in predominantly middle- to high-income neighborhoods (L-H), n≥50 at each site.
- Adolescents from high-income households attending schools in nearby predominantly middle- to high-income neighborhoods (H-H), n≥50 at each site.

Although recruitment of the adolescents will be by convenience sampling, the numbers in each of these three categories will be monitored with the aim of ensuring a roughly equal sex distribution. To prevent any potential for stigmatization, students in middle- to high-income schools who volunteer for participation will be purposively selected according to the residential suburb and nearest street intersection address (L-H and H-H). The basis for the selection will not be shared with the participants beyond the objective of including adolescents who commute to school and that we will aim for geographic representativeness in the sample.

Given the time committed to examinations in the final year of high school and the settling-in period in the first year of high school, this study will target adolescents aged 13 years or older from the second to the penultimate years of high school. As part of the consent process, these adolescents will indicate whether they would be interested in participating in the *citizen scientist* component of the study, which will involve a greater time commitment (Table 1).

Table 1. Research activities and objective-specific methodology.

Socioecological domains	Measures	Objectives
Individual (adolescents)	• Nutritional knowledge survey • Food frequency questionnaire • Self-reported PAa tool • Anthropometry • Demographics • Accelerometery (optional)	1, 3, 6, and 7
Household (of citizen scientists)	• Household multidimensional poverty index • Household demographics and food security • Anthropometry (household members-optional) • In-depth interviews (foodways and PA)	2, 6, and 7
Neighborhood	• Citizen scientists lived experience using EpiCollect5 tool • Researchers' data collection of healthy food and PA opportunities using EpiCollect5 Tool • NEWSb Africa (Environmental Walkability) of adolescents- optional	3, 6, and 7
Home-to-school journey (citizen scientists)	• Citizen scientists' lived experience using the EpiCollect5 tool	5, 6, and 7
School	• School health environment (policies, facilities, grounds, and resources for healthy eating and PA audit tool) • Formal and informal food vendors audit tool	4, 6, and 7

[a]PA: physical activity.

[b]NEWS: Neighborhood Environment Walkability Scale.

Kenya

In Kenya, we will follow the same protocol, with one exception. Adolescents from the H-H category will not be included because of logistical challenges inherent in accessing these schools and adolescents (ie, these schools tend to be private schools and are more restrictive about the activities that they allow and parents support on the school premises). As such, adolescents will be recruited in two categories (n≥75 in each category): L-L and L-H (comprising government schools in high-income areas, with a mixture of children from both low- and higher-income households).

The socioeconomic categorization of the participants' neighborhoods and schools into low and middle to high will be determined using a combination of land and property value indices and socioeconomic index map of the locations of their residential areas and schools, respectively.

South Africa (Johannesburg)

In Johannesburg, female adolescents (n≥150) aged 18-24 years who have transitioned out of high school will be recruited from an ongoing larger study, the Healthy Life Trajectories Initiative enumeration platform, which includes individual and household data from more than 2000 households. The Healthy Life Trajectories Initiative platform enables the identification and recruitment of households from low- and high-income settings. Households with adolescents aged 18-24 years will be contacted and invited to participate in the study. The two socioeconomic categories of the participants' neighborhoods and schools into low, middle, and high will be determined using a combination of land and property value indices and socioeconomic index map of the locations of their residential areas and schools, respectively, or household assets.

Data Collection

Details of data collection from the different socioecological domains are described herein and summarized in Table 1.

Individual Data

Adolescents in schools will have prearranged appointments during or after school, as approved by the school authorities, to participate in the study. Data collection for adolescents who transitioned out of school will be conducted at the research site (South African Medical Research Council/Wits Developmental Pathways for Health Research Unit) in Johannesburg.

Questionnaires

Adolescents will be asked to respond to interviewer-administered or supervised self-administered questionnaires (Table 1). The dietary patterns questionnaire will be adapted for each context from the International Study of Childhood Obesity, Lifestyle and the Environment study, a multicountry study of children from 12 countries in 6 continents [17,18]. The nutrition knowledge questionnaire will be adapted from two previously validated instruments [19,20] because it has not been used in these contexts previously. Internal consistency will be assessed using interitem analysis. The PA questionnaire will be adapted from an instrument that has successfully been used in South African adolescents from low-income and rural settings, and it has been validated against objectively measured PA [21].

Anthropometric Measurements

Height and weight will be measured using standardized procedures [22] in a private room by a team of uniformly trained research assistants to minimize the effect of interobserver variation, using a stadiometer and calibrated scale, respectively.

Waist circumference will be measured with a nonelastic fiberglass retractable anthropometric tape following standard procedures for measurement [22]. This process will be repeated, and the average of the two circumferences will be used in the analysis (with a third measurement obtained if the first two measurements are more than 0.5 cm apart).

Household Data

Household-level data (quantitative and qualitative) will be collected from a subset of adolescents (citizen scientists) and their households as described herein. Before this, pilot interviews using the qualitative tools were conducted at all sites.

Objective PA Measurements

In a subset of adolescents (citizen scientists) for the sites that conduct this aspect of the study, daily PA will be measured using small motion sensors known as accelerometers (Actigraph GTX3+ [ActiGraph, LLC] or Axivity [Axivity Ltd] monitors). These devices—all smaller than a matchbox—will be worn on a belt around the waist or on the wrist. The participants will be asked to wear these monitors continuously for a week and remove them only when bathing, showering, or swimming. Data collected with at least 10 hours of uninterrupted wear time for at least 4 days will be considered complete. Nonwear periods are defined as any period of at least 30 minutes of continuous zero counts. We used the World Health Organization criteria for sedentary time and moderate- and vigorous-intensity PA as follows: sedentary time: time spent sitting or lying down with low energy expenditure, such as when watching TV or sitting in class; moderate activity: activity that moderately raises the heart rate, such as walking and performing household chores during the week; and vigorous activity: vigorous heart rate–raising activity during the week. Time spent in sedentary activity and moderate- and vigorous-intensity PA will be determined along with the PA levels in different domains. Given the arbitrary nature of the accelerometer count–based cut-offs and the difference in unit expression across accelerometer models, we will report accelerometry data in standardized units of acceleration (m/s^2) [23,24].

Household Socioeconomic Demographic and Anthropometric Measurements

The head of the household or a member of the household nominated by the adolescent citizen scientist will be invited to participate in the study after which a household survey will be completed. This consists of a multidimensional poverty index tool, will be used to capture household access to services and assets, physical structure of the home, household demographics, education, social grants, employment status, and the Food Insecurity Experience Scale [25] to capture household food security. This survey will be completed during the initial household visit.

During this visit, all household members who have provided consent, including children (aged above 5 years) who can assent, will have anthropometric measurements taken using the same standardized methods as used for adolescent measurement.

In-depth Interview on Household Foodways

Trained research team members will conduct semistructured, in-depth interviews with the previously consented primary adult caregiver about the factors that influence the diet and PA behavior of members of the household. This interview will include guiding questions concerning *foodways* [26], including food procurement, storage and preparation, food choices and challenges, leisure time activities, and the meaning and significance of food and PA within families.

Neighborhood and Journey-to-School Data

Lived experiences and perceptions of their neighborhoods will be completed by the adolescents using two different tools as follows:

Neighborhood Walkability Using Neighborhood Environment Walkability Scale-Africa Questionnaire

The Neighborhood Environment Walkability Scale-Africa will be used to capture participant perceptions of the conduciveness of their built environment to walking and similar physical activities. This tool has been validated in several sub-Saharan African countries, including Kenya, Cameroon, and South Africa [27].

Adolescent Lived Experience Using the EpiCollect5 Tool

A subset of the 150 adolescents recruited will be invited to participate in the *citizen scientist* components of the project (objectives 3 and 5) to collect data within their neighborhood and on their journey to and from school using the EpiCollect5 tool developed by the Centre for Genomic Pathogen Surveillance as part of the Big Data Institute at Oxford University (a description has been provided later in this section). This subsample of adolescents (citizen scientists) will specifically include those self-identified as peer leaders (in school club leadership positions), in addition to general students. Approximately 30-45 adolescents will be recruited from each site as follows: 10-15 adolescents will be recruited from schools in low-income settings (L-L category), and 15-30 adolescents will be recruited from each site in higher-income settings (a mix of adolescents from the L-H and H-H categories detailed previously).

Citizen science is a multidimensional approach to research that considers the challenges experienced by different communities as well as the cultural diversity and differences among the residents. It involves members of these communities and the broader public working with scientists to collect and analyze data [28]. This approach has been used to promote and increase PA and other healthy behaviors [29]. Although it has been used mostly in developed countries, the citizen science approach has been used to determine the enablers and barriers of PA in adults from a low-income urban area in South Africa [30] and in adults and adolescents in Mexico [31].

The citizen scientists will be trained to use the EpiCollect5 tool [32], a simple mobile app, to map and describe their journey to and from school and neighborhood-level factors that affect their diet and PA (*the walk*). The mobile app data consist of geotagged *photovoice* or voice notes, photographs, and global positioning to confirm their location within the community setting. The adolescents will have a list of guiding instructions and questions for these walks. Some of the information they will be asked to capture include the following: food outlets in the area; food and drink advertisements on radio or television; locations at which they buy or are given food and drink; other food options on offer at such locations; locations at which they do not eat or spend time and why; and the factors that hinder or facilitate their PA, such as gym facilities, fields, and so on.

After the EpiCollect5 data collection is complete, to gain further insights into the adolescent lived experience, we will convene focus group discussion workshops with the participants, face to face or virtually, to review their experience as citizen scientists and their observations of their food and PA environments. The citizen scientists will be provided with deidentified photographs and associated narratives of the various EpiCollect5 tool records. In small groups, they will be trained to sort through the various photographs and identify themes. Once themes have been identified, the group will be asked to prioritize those factors that may be barriers to, or facilitators of, healthy food choices and PA opportunities and, more specifically, those that may be able to be changed through advocacy or by engaging with other factors [33]. In addition, as part of the knowledge exchange activities, we will train selected citizen scientists in advocacy and presentation skills to present their findings in collaboration with researchers in a virtual or face-to-face meeting at the end of the data collection phase. Adolescents, school stakeholders, and food vendors around the schools will be invited to this meeting, the purpose of which would be to share results from the study and to hear from these actors on their different roles in contributing to the food and PA environments and possible interventions to make these healthier.

Researcher Measurement of Healthy Food and PA Opportunities Using the EpiCollect5 Tool

Researchers will use the same EpiCollect5 tool to provide observational measures of access to healthy affordable food and the attributes of the built environment that promote or create a barrier to PA in the domains of transport, sport, or leisure. This will involve geocoding the various amenities, including food outlets (retail, spazas or informal traders and vendors, fast food outlets, restaurants, and so on), PA sites (parks, gyms, and transport hubs within a 1000-m buffer of households), advertising of fast food and sugar-sweetened beverages, and community assets within a 1000-m buffer of each participant's residence. To account for daily variability in the food and PA environments, data collection will be conducted on 2 separate days when the environments might be expected to change, for example, on weekdays and weekends or on market and nonmarket days.

Recordings will be transcribed, existing nutritional information will be obtained for foods where possible (eg, from manufacturers' websites), and the foods will be categorized (1) by food group and (2) as more or less healthy.

School Environment Data

In consultation with the school leadership, a teacher liaison will be recruited as the school *point person*. After obtaining consent, the teacher liaison will complete an interviewer-administered questionnaire and observational checklist on food- and activity-related school policies and on the school diet and PA environments, as detailed herein.

Audit of School Policies

An audit of the school policies related to diet and PA will be conducted using an observational checklist that will be completed by study staff combined with a questionnaire completed by the teacher liaison in the school. This will include school policies on physical education and healthy eating.

Audit of School Environment

An audit of the built environment in and around selected schools will be completed by the study staff using an observational checklist. This will be combined with a questionnaire completed by the teacher liaison. The audit will assess transport and traffic around the schools and places inside the school grounds to engage in PA (play). The study staff will systematically walk around in the immediate area surrounding the schools (1000-m radial buffer), coding the number, typology, and locations of formal and informal vendors and noting the presence of food shops and vending machines on and around the school grounds.

Audit of Food Vendors Around Schools

Additional information will be collected on informal vendors situated around the selected schools and the types of food and beverage items they sell. These assessments will be repeated on different days and at different times of the day to assess the reliability of the observation tool and variability in the environment. All data will be collected using the EpiCollect5 tool, which allows for the electronic capture of audio, photographic, and text data. Voice recordings will be used to describe informal vendors and the food and beverages on offer, using approaches developed and tested in previous studies [34,35]. We will collect information on aspects such as (1) type of food outlet, (2) kind of food outlet (formal or informal), (3) brands and types of food and beverages sold, (4) most frequently purchased food items, (5) prices of healthy and unhealthy foods, and (6) strategies adopted for sales promotion.

Protocol Adaptation Because of the COVID-19 Pandemic

Although the aim and objectives of the study remain unchanged, the current context of the global COVID-19 pandemic necessitated some adaptations of research activities, given that data collection was incomplete when lockdown restrictions were implemented at the GDAR partner country research sites. Amendments to specific methods to achieve some of the objectives of the protocol became essential because of movement restrictions at the GDAR partner country sites. These amendments are imperative to capture the levers associated with the diet and PA of citizen scientists and their households before and during the pandemic efficiently and cost-effectively, while simultaneously ensuring the safety of the participants and

researchers. Furthermore, these amendments take account of the *new normal* circumstances such as mandatory social distancing and total or partial lockdown of countries, both of which have been shown to affect the food and built environments [36]. The amendments made that were relevant to the data collection methods and data analysis in objectives 2, 3, and 5 are as follows:

Objective 2: Explore household exposures that may influence diet and PA behavior in adolescents from low-to higher-middle–income communities.

The original protocol required face-to-face interviews with the parent or caregiver of the citizen scientist. This method will be revised to include conducting phone interviews with the parent or caregiver, and the guiding questions will be modified to include questions concerning the changes to their diet and PA and other related factors as a result of the COVID-19 pandemic. For example, "Are there any changes to the diet and physical activity of your household during the COVID-19 crisis compared with pre-COVID?"

Objective 3: Identify neighborhood-based exposures that may influence diet and PA behavior in adolescents, from low- to higher-middle–income communities.

Objective 5: Identify exposures that may influence diet and PA behavior in adolescents on the journey between home and school.

According to the original protocol, the citizen scientists and research team members were to conduct *walk-along interviews* in their neighborhood using the EpiCollect5 mobile app to achieve objectives 3 and 5. Thereafter, the citizen scientists by themselves were to capture their journey to school and school lived experiences using the mobile app. These activities might not be feasible as planned because of safety reasons and COVID-19 restriction measures that are in place at the GDAR partner country sites. Consequently, phone interviews with citizen scientists about their *lived experience* and factors that shape or influence their diet and PA behaviors before and during the COVID-19 pandemic will be conducted.

Analysis Plan

Quantitative Analysis

Multivariable regression analyses examining the associations between the school and home environments and dietary patterns, nutritional knowledge, consumption of specific food groups such as fruit and vegetables, BMI, total PA, and domains of PA will be conducted. We will add interaction terms to explore the distribution of environment-behavior associations by country, socioeconomic area, and socioeconomic status of the adolescents' households.

Qualitative Analysis

Data preparation for analyses will follow the standard guidelines for qualitative research strategies [37]. The voice notes of the citizen scientists' focus group discussions (workshop) and household in-depth interviews will be transcribed verbatim. Each citizen scientist's voice note and transcription will be linked to its other relevant files (ie, an electronic version of the focus group seating map, notes on nonverbal communication and other issues observed, typed memos, typed notes from the debriefing session, and a list of actual vs scheduled participants). The participants' anonymity and confidentiality will be protected for all reporting purposes. The recordings will be kept electronically in password-secured files for 10 years before they are deleted.

We will focus on thematic data analyses. In line with standard practice [38], data analysis will be conducted on an ongoing basis that will begin with the first interviews scheduled and focus groups conducted and will continue throughout the study. Each moderator, notetaker, and research assistant will record in a reflective manner their thoughts about each focus group session, individual interview interactions, and community observations. They will pay special attention to ideas and issues discussed, similarities and differences among the focus groups and individual interviews conducted, things to keep in mind for subsequent contacts, and possible questions for future interactions. During data collection, the investigators and research assistants will meet several times to discuss their findings and identify emerging ideas and topics.

The next step of data analysis will occur when data collection is complete. After the transcription of the qualitative data has been completed, the codebook will be developed inductively, focusing on the objectives of the study and the data collected. Using procedures consistent with textual and content analysis, the focus group and interview data collection personnel and members of the research team will review the transcripts. Each transcript will be read several times and coded line by line. We will use Excel (Microsoft Corporation) and NVivo (QSR International) to highlight words or sentences that capture the critical issues and thoughts identified by the participants. These central categories identified within the material will also be documented according to the preidentified research questions. This process will help us to identify the connections among the categories as part of the clustering process in qualitative analyses. The clusters of categories will facilitate the identification of themes within the data. These themes will then be grouped according to the different health behaviors that are the focus of the qualitative work (engaging in citizen science, food, and PA environment). Deviant cases will also be discussed.

The use of different interviewers, focus group moderators, and notetakers that we aim to have in this study should decrease the likelihood that the findings emerging from each of these data collection modes are a result of personal bias or leading questions. In addition, a review of the transcripts by additional research team members will be conducted to ensure that the findings are grounded in the data.

Data Management

Assessment standardization and data quality assurance and fidelity will be optimized through centralized training and oversight of the data collection sites to ensure appropriate handling of sensitive information, uniformity in data collection, data entry, and data quality. Any data resources containing personal health information or otherwise potentially identifiable

information will use industry-standard encryption such as Advanced Encryption Standard-256.

For the quantitative data (data security), Advanced Encryption Standard-256 encryption will follow the survey data through its life cycle, when at rest or in transit. Data will be collected and transmitted regularly to the REDCap (Research Electronic Data Capture) data server. The REDCap data server is a Health Insurance Portability and Accountability Act–compliant, firewalled environment with daily automated onsite and offsite backups. The data server is continuously monitored for suspicious intrusion activity.

EpiCollect5 is part of the Big Data Institute at Oxford University and hosted at a UK data center with cloud hosting provider, Digital Ocean. Digital Ocean is fully General Data Protection Regulation compliant and accredited at Cloud Security Alliance STAR Level 1. To prevent unauthorized access and for secure data storage, mobile devices (Android [Google LLC] and iOS [Apple Inc]) will be encrypted and password or fingerprint protected. Data are transferred from mobile devices to the application server using Hypertext Transfer Protocol Secure, and the Transport Layer Security certificate uses SHA-256 with RSA (Rivest-Shamir-Adleman) encryption as a signature algorithm.

Transcripts from qualitative data will be pseudoanonymized (removing direct mention of identifiers) during the quality checks by the researchers after transcription, and audio recordings will be deleted after transcription and quality checks. The only information kept and linked to participant IDs will be broad demographic and role descriptors. Anonymized transcripts will be uploaded to NVivo, an encrypted web-based qualitative analysis software.

Data will be stored, as described previously, at each collaborating country site and transferred between sites through the Secure File Transfer Protocol software set up by the University of Cambridge.

Researcher Debrief or Reflection

As described in the analysis plan for objectives 3 and 5, a key qualitative strategy will be memo taking and discussion among the team members of the research activities. These will be ongoing throughout the fieldwork and will be documented in the form of typed notes. These notes and other observations will be discussed at meetings of the data collection staff to document shared and distinct observations of the fieldwork. These data will be analyzed using the techniques described in the analysis plan.

Results

The primary objective and outcome of the proposed study described in this protocol paper is to determine the barriers and facilitators (levers) of healthy diet and PA of adolescents in their household, neighborhood, and school environments and during the journey from home to school. It is also to compare the similarities and differences of these levers among settings and across socioecological domains. The secondary outcomes include exploring the potential of a participatory citizen science approach to build agency among adolescents to inform future policy to promote a healthy diet and PA. The study described in this protocol was primarily funded through a UK NIHR grant in 2017 and approved by the relevant institutional ethics review boards in the country sites (South Africa, Cameroun, and Jamaica in 2019, and Kenya in 2020). As of December 23, 2020, we had completed data collection from adolescents (n≥150) in all the country sites, except Kenya, and data collection for the subgroup (n=30-45) is ongoing. Data analysis is ongoing and the outputs of findings from the study described in this protocol are expected to be published by 2022. The study timeline is detailed in Table 2.

Table 2. Timeline of the study.

Activity	2019	January-March 2020	April-June 2020	July-September 2020	October-December 2020	January-March 2021	April-May 2021	June-December 2021
Preparation								
Ethics submission	✓[a]	✓						
Initial school enquiries	✓	✓						
Staff recruitment	✓	✓						
Standard operating procedures: anthropometrics and data collection tool development and adaptation	✓							
Identify schools	✓	✓						
Staff training		✓						
Pilot tools		✓						
Data collection								
Adolescent recruitment		✓	✓	✓				
Individual adolescent data collection		✓	✓	✓	✓	✓		
Household data collection				✓	✓	✓		
Neighborhood and journey-to-school data				✓	✓	✓		
School environment data				✓	✓	✓		
Data analysis								
Data analysis						✓	✓	✓
Results synthesis workshop						✓		
Write-up of outputs								
Write-up and dissemination of outputs							✓	✓

[a]Activity is performed during the time period.

Discussion

Importance of This Protocol Paper

This protocol paper for our study describes an investigation into the potential levers that influence adolescent diet and PA in their home, neighborhood, and school environments, as well as in the dynamic exposures that adolescents experience on their routine journey between home and school. We aim to explore the interactions between individual-level factors and these upstream determinants in various socioeconomic groups. The adolescent life-stage offers an opportunity to improve adolescents' lifestyle behaviors for future generations, which may also lessen intergenerational NCD risk and burden. We envisage that by engaging in *citizen science*, adolescents will develop individual and collective self-efficacy such that they can identify barriers to affordable healthy eating and PA and proffer solutions. We further anticipate that this approach will serve to engage, empower, and connect school-aged *citizen scientists* as catalysts for change in their communities.

The results from this study will feed into policy round table engagement activities to be conducted as part of the broader GDAR research portfolio to facilitate sharing of data with policy makers and stakeholders and inform the co-design of interventions in the built environment that support healthy eating and active living behaviors.

Beyond this study, we hope that participation in this type of research will encourage and inspire adolescents to explore further the possibility of becoming lifelong social catalysts for positive change in their own communities and beyond. By training citizen scientists in low-resource settings to gather evidence, analyze, and disseminate the findings, the community may be able to advance solutions to the barriers to active living and healthy eating, often outside of the health sector.

Strengths and Limitations

The main strength of this protocol is its novel approach, which triangulates convergent mixed methods design, including survey, observational, and ethnographic data, with citizen science

research. This protocol is designed to better understand the unique sociocultural, environmental, ecological, and policy levers that may contribute to effective and sustainable interventions. The study also encompasses levers across socioecological levels (individual, home, school, journey to and from school, and the neighborhood) that could affect the diet and PA of adolescents. Another strength of the proposed research protocol is that it is designed to empower adolescents to develop advocacy skills and individual and collective self-efficacy such that they will be able to engage local *actors* and stakeholders to address the barriers to affordable or accessible healthy eating and PA.

This study is exploratory and hypothesis generating in nature, and it is intended that the collection of a number of health behavior outcomes across a wide range of settings (and across and among country sites) will provide information on the differences and variations among groups, thus informing subsequent hypothesis testing in larger-scale research. The study limitations include the fact that the study being described will be conducted in only 1 city in each of the countries, except for South Africa with 2 cities, but with participants from different age groups, which may limit the generalizability of the findings to other regions within these countries. Furthermore, data will be collected from 1 to 3 schools from different socioeconomic areas in each city, which may not be representative of the different categories of adolescents in our study. The age group of high school adolescents included in the study may not be representative of the entire spectrum of adolescence, particularly the earlier phase of this life period. The analysis plan does not explicitly take into account the ethnicity of the participants, which might have an impact on their diet and PA, particularly in South Africa where ethnicity is more heterogeneous. However, although this is not included in the proposed cross-country comparative analysis because of the relative racial homogeneity in other countries, this can be explored further in a South African in-country analysis.

On the basis of the insights that are achieved through the study, expanding subsequent research to a broader number of cities and more representative adolescent age groups may be indicated.

Conclusions

The development of research with a focus on the socioecological determinants of diet and PA in LMIC settings and the employment of innovative methodologies to interrogate and map the contexts of these determinants will generate much-needed data to understand the levers that can be leveraged to improve health outcomes. This protocol details a mixed methods study to explore potential levers for intervention to improve adolescent diet and PA at varying socioecological levels from the home and neighborhood to the school environments and the dynamic exposures between home and school. The inclusion in the sample of caregivers and community members who play key roles in decision making about diet and PA is expected to add to the comprehensive nature of the data and the inferences that would be drawn from them. The individual and public involvement processes used will support the development of awareness and advocacy skills among adolescents, which are important for peer-led dissemination of information about NCD risk factors and advocacy for healthier food and built environments to reduce the risk of experiencing NCDs in adolescence and subsequent adulthood.

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Authors' Contributions

FAOW and PW led the conceptualization, initial drafting, and overall drafting of the manuscript supported by ERIM. TO (senior author) co-led the conceptualization of the research proposal and contributed to drafting the manuscript. LKM co-led drafting of significant components of the manuscript and overall drafting process. CO, ERIM, GM, IG, and ABP, and CMT were responsible for drafting and editing the subsections of the manuscript. JAS, FA, JCM, YW, CMT, MKTR, EVL, KJO, SAN, VW, MM, and ACK contributed to manuscript editing and finalization.

Conflicts of Interest

None declared.

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Abbreviations

GDAR: Global Diet and Activity Research
H-H: middle- to high-income home neighborhoods and middle- to high-school neighborhood
L-H: low-income home neighborhoods and middle- to high-income school neighborhood
L-L: low-income home neighborhood and low-income school neighborhood
LMIC: low- and middle-income country
NCD: noncommunicable disease
NIHR: National Institute for Health Research
PA: physical activity
REDCap: Research Electronic Data Capture
RSA: Rivest-Shamir-Adleman

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Protocol

Rapid Detection of Extensively Drug-Resistant Tuberculosis in Clinical Samples Using a Novel Tabletop Platform: Protocol for a Prospective Clinical Study

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Abstract

Background: The lack of accurate and efficient diagnostic devices for extensively drug-resistant tuberculosis (XDR-TB) makes it a severe threat to global public health. A prospective clinical study in an intended-use cohort was designed to evaluate the Akonni Biosystems XDR-TB TruArray and lateral flow cell (XDR-LFC) to address this gap in tuberculosis diagnostics.

Objective: This paper presents the protocol for a study that aims to document the conceptualization and design of this evaluation method for early dissemination while data collection and analysis are ongoing.

Methods: The clinical study was conducted in three phases. The first phase was to observe changes in bacterial load and culture positivity in patient sputa over time and better understand the diversity of prospective clinical samples. The second phase was to prospectively collect clinical samples for sensitivity and specificity testing of the Akonni Biosystems XDR-LFC device. Lastly, the third phase was to explore the anti-TB drug concentrations in serum throughout the drug-resistant tuberculosis treatment.

Results: The methodology described includes the study design, laboratory sample handling, data collection, and the protection elements of human subjects of this clinical study to evaluate a potential new XDR-TB diagnostic device. A total of 664 participants were enrolled across the three phases. The implemented complex systems facilitated a thorough clinical data collection for an objective evaluation of the device. The study is closed to recruitment. The follow-up data collection and analysis are in progress.

Conclusions: This paper outlined a prospective cohort study protocol to evaluate a rapid XDR-TB detection device, which may be informative for other researchers with similar goals.

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KEYWORDS

tuberculosis; drug-resistant; extensively drug-resistant; diagnostic; rapid treatment methods; protocol; drug susceptibility testing; prospective cohort study

Introduction

Background

Regional increases in the prevalence of drug-resistant tuberculosis (DR-TB) pose a significant threat to global tuberculosis (TB) control [1,2]. The World Health Organization (WHO) defined extensively drug-resistant tuberculosis (XDR-TB) as multidrug-resistant (MDR) or rifampicin-resistant (RIF-R) tuberculosis strains that are also resistant to fluoroquinolone (FQ) and either bedaquiline or linezolid (or both) [3]. XDR-TB has been associated with up to 80% mortality and is considered virtually untreatable in many parts of the world [1,4]. In 2018, the WHO estimated that there were approximately half a million new cases of DR-TB; however, only about 37% of those were detected and reported due to scarcity of rapid, efficient, and cost-effective solutions for detecting the resistance [1].

Early and rapid DR-TB detection and treatment with appropriate drugs are the essential effective control strategies to reduce DR-TB transmission and improve treatment outcomes. The 2020 WHO Global TB Report highlights that a pillar of the End TB Strategy and the United Nations (UN) Sustainable Development Goals (SDGs) requires intensified effort toward major technological developments by 2025, including rapid point-of-care tests for detecting drug resistance [5]. Current phenotypic drug susceptibility testing (pDST) can take up to 16 weeks to complete [6]. If not detected and treated rapidly, the continued XDR-TB transmission can cause massive disruptions to health care systems, economies, and lives on a local, national, and global scale. Unfortunately, despite the increasing global prevalence of XDR-TB, there are still no US Food and Drug Administration (FDA)–approved diagnostic platforms for the rapid diagnosis of XDR-TB, leaving individuals vulnerable to potential exposure.

There is a critical need for a rapid, highly sensitive, and specific tabletop platform to diagnose XDR-TB from patient samples directly. This clinical study was designed to combine the experience, resources, and existing diagnostic testing capabilities of the Global Consortium for Drug-resistant Tuberculosis Diagnostics (GCDD) (NIAID U01AI082229) with the technological innovation and industry knowledge of Akonni Biosystems to evaluate a rapid XDR-TB detection platform based on the detection of resistance-conferring mutations. During the initial design and development stage, the research team expanded and validated an existing prototype, the gel element microarray (GEM) platform (NIAID RC3 AI089106 and R43 EB011274), to detect clinically relevant single nucleotide polymorphisms that confer resistance in XDR-TB strains (NIAID R01AI111435). This paper describes the design and methods of a clinical study for evaluating the Akonni Biosystems XDR-TB TruArray and lateral flow cell (XDR-LFC) (Fredrick).

Study Setting

The Republic of Moldova is a former Soviet republic located between Romania and Ukraine with a population of approximately 4 million people [7]. Its capital, Chisinau, is the most densely populated city, with about 640,000 residents [7]. The WHO ranks Moldova as one of the top 10 countries with the highest global multidrug-resistant tuberculosis (MDR-TB) burden [8]. The country reported approximately 24% new TB cases and 61% MDR-TB cases (previously treated with first-line drugs) in 2018 [8]. The Moldovan National TB Reference Laboratory (NRL) of the Phthisiopneumology Institute (PPI), Chisinau, has a staff of 25 and processes about 25,000 acid-fast bacilli (AFB) smears, 10,000 Xpert tests, 30,000 *Mycobacterium tuberculosis* (*Mtb*) cultures, and 10,000 culture-based pDST per year. Additionally, the NRL manages three regional TB laboratories and a sputum courier system that transports samples to and from these regional laboratories. The PPI was one of the three international laboratories that participated in the GCDD trial, and instituted a formal laboratory validation for relevant TB laboratory tests to ensure strict adherence to laboratory controls. Their previous research collaboration, along with high rates of DR-TB, made Moldova an ideal setting for the study in an intended-use population.

Study Purpose and Aims

This study was designed primarily to determine the accuracy of the Akonni XDR-LFC device for detecting XDR-TB in an intended-use cohort. Participants were enrolled in three distinct but complementary phases at the Chisinau Municipal Hospital and regional TB treatment centers in the Republic of Moldova from 2014 to 2019, and were followed up for 2 years. Phase 1 involved exploring the changes observed in a TB bacterial load and culture positivity in patient sputa over time to understand the diversity of possible clinical samples, and validating the patient recruitment methods, laboratory processing procedures, and data collection instruments. In phase 2, we enrolled patients and collected prospective clinical samples from patients at risk for DR-TB to evaluate the sensitivity and specificity of the XDR-LFC instrument for detecting XDR-TB directly in clinical samples compared to reference DST. After the study initiation, an additional aim was included to explore the anti-TB drug concentrations in serum over the DR-TB treatment course and to provide preliminary data for future studies on the patient treatment response to the DR-TB treatment regimens.

Methods

Protocol Design

Phase 1 of the study was a prospective cohort study with serial sputum sampling. The sputum samples were collected from participants at the medical facilities daily on days 2-14, weekly on days 21, 28, and monthly on days 56, 84, 112, 140, and 168. At each sputum collection encounter, the study staff conducted a brief interview with the patient and a clinical assessment. Medical record data abstraction also occurred at these time points and an image of the directly observed therapy (DOT) record was collected.

Phase 2 was a prospective cohort study with a 24-month follow-up to assess a patient's TB status and treatment outcomes. The sputum and blood samples were collected at the enrollment visit, along with the participant's interview and medical record data abstraction. The patient records in the national TB registry will be reviewed at 24 months postenrollment to document the patient outcomes according to

the WHO definitions (cured, completed, dead, failed, defaulted, and transferred) [8], and will be completed for all participants in 2021.

The eligible phase 2 participants were invited to enroll for the "phase 2+" arm of the study to evaluate the anti-TB drug concentrations in serum. Participants who consented to phase 2+ were followed up at day 7, 14, 28, 56, 84, 112, 140, and 168. At each time point, blood and sputum were collected, a brief patient interview and clinical assessment were conducted, and the medical record data, including an image of the DOT record, was abstracted and collected.

Previously published studies have utilized similar serial sample collection methods, and the outcome reviews aligned with the WHO treatment outcome guidelines [9,10]. The trial was not registered with ClinicalTrials.gov because this study was a prospective observational cohort study and did not meet the criteria for randomized controlled trials.

Eligibility Criteria

Each phase had independent inclusion and exclusion criteria (Table 1). No phase included institutionalized or incarcerated subjects or pregnant women. Pregnant women were excluded because the medications required by the Moldovan National TB Program are not approved for use in pregnancy. Institutionalized and incarcerated subjects were excluded because the study was designed to evaluate this device in a general population and was not designed to assess the unique considerations of incarcerated or institutionalized populations. The study also required that the subjects produce at least 8.5 mL of sputum, a sample amount sufficient for all study procedures, at the enrollment.

Table 1. Inclusion and exclusion criteria by study phase.

Criteria	Phase 1	Phases 2 and 2+

Inclusion criteria	• ≥18 years of age
	• RIF[a] resistant by the GeneXpert *Mtb*[b]/RIF assay
	• Enrolled within 1 week of RIF resistance determination by GeneXpert
	• Not treated for TB[c] for at least 4 weeks
	• Intend to remain in Moldova for 24 months
		• ≥5 years of age
		• Suspected or confirmed clinically active TB disease (at least one of the following):
		  • AFB[d] sputum smear positive within prior 7 days
		  • GeneXpert positive within prior 7 days
		  • Clinical suspicion of TB
		• And suspected or confirmed DR-TB[e] (defined as at least one of the following):
		  • Received >1 month of treatment for a prior TB episode
		  • Suspected of failing standard TB treatment
		  • Close contact with a known DR-TB case
		  • Diagnosed with RIF-R[f] within the past 30 days
		  • Previously diagnosed with MDR-TB[g] and suspected of failing a standard MDR-TB treatment regimen

Exclusion criteria	• Pregnant women • Institutionalized or incarcerated patients • Patients unable to produce 8.5 mL of sputum for the study testing	• Pregnant women • Institutionalized or incarcerated patients • Patients unable to produce 8.5 mL of sputum for the study testing • Started treatment for the current TB episode more than 14 days prior to the enrollment date

[a]RIF: rifampin.

[b]*Mtb*: *Mycobacterium tuberculosis*.

[c]TB: tuberculosis.

[d]AFB: acid-fast bacilli.

[e]DR-TB: drug-resistant tuberculosis.

[f]RIF-R: rifampin resistant.

[g]MDR-TB: multidrug-resistant tuberculosis.

Recruitment

Moldova's national online TB registry, SIME-TB, was utilized to recruit potential participants for both primary phases of the study. The registry contains demographic data of all newly diagnosed TB cases. GeneXpert MTB/RIF devices were available at microscopy centers across Moldova, and the results were entered in SIME-TB within 1 to 4 days. All RIF-R patients were directed to go to one of the four regional TB clinics: 2 in Chisinau, 1 in Balti, and 1 in Vorniceni. The study physicians reviewed the SIME-TB and the patient intake logs for newly admitted patients to these TB clinics daily to identify patients suspected of suspected of TB or DR-TB. Once the potential participants were identified, the study staff approached the patients for screening, informed consent, and enrollment.

Samples and Testing

As described in the Protocol Design section, the sputum and blood samples were collected at specified time points during each study phase. A minimum sputum volume was set for enrollment sample collection to ensure sufficient samples for all sputum tests. If a patient could not produce an 8.5 mL sputum

sample initially, they were requested to try again in 2 hours following the first attempt; the samples were then pooled and measured again. Earlier experience with the GCDD trial showed that most patients could produce an 8.5 mL sputum sample required for the study. The follow-up sample collection did not have the minimum volume requirement.

The standardized procedures for processing the patient samples for testing are described below. Detailed reference figures were included in the study protocol to ensure a high degree of consistency. Solid culture using the Lowenstein–Jensen (LJ) medium and liquid culture using mycobacteria growth indicator tube 960 (MGIT 960) (Becton, Dickinson and Company) were performed using the validated protocols recommended by the WHO [11], consistent with the National TB Program (NTP) standards [11], and the manufacturer's instructions [12]. Samples of *Mtb* DNA were extracted for shipment to the University of California, San Diego (UCSD), for next-generation sequencing (NGS).

Phase 1

Figure 1 shows the standardized flowchart of the day 1 (enrollment) sputum sample (≥8.5 mL) division and processing. The collected sputum sample was processed as follows:

- Raw sputum was processed to sediment (2.5 mL) a subsample of raw sputum
  - AFB smear was performed (0.1 mL)
  - A subsample of the sediment was frozen for later field testing by Akonni LFC (1.1 mL)
  - DNA was extracted from the sediment for shipment to the UCSD for NGS (0.5 mL)
- Solid LJ culture (0.2 mL; put on beads and frozen after growth)
- MGIT liquid culture (0.5 mL)
- MGIT DST reference testing was performed on confirmed *Mtb* positive specimens

Figure 1. The phase 1 enrollment sample processing flowchart. AMK: amikacin; CAP: capreomycin; INH: isoniazid; KAN: kanamycin; LEV: levofloxacin; LJ: Lowenstein–Jensen; MGIT: mycobacteria growth indicator tube; MOX: moxifloxacin; *Mtb*: *Mycobacterium tuberculosis*; PZA: pyrazinamide; RIF: rifampin; SMOR: single molecule-overlapping read; STR: streptomycin.

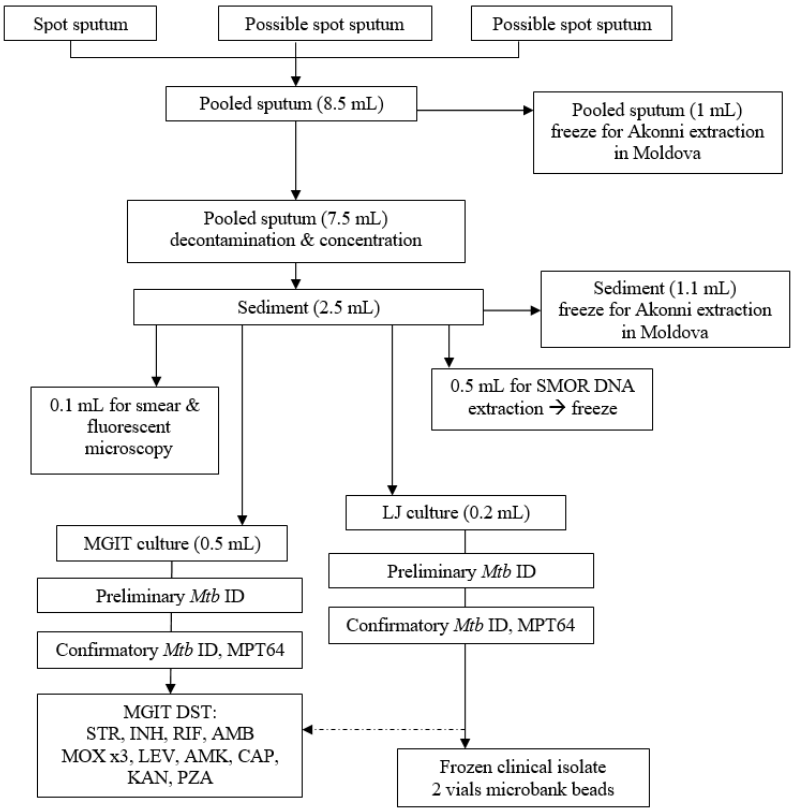


Table 2 displays the prioritization of testing for sputum samples <8.5 mL at the follow-up. The follow-up sputum samples (maximum 20 per participant) were processed as follows:

- Raw sputum was processed to sediment
- AFB smear was performed
- A subsample of the sediment was frozen for later field testing by Akonni LFC
- Crude heat lysis extraction from the sediment for shipment to the UCSD for NGS
- Solid LJ culture (put on beads and frozen after growth)

Figure 2 shows the standardized flowchart of the procedures used to ensure consistent sample processing. The first sputum and last culture positive sputum collected in phase 1 underwent DST using the MGIT 960 following the 2012 WHO recommendations for critical concentrations [11]: INH 0.1 µg/mL; RIF 1.0 µg/mL; ethambutol (AMB) 5.0 µg/mL; pyranzinamide (PZA) 100 µg/mL; KAN 2.5 µg/mL; AMK 1.0 µg/mL; CAP 2.5 µg/mL; levofloxacin (LEV) 1.5 µg/mL; and moxifloxacin (MOX) at 0.25 µg/mL, 0.5 µg/mL, and 2.0 µg/mL.

Table 2. Prioritization of testing for sputum samples <8.5 mL at the follow-up visits.

Pooled sputum	Sputum frozen	Sediment	Sediment frozen	AFB[a] smear	SMOR[b] DNA extract	LJ[c] culture
>7.5 (mL)	1.0	2.5	1.1	0.1	0.5	0.2
6.5-7.4 (mL)	0.5[d]	2.0[d]	1.1	0.1	0.5	0.2
5-6.4 (mL)	0[e]	1.5[d]	0.55[d]	0.1	0.5	0.2
<4.9 (mL)	0[e]	1[d]	0[e]	0.1	0.5	0.2

[a]AFB: acid-fast bacilli.

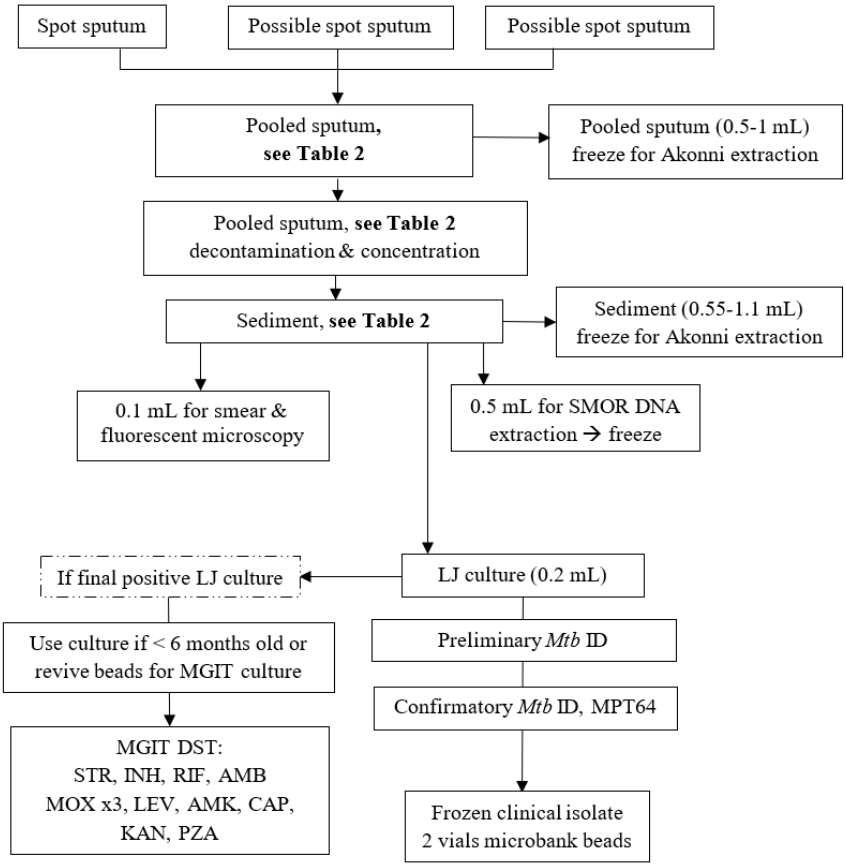
[b]SMOR: single molecule-overlapping read.

[c]LJ: Lowenstein–Jensen.

[d]Reduced volume for the procedure.

[e]The procedure was skipped.

Figure 2. Phase 1 follow-up sputum sample processing schema. AMB: ethambutol; AMK: amikacin; CAP: capreomycin; INH: isoniazid; KAN: kanamycin; LEV: levofloxacin; LJ: Lowenstein–Jensen; MGIT: mycobacteria growth indicator tube; MOX: moxifloxacin; *Mtb*: *Mycobacterium tuberculosis*; PZA: pyrazinamide; RIF: rifampin; SMOR: single molecule-overlapping read; STR: streptomycin.



Phase 2

The first 54 participant specimens underwent standard testing and had both raw sputum and sediment samples evaluated using the Akonni XDR-LFC device. A comparison of the LFC results from the raw sputum and the sediment guided the decision about which sample to use for LFC analysis for the remaining specimens. The raw sputum was used for the remainder of the samples and standard testing.

Phase 2 Standard Testing

The day 1 (enrollment) sputum sample was divided as follows (Figure 3):

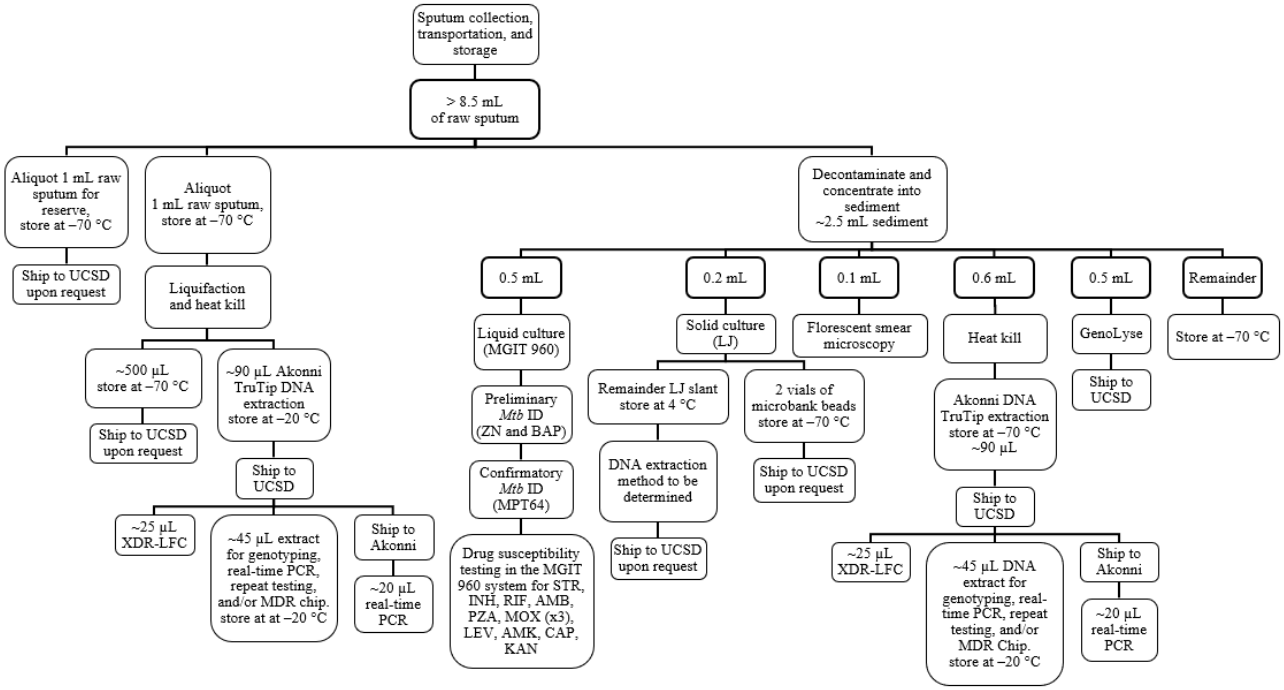
- For a subsample of raw sputum
  - Extracted DNA was frozen or run in real time with Akonni XDR-LFC (1 mL)
  - Raw sputum was kept in reserve for repeats or future testing (1 mL)
- Raw sputum was processed to sediment (~2.5 mL)
  - AFB smear was performed
  - Extracted DNA was frozen or run in real time with Akonni XDR-LFC
  - Hain GenoLyse extraction DNA was batched and shipped to the UCSD for NGS
  - Solid LJ culture (put on beads and frozen after growth)

- MGIT liquid culture

- *Mtb* confirmation testing was done
- MGIT DST (for INH, RIF, AMB, PZA, STR, KAN, AMK, CAP, LEV, and MOX at 3 concentrations) was performed on the confirmed *Mtb* positive specimens

The day 1 (enrollment) blood sample was collected in a 10-mL red-top tube, allowed to clot, centrifuged at 1300 g for 20 minutes to separate the serum, and frozen for storage at –70 °C.

Figure 3. Phase 2 specimen flowchart for the first 54 participant samples. AMB: ethambutol; AMK: amikacin; CAP: capreomycin; INH: isoniazid; KAN: kanamycin; LEV: levofloxacin; LJ: Lowenstein–Jensen; MGIT: mycobacteria growth indicator tube; MOX: moxifloxacin; *Mtb*: *Mycobacterium tuberculosis*; PCR: polymerase chain reaction; PZA: pyrazinamide; RIF: rifampin; SMOR: single molecule-overlapping read; STR: streptomycin; UCSD: University of California, San Diego.



XDR-LFC Device Procedure

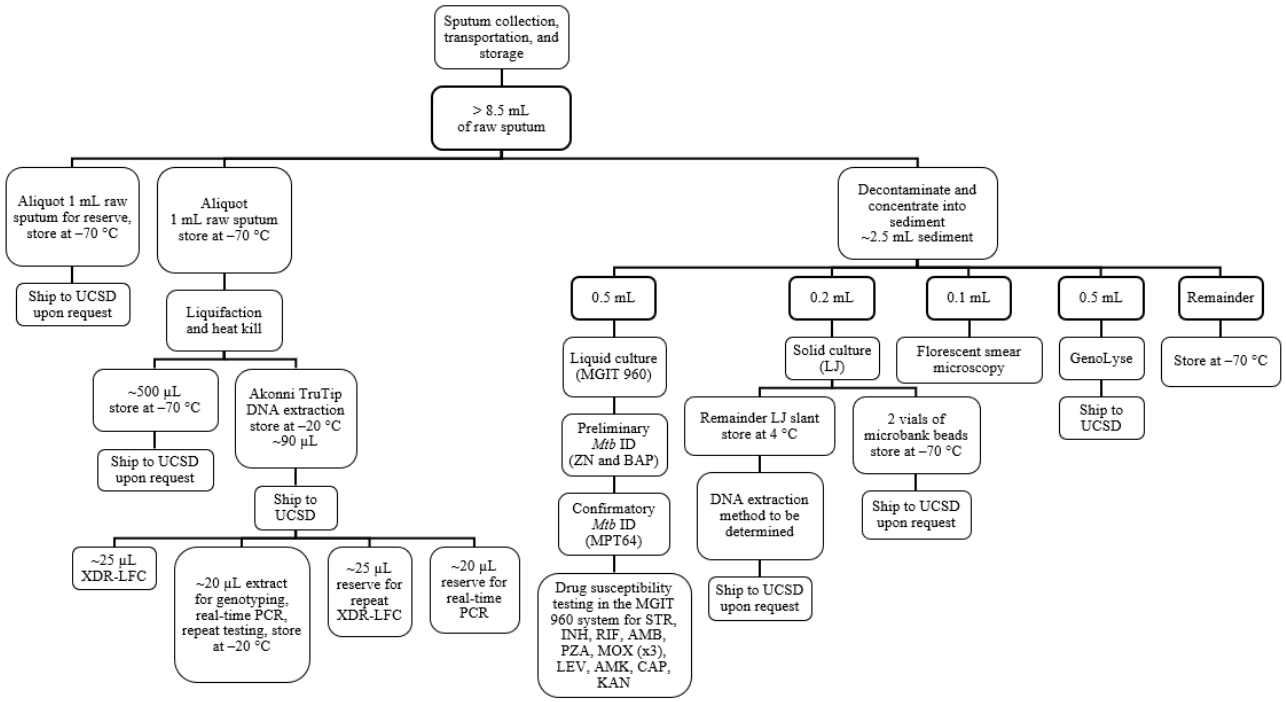
The Akonni XDR-LFC device first extracts DNA from the heat-killed sputum using the Akonni TruTip workstation [13]. A laboratory technician transfers the extracted DNA to the XDR-LFC and places it in a polymerase chain reaction (PCR) thermocycler for DNA amplification and hybridization to specific molecular GEM probes printed on the XDR-LFC. After washing, the technician then places the XDR-LFC on the Akonni imaging device where the individual molecular GEM probes are illuminated. The illumination pattern characterizes the DNA signature of the sample (eg, wild type, single nucleotide polymorphisms, etc). The DNA extraction occurred at the PPI in Moldova on the TruTip workstation using extraction kits provided by the Akonni. A set of extracted DNA was run as a validation set on the XDR-LFC device in Moldova; however, all clinical samples used for analyses to date have been run at the UCSD.

Phase 2+

The day 1 (enrollment) and the follow-up samples were processed as follows (Figure 4):

- Raw sputum was processed to sediment
- AFB smear was performed
- Solid LJ culture (put on beads and frozen at –70 °C after growth)
- The remainder of the sediment was frozen at –70 °C

Figure 4. Phase 2 specimen flowchart for the remaining samples. AMB: ethambutol; AMK: amikacin; CAP: capreomycin; INH: isoniazid; KAN: kanamycin; LEV: levofloxacin; LJ: Lowenstein–Jensen; MGIT: mycobacteria growth indicator tube; MOX: moxifloxacin; *Mtb*: *Mycobacterium tuberculosis*; PCR: polymerase chain reaction; PZA: pyrazinamide; RIF: rifampin; SMOR: single molecule-overlapping read; STR: streptomycin; UCSD: University of California, San Diego.



Phase 2+ Blood Samples

There were 2 possible options for the blood draw. Option 1 was to draw blood at each of the 8 follow-up visits, and 2 samples were drawn from each patient at specific postdose time points. Option 2 included drawing blood at 2 follow-up visits, and 5 samples were drawn from each patient at specific postdose time points. A measured amount (10 mL) of blood (red-top tube) was collected from each participant, and the serum was separated, aliquoted, and frozen at –70 °C following standard blood collection and processing procedures.

Patient Data Collection and Management

The patient data for phases 1 and 2 of this study were collected through face-to-face interviews, medical record reviews, and laboratory procedure documentation. The data were entered electronically using a data capture system built with the web-based software, QualtricsXM (Qualtrics). The data were entered into online forms with tablets provided to the staff in Moldova. Paper forms as backup were available in the event of any technical error. The Qualtrics surveys allowed access to questionnaires during unreliable internet as well—data could be entered and saved, and subsequently uploaded when the internet was available. The network of questionnaires built for this study employed an authenticator within Qualtrics; this tool confirmed that the ID a clinician intended to enter data for was still active and reduced the likelihood of applying the wrong data to a study ID number. The study ID assignment utilized a prefix of BP-A or BP2- to differentiate the participants enrolled in phase 1 and phase 2, respectively. This system benefits both data management and laboratory sample management aspects of the study. The samples generated from the study were accompanied by a 2-letter suffix code to indicate the sample type.

Electronic data capture was also utilized for front-end validation of data, ensuring that the data could only be entered in an expected range or format. Once the data were received by the data team, they were reviewed for any missing values and internally or externally invalid responses. The data team followed up these issues on an ongoing basis with the study staff in Moldova. Corrections to the data were documented systematically in a data cleaning log, and a syntax was used to merge data into a final and complete data set for analysis.

Research Ethics

The study was approved by the UCSD Human Research Protections Program (Project #161864), and the Ethics Committee of the PPI “Chiril Draganiuc.” The consent document translation was completed by the study staff in Moldova fluent in Romanian. The participants were compensated with an equivalent of US$10 per patient per visit for time and travel; the compensation was customary and allowable by local norms, as well as the UCSD and Moldova IRB requirements. All participants were assigned a unique study identifier; no personally identifiable data were documented on the study questionnaires. A document linking the patient’s name to the study ID was stored securely in locked study files for follow-up purposes only. These records were destroyed upon completion of data collection. The questionnaires were stored in a separate secure location at the PPI and were archived for at least 5 years. No identifiable data were shared outside of the research team. The results from the XDR-LFC were used for research purposes only, and because they were not run in real time, it was not possible to use these experimental results for clinical

decision-making. This protected the participants from any potential misuse of the experimental results.

Results

Participant Characteristics

The study enrolled 25, 639, and 40 participants in phases 1, 2, and 2+, respectively. The 40 participants in phase 2+ were part of the 639 participants enrolled in phase 2. In each phase of the protocol, the primary outcomes of interest were culture status, smear status, and phenotypic drug susceptibility for the 10 study drugs (Table 3).

Additional data collected from the participants for epidemiological analyses included age, gender, race, ethnicity, marital status, income, education, previous treatment for TB, comorbid conditions (including HIV), social risk factors (drug use, prior incarceration, group housing, cigarette use, alcohol use), and geographical location at key time points in the TB episode. The clinical variables documented were height, weight, TB drugs used in previous treatment episodes, previous DST results, and prior culture results. Self-reported comorbid conditions were compared with the medical records.

Table 3. The primary outcome variables.

Variable	Description or concentration
Bacteriological confirmation	
Culture	Solid or liquid culture
AFB[a] smear	AFB smear microscopy with grade
MGIT[b] 960 DST[c] results (µg/mL)	
Isoniazid (INH)	0.1
Rifampin (RIF)	1.0
Ethambutol (AMB)	5.0
Pyrazinamide (PZA)	100
Streptomycin (STR)	1.0
Kanamycin (KAN)	2.5
Amikacin (AMK)	1.0
Capreomycin (CAP)	2.5
Levofloxacin (LEV)	1.5
Moxifloxacin at 0.25 (MOX0.25)	0.25
Moxifloxacin at 0.5 (MOX0.5)	0.5
Moxifloxacin at 2.0 (MOX2.0)	2.0

[a]AFB: acid-fast bacilli.

[b]MGIT: mycobacteria growth indicator tube.

[c]DST: drug susceptibility testing.

Molecular Assay Findings

A comparison of the LFC to reference standard pDST was made by calculating the sensitivity and specificity of the LFC and comparing it with the reference standard pDST results for the drugs under study. Similarly, a comparison of the LFC to genotypic DST was made by calculating the positive and negative percent agreement of the LFC and comparing it with the sequencing results of the study. The standard percent agreement calculations for both phenotypic and genotypic comparisons were assessed by the ability to correctly classify MDR-TB and XDR-TB. For the follow-up analyses, the culture conversion at 6 months will be assessed by mutation, class of drug, and resistance profile. Logistic regression will be used to account for the treatment regimens and other risk factors typically associated with poor treatment outcomes. When 24-month follow-up data become available, the survival curves will be calculated for each mutation, class of drug, and resistance profile (susceptible, MDR, XDR, etc) based on the LFC results, considering the risk factors commonly associated with TB mortality. In addition, using logistic regression, the contributions of specific mutations to poor treatment outcomes will be assessed, taking into account the risk factors typically associated with poor treatment outcomes at 24 months. A comparison of multiple cultures, smear, and molecular diagnostic techniques will be performed using the serially collected phase 1 sputum samples. The anti-TB drug concentrations in the serum over the course of treatment and the associated patient response to the treatment collected during phase 2+ will be analyzed subject to future funding. As of April 2021, this study is closed to recruitment. The follow-up data collection and analysis are in progress.

Discussion

This paper aimed to disseminate the protocol for a prospective cohort study to evaluate a device for detecting XDR-TB rapidly. Future publications from this study will address these findings. The absence of an FDA-approved rapid diagnostic for XDR-TB diagnosis in the United States and the lack of a near-patient tabletop integrated solution worldwide necessitates accessibility to a highly sensitive and specific molecular assay for rapid detection of XDR-TB globally. Such a device and assay would significantly improve the treatment timelines and allow for more successful patient outcomes. We continue to analyze the study samples gathered, as they are an invaluable resource to evaluate new diagnostic devices as they become available.

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Authors' Contributions

NH wrote the manuscript and contributed to study design and data management. MS provided study oversight. DC and NC conducted participant interviews and collected data. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AFB: acid-fast bacilli
AMB: ethambutol
AMK: amikacin
CAP: capreomycin
DOT: directly observed therapy
DR-TB: drug-resistant tuberculosis
DST: drug susceptibility testing
FDA: US Food and Drug Administration
FQ: fluoroquinolone
GCDD: Global Consortium for Drug resistant Tuberculosis Diagnostics
GEM: gel element microarray
INH: isoniazid
KAN: kanamycin
LEV: levofloxacin
LFC: lateral flow cell
LJ: Lowenstein–Jensen
MDR-TB: multidrug-resistant tuberculosis
MGIT: mycobacteria growth indicator tube
MOX: moxifloxacin
***Mtb*:** *Mycobacterium tuberculosis*
NGS: next-generation sequencing
NRL: National TB Reference Laboratory
NTP: National TB Program
pDST: phenotypic drug susceptibility testing
PCR: polymerase chain reaction
PPI: Phthisiopneumology Institute
PZA: pyranzinamide
RIF: rifampin
RIF-R: rifampicin-resistant
STR: streptomycin
TB: tuberculosis
UCSD: University of California, San Diego
WHO: World Health Organization
XDR-TB: extensively drug-resistant tuberculosis

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Protocol

Health Care Providers and the Public Reporting of Nursing Home Quality in the United States Department of Veterans Affairs: Protocol for a Mixed Methods Pilot Study

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Abstract

Background: In June 2018, the United States Department of Veterans Affairs (VA) began the public reporting of its 134 Community Living Centers' (CLCs) overall quality by using a 5-star rating system based on data from the national quality measures captured in CLC Compare. Given the private sector's positive experience with report cards, this is a seminal moment for stimulating measurable quality improvements in CLCs. However, the public reporting of CLC Compare data raises substantial and immediate implications for CLCs. The report cards, for example, facilitate comparisons between CLCs and community nursing homes in which CLCs generally fare worse. This may lead to staff anxiety and potentially unintended consequences. Additionally, CLC Compare is designed to spur improvement, yet the motivating aspects of the report cards are unknown. Understanding staff attitudes and early responses is a critical first step in building the capacity for public reporting to spur quality.

Objective: We will adapt an existing community nursing home public reporting survey to reveal important leverage points and support CLCs' quality improvement efforts. Our work will be grounded in a conceptual framework of strategic orientation. We have 2 aims. First, we will qualitatively examine CLC staff reactions to CLC Compare. Second, we will adapt and expand upon an extant community nursing home survey to capture a broad range of responses and then pilot the adapted survey in CLCs.

Methods: We will conduct interviews with staff at 3 CLCs (1 1-star CLC, 1 3-star CLC, and 1 5-star CLC) to identify staff actions taken in response to their CLCs' public data; staff's commitment to or difficulties with using CLC Compare; and factors that motivate staff to improve CLC quality. We will integrate these findings with our conceptual framework to adapt and expand a community nursing home survey to the current CLC environment. We will conduct cognitive interviews with staff in 1 CLC

to refine survey items. We will then pilot the survey in 6 CLCs (2 1-star CLCs, 2 3-star CLCs, and 2 5-star CLCs) to assess the survey's feasibility, acceptability, and preliminary psychometric properties.

Results: We will develop a brief survey for use in a future national administration to identify system-wide responses to CLC Compare; evaluate the impact of CLC Compare on veterans' clinical outcomes and satisfaction; and develop, test, and disseminate interventions to support the meaningful use of CLC Compare for quality improvement.

Conclusions: The knowledge gained from this pilot study and from future work will help VA refine how CLC Compare is used, ensure that CLC staff understand and are motivated to use its quality data, and implement concrete actions to improve clinical quality. The products from this pilot study will also facilitate studies on the effects of public reporting in other critical VA clinical areas.

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KEYWORDS

nursing homes; public reporting; quality

Introduction

Background

Public reporting seeks to improve quality by addressing informational asymmetries in health care [1]. This mechanism has been used in the nursing home sector since 2002, when the United States Centers for Medicare and Medicaid Services (CMS) launched the Nursing Home Compare website, which enables consumers to make choices based on quality [2,3]. These *report cards* theoretically incentivize nursing home providers to compete on quality by, for example, investing in quality improvement (QI) to maintain or increase market share [4]. Previous studies found that quality on some postacute quality measures improved after the launch of Nursing Home Compare, especially in nursing homes that began QI activities in response to their report cards [5] or that were subject to public reporting requirements [6]. Nursing home–level use of antipsychotic medications [7] and physical restraints [5], ambulation [6], and pain prevalence [4,5] improved, largely driven by actions that nursing home providers took to enhance care quality [4]. In a separate study, Mukamel et al [8] used the Nursing Home Compare survey to understand nursing home administrators' responses to Nursing Home Compare. An initial survey in 2004 (724/1502, 48.2% response rate) found that although 80% of nursing home administrators had viewed their first report card, subsequent action depended on their perception of the validity of the scores [8]. Many administrators (40%) were ambivalent about the validity of quality measures. Nursing homes with poor scores were also more likely to act than nursing homes with better scores. Overall, 63% further investigated their scores, 42% changed the priorities of existing QI efforts, and 20% started new QI programs. A small but critical number of nursing homes used potentially dysfunctional strategies, that is, reallocating staff from other activities to care related to a poor-performing quality measure (a *teaching-to-the-test* response; 9%) and changing the types of patients admitted (*cream-skimming*; 4%). A second survey administered in 2007 found that more administrators (57%) believed that quality measures reflect the true quality of care, but up to 80% admitted to making no major investments in response to report cards [9].

In the United States Department of Veterans Affairs (VA), nursing homes—known as Community Living Centers (CLCs)—exhibit variable levels of measured quality [10,11]. National internal-to-VA reporting of quality measures began in fiscal year (FY) 2016 with CLC Strategic Analytics for Improvement and Learning. In early 2018, CLC Strategic Analytics for Improvement and Learning was augmented with additional data and became CLC Compare. It is modeled on Nursing Home Compare and uses CMS metrics to calculate quality performance. In addition to providing detailed information, it rates each CLC from 1 to 5 stars on overall performance using a composite measure based on unannounced surveys (ie, inspections), Minimum Data Set (MDS)–based quality measures, and staffing [12]. Until recently however, veterans and others outside of VA had no means for assessing how well CLCs perform on these important measures. In June 2018, the overall CLC Compare star ratings became accessible through the public-facing *Access to Care* website [13]. By providing simple, CLC-specific report cards, the VA aims to facilitate direct comparison with community nursing homes and provide veterans with greater information about their options for long-term care [14].

CLC Compare has substantial and immediate implications for CLCs. First, CLCs have had little time to prepare for public reporting. Through the VA Office of Geriatrics and Extended Care (GEC)'s visits to support and educate underperforming CLCs, we are beginning to understand how benchmarking affects low performers. However, we lack the means to systematically assess the impact of internal and external reporting. Second, we have anecdotal evidence that CLC staff are worried about quality comparisons between CLCs and community nursing homes. Compared with community nursing homes, CLCs fare worse on most quality measures. For example, in the first quarter of FY 2018, the VA CLC national average for the percentage of short-stay residents who reported moderate to severe pain was 33.78%; in community nursing homes, it was 13.01% [15]. In long-stay residents, the pain numbers were even worse: 32.53% in VA versus 6.62% in the community. The current CMS state-based cut point system used in CLC Compare also does not account for the system-wide national standards governing CLCs. A recent qualitative study by Miller et al [16] found that some VA staff who made nursing home

referrals perceived that CLCs provide superior quality of care than other long-term care options. However, we have a limited understanding of CLC staff members' views of more objective comparisons. Finally, CLC Compare is designed, in part, to spur improvement. However, we do not know the aspects of CLC Compare that are helpful for ongoing QI activities or in what way, if any, public reporting motivates CLCs.

Staff responses to performance metrics may not be intended. For example, in the VA, recent allegations of maladaptive responses to public reporting of VA hospital performance included selective admission of low-risk patients while turning away veterans with complicated needs [17,18]. Similar *dysfunctional* practices have been documented in community nursing homes [6,19-22]. Therefore, it is critical to understand how individual CLCs respond to CLC Compare, so that we can help (1) identify and support positive reactions and (2) ameliorate unanticipated or potentially maladaptive ones.

Having the means to accurately assess responses to report cards and the mechanisms driving QI in long-term care is the first step in building the capacity for public reporting to spur improvement [23]. The Nursing Home Compare survey, although a good first step, is not viable for current use in CLCs. It is specific to community nursing homes, whose motivations to improve quality are largely market driven [24,25] and differ from those of CLCs. Survey items are designed to capture a wide range of activities available to nursing homes in response to public reporting (eg, changes in protocols and staff allocation, work organization, and staffing). However, the survey does not examine staff members' challenges in interpreting or acting on report card information. In addition, it does not assess the potential sources of staff member stress stemming from the public reporting process. The survey also does not assess in-depth information about 2 essential ingredients for successful QI: staff commitment to improvement and staff willingness or capacity to change day-to-day routines [8,26]. By focusing exclusively on actions that providers took in the past, the survey fails to capture information that could be leveraged for future intervention.

The GEC recently conducted a national survey to provide a snapshot of the VA's geriatrics and extended care programs. This offers only a glimpse into CLCs' ongoing quality assurance activities and the job types involved in quality assurance and monitoring CLC Compare data. To find critical leverage points, we need a richer survey that captures barriers and facilitators to the use of CLC Compare for QI, immediate reactions to the public reporting system, and factors that may influence its use. Our PROACTIVE (Public Reporting Responses and Opportunities Among CLC Teams: Investigating the Current Environment) study therefore proposes to adapt and expand the Nursing Home Compare survey for meaningful use by VA researchers and operations.

Conceptual Framework: Strategic Orientation

A conceptual framework of strategic orientation guides this study because a nursing home's principle strategic orientation is an important determinant of whether, when, and how it responds to the publication of its quality information. Major strategic orientations can be grouped into typologies. In this study, we will use the Miles and Snow typology [27] to categorize CLCs' strategic orientation to public reporting. This valid and reliable [28] typology has been used extensively in studies of hospitals, health maintenance organizations, colleges, banks, life insurance companies, manufacturing industries [29], and community nursing homes [9]. It describes organizations as complete systems with internally consistent sets of attributes that define their dynamic interactions with the environment. In the Miles and Snow typology, there are 3 *viable* strategic types (prospector, defender, and analyzer) and 1 *nonviable* type (reactor; Textbox 1). Prospectors are innovative and growth oriented, search for new markets and new growth opportunities, and encourage risk taking. Defenders protect current markets, maintain stable growth, and serve current customers. Analyzers maintain current markets and current customer satisfaction with a moderate emphasis on innovation. Unlike the 3 viable strategies, reactors have no clear strategy, react to changes in the environment, and drift with events. In their application of the Miles and Snow typology, Zinn et al [9] found that a nursing home's strategic type was related to the propensity to improve quality. For example, innovative and flexible nursing homes (prospectors) were more likely to leverage the *environmental shock* resulting from Nursing Home Compare to gain advantage over their competitors, for example, by investigating the causes of and acting quickly upon poor scores. Conversely, nursing homes that focused only on performing well in a limited set of core services (defenders) were more likely to take no action at all.

Textbox 1. Miles and Snow typology of strategic orientation.

Prospector

- The nursing home responds rapidly to early signals of market opportunities to provide new services, even if some prove to be less successful than others.

Defender

- The nursing home focuses on providing and improving a set of services that have remained stable in time.

Analyzer

- The nursing home maintains a relatively stable base of services but will move into new areas that prove successful for others.

Reactor

- None of the above consistently describes the nursing home's approach to providing services.

Significance

The June 2018 launch of CLC Compare provides us with a unique and time-sensitive opportunity to gauge early CLC reactions to this significant environmental shock. Just as public reporting of VA hospital performance may have led to unanticipated negative responses among some providers [17,18], there is potential for CLC Compare to have unintended consequences on CLC staff and, ultimately, the 40,000 vulnerable veteran residents they serve. It is thus critical that we quickly and accurately understand how individual CLCs respond to CLC Compare so that we can help identify and support positive reactions among CLC staff and ameliorate unanticipated or potentially maladaptive ones.

The proposed study directly responds to the national VA priority of *greater choice for veterans*, in that it will result in a product to examine CLC staff perceptions of CLC Compare as "a readily accessible, data-rich environment to support efficient and effective health care decision making" [30]. It is also highly consistent with the VA Health Services Research and Development Service's *aging, long-term care, and caregiving* priority domain, in which a subpriority is the "alignment of measurement with long-term services and support, home and community based services aligned with Medicare" [31].

Findings from the proposed study will immediately inform ongoing initiatives to improve CLC quality of care, thus ensuring a return on VA's considerable investment in CLC Compare public reporting. The qualitative component of this study, in particular, is designed to elicit information not easily captured by existing surveys, that is, staff motivations to improve CLC quality, challenges with interpreting or applying information from quality report cards, staff commitment to QI, and staff willingness or capacity to change their day-to-day routines. We know that such information is essential for successfully implementing improvements in care. For example, the study findings will immediately inform VA's CLCs' Ongoing National Center for Enhancing Resources and Training, the platform through which GEC provides frontline QI coaching to all 134 CLCs. The GEC will also use findings to help ensure ongoing CLC staff ownership of methods for improving quality.

Veterans whose complex health needs require nursing home care represent one of the VA's most vulnerable populations. VA's 134 CLCs serve an average of 9991 veterans daily [32], at an annual cost of US $3.6 billion [33]. The need for skilled nursing and rehabilitative care provided by CLCs is expected to increase as the veteran population ages. Indeed, the number of highly service-connected (priority 1a) veterans for whom the VA must provide nursing home care may reach 1 million by 2023 [34]. This pilot study will help us meet our short-term goal of capturing the breadth of specific actions that CLC staff take in response to their CLC's public data. Our immediate next step will be to widely administer the resulting survey to understand all 134 CLCs' responses to CLC Compare, thereby furthering the scientific knowledge base on public reporting and simultaneously enabling GEC to identify and support CLCs' positive reactions and ameliorate negative ones. Future work will examine the impact of CLC Compare on veterans' clinical outcomes and satisfaction and inform the development and implementation of interventions to increase the use of the CLC Compare report cards for QI purposes.

VA expects veterans and their agents to be well informed about their care options and to be active in their care planning [35]. CLC Compare is one of many sources for health care information. In fact, the Access to Care website that publishes CLC Compare also includes numerous report cards on VA medical center quality (analogous to CMS' Hospital Compare), outpatient quality, patient experience, and VA-contracted community nursing homes. Access to Care is not the only avenue through which VA and non-VA comparisons can be made. Other VA efforts to garner greater public transparency include the 2016 reintroduction of quality data from VA hospitals on the CMS' Hospital Compare website [36]. We anticipate that products stemming from this pilot study will be instrumental for future studies that examine the impact of public reporting in these other critical areas.

Methods

Overview

Table 1 summarizes our 2 study aims, research activities, and the study participants involved in each.

Table 1. PROACTIVE (Public Reporting Responses and Opportunities Among Community Living Center Teams: Investigating the Current Environment) study overview.

Aim and summary	Research activities and study participants
1. Qualitative data collection and analysis	Semistructured interviews of 12 purposively selected staff in 3 CLCs[a] (randomly selected from consistent 1-star, 3-star, and 5-star CLCs)
2. Survey adaptation, pretesting, and pilot testing	Consultation with the study advisory group, cognitive interviews of 4 staff in 1 CLC, and survey administration to the purposively selected staff at 6 CLCs (randomly selected from consistent 1-star, 3-star, and 5-star CLCs)

[a]CLC: Community Living Center.

Study Advisory Group

This study is guided closely by a study advisory group comprising VA operations, clinical, and research leaders in long-term care quality measurement. This group participates in quarterly conference calls to provide input on study methods, provide feedback on our semistructured interview guide, and suggest improvements to the survey before pilot dissemination.

Aim 1: Qualitative Study of CLC Staff Experiences With CLC Compare

Site Selection

The study sample comprises 3 CLCs (1 1-star CLC, 1 3-star CLC, and 1 5-star CLC), selected based on their star rating for the latest two quarters of CLC Compare. Specifically, we will identify all CLCs that have scored consistently in 2 consecutive reporting periods and then select 1 CLC at random from each star category (eg, a CLC with a 1-star rating in FY 18 quarter 1 and FY 18 quarter 2). We will contact the medical center directors of the selected CLCs to request study participation. If a contacted CLC declines to participate, a replacement will be selected using the procedures described above.

Interview Participant Recruitment

We aim to conduct 4 semistructured interviews at each CLC, for a total of 12 interviews. We will work with leadership points of contact at participating CLCs to help identify job categories involved in public reporting, that is, medical directors for geriatrics and extended care, resident assessment (ie, MDS) coordinators, quality managers, nurse managers, and assistant nurse managers, whom we will also target for participation in subsequent survey activities. We will ask the points of contact to provide VA email addresses of the identified job categories. To recruit participants, we will send email invitations. A maximum of 6 email reminders will be sent, with opt-out information. To encourage study participation, emails will include study information and letters of support from GEC, and our team has successfully used these procedures to recruit CLC staff for interviews [37]. When a staff member agrees to participate, we will set a mutually agreeable time for an interview.

Interview Guide Development

The content of our proposed interview guides is informed by our conceptual framework of strategic orientation [27] and studies of community nursing home administrators' experiences with the implementation of Nursing Home Compare report cards [8,9] (refer to Multimedia Appendix 1 for the interview guide). It will be continually refined with input from the study team and our study advisory group. Specifically, we will ask participants to discuss (1) factors that motivate staff to improve CLC quality; (2) staff commitment to and difficulties with using CLC Compare for QI purposes; and (3) specific actions staff have taken in response to their CLC's public data, including unintended consequences.

Interview Methods

Semistructured interviews lasting approximately 60 minutes will be performed by telephone. Interviews will be conducted by the principal investigator (CBP) and project manager (VC) and audio-recorded with the permission of study participants.

Data Analysis

The VA's Centralized Transcription Services Program will transcribe all audio-recorded interviews verbatim. We will save them in NVivo 10, a qualitative coding and data management program [38], on a secure VA network. We will use an open coding approach to identify recurring patterns and themes in transcribed interviews [39], which will be deductive to the extent that it will be guided by a priori codes that we will develop before coding and inductive to the extent that new codes may be developed during coding.

Initial codes will be derived from concepts drawn from a broad literature search on nursing home public reporting and topics covered by the interview protocol. Initial codes will be refined through a process in which each researcher will read through 2 transcripts and independently generate suggestions for new codes, for modifications to or eliminations of old codes, or for combining codes into broader analytic categories. We will discuss the findings and reach a consensus on the final coding scheme. To ensure quality control, we will first code the same 2 transcripts, discuss in weekly team meetings the extent to which we consistently applied the same codes to the same text segments, and resolve discrepancies by reaching a consensus about the most appropriate code. Second, each of us will code our own set of remaining transcripts. We will continue to meet weekly to discuss and reach a consensus about new codes, insights, and challenges.

Aim 2: Adapting a Survey to Capture CLC Staff Experiences With CLC Compare Public Reporting

Original Nursing Home Compare Survey

The Nursing Home Compare survey created by Mukamel et al [8] was designed to capture a wide range of activities available to nursing homes, such as changes in protocols and staff allocation, work organization, and staffing. A second iteration of the survey asked many of the same questions as the first, with additional questions seeking information on the extent to which quality measures, deficiencies, and staffing influenced medical referrals; contracts with managed care organizations; and *when* actions were taken as a direct result of the publication of the quality measures (vs *what* specific quality measures drove the actions). The original 19-item survey was estimated to take only 10 minutes to complete.

Adapting the Survey

We will follow standard instrument adaptation procedures to create a survey that represents CLCs' experience with public reporting. The Nursing Home Compare survey, our conceptual framework of strategic orientation, and the public reporting literature will help define new potential domains for the survey. We will use aim 1 findings to inform mutually exclusive, overarching domains that encompass the breadth of possible CLC perceptions and reactions to public reporting (eg, *Changes to Staffing*) and then create objectives for items within each domain (eg, items within the *Changes to Staffing* domain should identify efforts to restructure existing staffing resources). After consultation with our study advisory group about the inclusion of the new domains and item objectives, we will construct survey items using language similar to the extant survey and verbatim responses from CLC staff to help reflect issues specific to the VA context. The resulting set of draft items will be shared again with the study advisory group for final approval.

We will ensure that the adapted survey, called the PROACTIVE survey, conforms to the best practices in survey design. That is, the survey will include simple wording and sentence

construction to promote respondents' accurate and reliable cognitive processing [40,41]; use *native* instead of *analytic* terms and phrases [42]; have reference periods appear as the first element in a question; have questions be explicit, specific, and of an appropriate length for the things we are asking about [43]; and incorporate definitions and instructions into the body of questions to ensure that all respondents have the same information when they answer a question.

To further ensure clarity and usability of the PROACTIVE survey, we will conduct cognitive interviews with up to 4 individuals occupying potential respondent types at 1 local VA medical center. Cognitive interviews are well-established and critical pieces of the presurvey evaluation process [44]. We will design our cognitive interviews to look specifically at participants' experiences with comprehension of and response to questions. Following a well-established approach for performing cognitive interviews [45], we will ask respondents to independently complete the survey. A member of the study team will then review each question with the respondent to elicit information on the respondent's interpretation of terms, the clarity of the instructions and survey items, and how the respondents answered the question. We will follow the procedures mentioned above to recruit the staff targeted by the actual survey, that is, staff involved in the public reporting process. This will include the CLC medical director, MDS coordinator, quality manager, nurse managers, and assistant nurse managers. As in aim 1, we will ask leadership to provide VA email addresses of identified CLC staff, whom we will contact separately. Each cognitive interview will last approximately 1 hour. Interviews will be audio-recorded, and respondents' experiences with each survey item will be summarized. Potential problems with questions may include respondents' lack of information, ambiguous terms, items not measuring intended constructs, items measuring constructs that are inapplicable to respondents, and items making discriminations that are too subtle for respondents. Problematic survey items will be revised or discarded by study team consensus.

Pilot Administration Site Selection

The sample will comprise 6 CLCs (2 1-star CLCs, 2 3-star CLCs, and 2 5-star CLCs), selected based on their star rating for the latest two quarters of CLC Compare. As in site selection for aim 1, we will identify all CLCs that have scored consistently over 2 consecutive reporting periods. CLCs whose staff participated in qualitative interviews (aim 1) or survey pretesting via cognitive interviews (aim 2) will be excluded from the pool of candidate sites. We will select 2 CLCs at random from each star category. The study team will recruit CLCs by emailing their leadership, explaining what is involved in study participation, and including support letters from GEC that emphasize the importance of the study to ongoing CLC QI efforts at their VA medical center. If selected CLCs do not wish to or are not able to participate, we will select a replacement from the appropriate star rating category.

Pilot Participant Recruitment

Although CLC frontline staff members do much of the actual QI work, they are typically not involved in making decisions about QI initiatives or where to focus resources. It is thus a more efficient use of resources in this pilot study to target staff in leadership roles that play a bigger role in their CLC's response to quality measure data. We will recruit staff at participating CLCs involved in the public reporting process, that is, medical director for geriatrics and extended care, MDS coordinators, quality managers, nurse managers, and assistant nurse managers. We will ask site points of contact to provide VA email addresses of CLC staff in these job categories, and we will email identified staff members separately.

Pilot Data Collection and Management

To recruit participants, we will send email invitations. A maximum of 6 email reminders will be sent, each with opt-out information. Emails to potential respondents will include study information and letters of support from the GEC. The emails will contain a link to a web-based version of the PROACTIVE survey, administered through REDCap (Research Electronic Data Capture; Vanderbilt University) [46], which will take approximately 10 minutes to complete. Once the survey is launched at a given CLC, we will seek to maximize response rates using a data collection approach based on the method by Dillman et al [47], adapted to email and web administration. We successfully used targeted emails with links to electronic surveys in our previous studies of CLC staff, with response rates of 39%-85% [25]. We anticipate that each CLC will have a minimum of 6 staff members involved in the public reporting process (assuming an average of 2 units per CLC). On the basis of the initial administration of the Nursing Home Compare survey [8], we anticipate a minimum 50% response rate, yielding at least three completed surveys per CLC.

Pilot Data Analysis and Assessment of Survey's Psychometric Properties

After the survey is closed at all 6 CLCs, data sets from RedCAP will be converted into SAS (SAS Institute Inc) data sets. Two researchers (CBP and DCM) will supervise data management and quality control. Analyses will be conducted using SAS software, version 9.4, and survey results will be examined by the quantitative study team in collaborative meaning-making sessions. The formative evaluation of our study will focus on our experiences at the level of the individual respondent and of the CLC. To assess how well our survey was received at the *individual* level, we will examine survey completion rates and completeness of data. To inform the survey's performance at the *CLC* level, we will review notes taken at weekly meetings of the quantitative team to assess research staff time and resources required for recruiting CLCs to participate in the survey pilot and successfully launching and administering the survey at each CLC. If we collect consistent answers from survey respondents within a given CLC, a subsequent large-scale survey administration will target only 1 representative staff member at the CLC (eg, the medical director for geriatrics and extended care). If responses vary within each CLC, however, large-scale administration will mimic this pilot administration in eliciting perspectives from a wide variety of job types.

No psychometric assessments were conducted on the Nursing Home Compare survey. Therefore, we propose to establish the PROACTIVE survey's preliminary psychometric properties by

examining the distribution of responses. This will allow us to identify problematic items, that is, those with missing values or that elicit a high proportion of the most negative (floor effect) or the most positive (ceiling effect) response options. Missing items may indicate questions that are unclear or difficult to understand. We expect low rates of true missing values because truly problematic items should be eliminated during survey pretesting via cognitive interviews. Items that cluster around a single response will be flagged for possible refinement, for example, by adjusting response options to capture variations in practice that are currently being grouped into a single response category.

In analyses of preliminary survey results, responses will be aggregated and analyzed at the level of the CLC. We will calculate descriptive statistics and means for the survey items. If >50% of respondents in each CLC provide an affirmative response to an item, we will consider their CLC to have taken that specific action in response to CLC Compare.

Sample Size Considerations

Only a limited number of staff are involved in making decisions about QI initiatives in each CLC, and we have only 6 participating CLCs. Therefore, we do not plan to conduct robust psychometric analyses, such as exploratory factor analysis, item response theory analysis, confirmatory factor analysis, and multitrait scaling analysis, in this proposed study. Robust exploratory factor analysis and item response theory analyses require 5-15 respondents per survey item [48-51]. We estimate that the PROACTIVE survey will consist of 20 items, so we would need a derivation sample of at least 100 respondents and an equally sized validation sample. Confirmatory factor analysis requires an even greater number of respondents in a validation sample [50,52], and multitrait scaling analysis requires a sample size of at least 180 to achieve 80% power, assuming differences between correlations of moderate effect size [53]. The number of CLCs is fixed (N=134), and we will therefore sample all of them in future large-scale studies.

Results

This pilot study was granted a human subjects research exemption from the VA Central Institutional Review Board in February 2019 and was funded in June 2019 (refer to Multimedia Appendix 2 for peer review comments). Data collection and analysis are ongoing. We expect the results of this pilot study, including qualitative findings and information about survey development, to be published in an international peer-reviewed journal in spring 2022. Preliminary results will be reported according to the consolidated criteria for reporting qualitative research [54]. Significant protocol amendments will be reported back to the research and development committee and will be reported in the primary results paper. Authorship will be granted to all participating authors according to the current principles stated by the International Committee of Medical Journal Editors.

Discussion

Dissemination and Implementation

The knowledge gained from our work will help our VA operational partner (GEC) refine how CLC Compare is used, ensure that staff understand and are motivated to use the data, and implement concrete actions to improve clinical quality. The dissemination of preliminary findings from this pilot study will take place in partnership with the GEC and CLC leadership and staff. GEC is very interested in (1) evidence of CLC Compare to improve CLC quality and (2) strategies for ensuring the ongoing CLC staff buy-in of continuous QI methods. The GEC has committed to using the resources of their office to promote the wider dissemination of pilot study products, and we will conduct presentations about this work to existing CLC leadership and provider groups. In addition, members of our team are actively involved in the nationwide implementation of the VA's program to support and advance QI in CLCs (CBP and CWH) [55] and coordinate the VA's Long-Term Services and Support Research Network (WLM). We will use these connections to further disseminate information about study results through in-person and virtual avenues. Dissemination of pilot study findings to the broader VA health care community and to the general field will be through progress reports, presentations at national conferences, and publications in peer-reviewed journals.

Future Research

The successful completion of this pilot study will augment our limited understanding of staff reactions to the public reporting of CLCs' quality data, their commitment to using CLC Compare, and drivers of staff involvement in CLC QI. We expect this study to (1) provide preliminary evidence of the role that CLC Compare public reporting plays in improving CLC quality and (2) result in a survey that fully captures CLCs' experiences with CLC Compare and points to intervention opportunities. Products based on this foundational work will include larger-scale longitudinal studies to assess the psychometric properties of the PROACTIVE survey via confirmatory factor analyses; to understand all 134 CLCs' reactions to the public reporting of CLC quality measures, including the impact of principle strategic orientation type, by using latent class analysis; to understand CLC frontline staff experiences with CLC Compare, their motivations for and challenges with QI, and adaptations to QI-related activities over time; to investigate the impact of CLC Compare on veterans' clinical outcomes and satisfaction; and to develop an intervention project to support meaningful use by the staff of CLC Compare. It will also provide a foundation for studying the effects of public reporting in other VA clinical areas, such as overall hospital performance, the quality of outpatient care, and veterans' experiences with health care providers [13].

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Conflicts of Interest

None declared.

Multimedia Appendix 1
PROACTIVE (Public Reporting Responses and Opportunities Among Community Living Center Teams: Investigating the Current Environment) interview guide.
[DOCX File , 16 KB - resprot_v10i7e23516_app1.docx]

Multimedia Appendix 2
Peer review comments from the VA Health Services Research and Development Service.
[PDF File (Adobe PDF File), 120 KB - resprot_v10i7e23516_app2.pdf]

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Abbreviations

CLC: Community Living Center
CMS: Centers for Medicare and Medicaid Services
FY: fiscal year
GEC: Office of Geriatrics and Extended Care
MDS: Minimum Data Set
PROACTIVE: Public Reporting Responses and Opportunities Among Community Living Center Teams: Investigating the Current Environment
QI: quality improvement
REDCap: Research Electronic Data Capture
VA: United States Department of Veterans Affairs

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Protocol

Physiological Measurements of Stress Preceding Incidents of Challenging Behavior in People With Severe to Profound Intellectual Disabilities: Longitudinal Study Protocol of Single-Case Studies

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Abstract

Background: Clients with severe to profound intellectual disabilities (SPID) and challenging behavior (CB) and the professional caregivers that support them are vulnerable to high stress levels, which negatively impact their well-being and the quality of care. CB is thought to result from an increase in the intensity and frequency of clients' stress experiences. In turn, staff members experience stress in dealing with this behavior, and stressed staff members might behave in ways that increase clients' stress levels, contributing to the origin and maintenance of CB. Research into these dyadic interactions between clients and staff is scarce for people with SPID, especially in real-life situations. The barriers of studying stress in this population include clients' difficulties in communicating stress experiences and the lack of an objective continuous measure of stress.

Objective: This paper presents a protocol for studying patterns of physiological stress in 15 client-caregiver dyads in the 30 minutes preceding incidents of CB compared to control periods without CB and the interplay between the stress levels of clients and professional caregivers.

Methods: We will conduct 15 single-case studies to assess patterns of physiological stress in dyads of clients with SPID and professional caregivers prior to CB in several Dutch residential institutes. Client-caregiver dyads will wear the Empatica E4 wristband for 20 sessions of 3 to 8 hours without interruptions of daily routines while caregivers report clients' CB. The physiological measures obtained will be electrodermal activity (microsiemens) and heart rate (beats per minute). A multilevel model with repeated measures at the incident level nested within the person level will be applied, employing separate models for electrodermal activity and heart rate to compare stress levels in the 30 minutes prior to incidents with control epochs. Covariates in the models include movement, temperature, and gender. In addition, cross-recurrence quantification analyses will be performed to study the synchronization between the stress levels of clients and professional caregivers.

Results: The Ethics Committee of the Radboud University (NL-number: NL71683.091.19) approved the study on February 12, 2020. In total, 15 organizations have declared their commitment to participate in the study. The first result is expected in the spring of 2022.

Conclusions: Study results will demonstrate whether changes in patterns of electrodermal activity and heart rate are apparent in the 30 minutes preceding an incident of CB compared to baseline levels when the client does not engage in CB. The synchronization between caregivers' and clients' physiological stress levels will be explored with cross-recurrence quantification

analyses. Insights into the physiological stress levels of clients and caregivers may contribute to a reduction of CB and an improvement of both clients' and caregivers' safety and well-being.

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KEYWORDS

challenging behavior; electrodermal activity; heart rate; intellectual disability; single-case research; stress

Introduction

Background

According to the Dutch Healthcare Inspectorate, approximately 20% of the 30,000 people with intellectual disabilities (ID) living in Dutch residential institutes show severe and enduring challenging behavior (CB) [1]. CB most often includes aggression or self-injury [1] and can severely diminish clients' quality of life [2]. The prevalence of CB increases with the severity of ID, resulting in a vulnerable group of clients with severe to profound ID (SPID) and CB [1,3]. Clients with SPID, especially in the case of CB, depend to a great extent on the support of professional caregivers in residential institutes for their physical and emotional well-being. It is well-established that CB can be stressful for caregivers, affecting caregivers' well-being and the quality of support they provide [4]. Caregivers have reported that they are often surprised by clients' CB and perceive the mere possibility of CB occurrence as highly stressful [5], which in turn may affect the stress experienced by clients. In addition, clients with SPID and CB perceive stress in a more frequent, intense, and sustained manner compared to the general population but lack sufficient coping skills to manage stress. Associations between stress and the origin and maintenance of CB have been reported, and CB is often a maladaptive response to stress [2]. This study addresses stress in clients with SPID and professional caregivers prior to incidents of CB.

The Importance of Professional Caregivers' Stress

Caregivers of clients with CB report more severe stress levels than other professionals serving clients with ID [6]. In several studies, caregivers rated clients' CB as a highly stressful aspect of their work, and associations between the exposure to CB and caregivers' stress have been repeatedly shown [7,8]. These associations may be moderated or mediated by caregivers' attributions, coping styles, beliefs, self-efficacy, and training [7,8]. Specifically, Bromley and Emerson [9] reported that stress when supporting clients with CB is related to "the 'daily grind' of caring, their difficulty in understanding the person's behavior, the unpredictability of the behavior, and the apparent absence of an effective way forward". Several organizational variables (eg, workload, job variety, and support) have been identified as stressors as well [8,10]. CB and stress have a clear impact on caregivers' psychological well-being and are associated with sickness, absenteeism, and staff turnover [10,11]. Importantly, stress impacts the quality of care [12]. The quality of care benefits from high-quality interactions between caregivers and clients [13], and inadequate caregiver-client interactions contribute to the origin and maintenance of CB [14]. Stress negatively affects the quality and quantity of these interactions and the caregiver's ability to deal with CB effectively [4,7]. Specifically, stressed caregivers interact less often with clients, engage in more negative and less positive interactions, and are more likely to behave in ways that contribute to the origin and maintenance of CB [7,14].

Understanding Stress in Clients With SPID and CB

CB may be a maladaptive response to perceived stress, and research has shown an association between clients' stress and CB [2]. Janssen, Schuengel, and Stolk [2] applied an explanatory model based on theories about stress and attachment to the development of CB among clients with SPID. According to this stress-attachment model, the combination of stress and insecure attachment puts people with SPID at risk for CB. Specifically, people with SPID perceive stress in a more frequent, intense, and sustained manner when compared to the general population, but often lack appropriate coping skills to deal with stressors [2]. To deal with stressors without sufficient coping skills, people fall back on the support of an attachment figure (ie, someone to whom one is securely attached) [15]. Access to typical attachment figures (ie, parents, close friends, and mentors) is limited in residential institutes [16]. Therefore, secure attachment to professional caregivers is important for clients to receive emotional support in stressful situations. Indeed, clients who show more secure attachment behavior towards caregivers show less CB [15]. Clients who do not experience high-quality interactions with caregivers are at risk of developing insecure attachment relationships, and an accumulation of stress might cause CB [17]. Limited cognitive skills have been identified as precursors of insecure attachment, increasing the risk for CB following stress in people with SPID [2].

Physiological Indicators of Stress

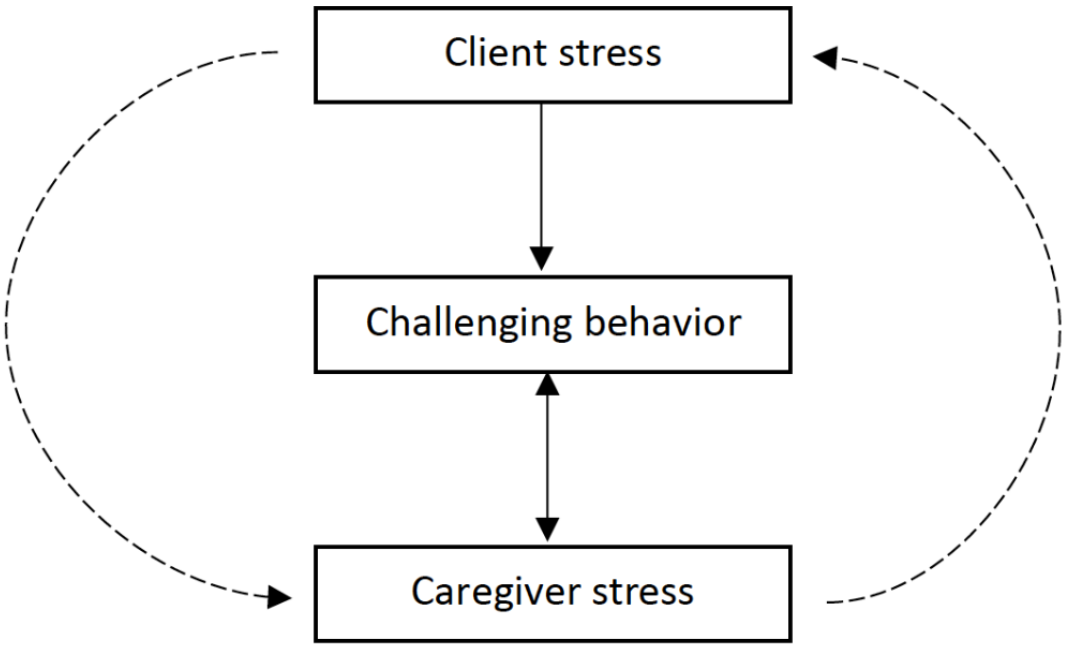
One of the difficulties in studying stress in clients with SPID and CB is the communicative shortcomings associated with clients' ability and caregivers' difficulties interpreting clients' communicative signals [2]. Although caregivers try to anticipate CB by relying on the mixed and difficult-to-interpret signals from clients that might indicate stress, caregivers lack insight into clients' stress experiences and report being surprised by CB [5]. Further, most research on caregiver stress relies on a range of questionnaires, measuring subjective experiences with variations based on, for example, caregivers' age and experiences. The results from these studies are hard to interpret due to methodological differences in measuring stress and the lack of an objective, continuous measure of stress [10]. Since psychologically stressful events change people's physiology, studying physiological stress increases insight into patterns of

stress that precede incidents of CB [2]. In addition, physiological measures of caregiver stress are significantly associated with burnout symptoms over time [11]. Both physical and emotional stress result in physiological responses characterized by the dual innervation of the autonomous nervous system [18]. During stressful events, increased activity of the sympathetic nervous system and decreased parasympathetic nervous system activity is typically observed, resulting in increased heart rate, electrodermal activity, and blood pressure [19]. However, more complex relations between the innervation of both branches and aggression have been observed as well [20]. Although physiological measures of stress have been studied repeatedly, most studies are conducted in experimental settings. The development of wearable wireless devices has increased the possibilities of measuring physiological indicators of stress nonintrusively and continuously in real-life settings [5]. Electrodermal activity (EDA) and heart rate (HR) are reliable physiological measures of stress that can be monitored with these wearables [21]. Some naturalistic studies have been performed to assess physiological stress using wearables in real-life settings. Rises in EDA [22-24] and HR [22] have been reported in the 30 minutes prior to aggression in psychiatric patients. Physiological stress and motion measures can be used to predict aggression to others in the upcoming minutes in people with autism spectrum disorder (ASD) [25]. In an earlier study, Noordzij, Scholten, and Laroy-Noordzij [5] have shown the possibilities of measuring EDA and HR in clients with SPID and the caregivers that support them during incidents of CB. In inpatient forensic mental health services, caregivers reflected on the utility of technological devices to provide early warnings for impending aggression [26].

Our Study

The literature has shown the predictive value of physiological measures of stress for upcoming aggression in psychiatric patients and people with ASD. Although the possibilities of using wearables to study physiological stress in clients with SPID and CB have been shown, not much is known about patterns of physiological stress prior to CB in clients with SPID or in the caregivers that support them. Since the existing literature shows the well-being of caregivers is affected by stressors associated with clients' CB, and the relationship with caregivers is important for clients to cope with stress and prevent CB, studying the reciprocity between clients' and caregivers' physiological stress is an eminent step in further increasing insights into patterns of stress and the origin of CB. Therefore, we hypothesize a reciprocal model in this study of stress and CB (Figure 1). The model suggests that: (1) client stress is associated with CB [2,15,17], (2) caregiver stress contributes to CB [4,7,14], (3) CB contributes to caregiver stress [6-9], and (4) caregiver stress impacts client stress and vice versa.

Figure 1. A reciprocal model of stress and challenging behavior in caregivers and people with severe to profound intellectual disability.



This naturalistic study explores patterns of physiological stress (ie, EDA and HR) in clients with SPID and professional caregivers prior to CB in Dutch residential institutes and the synchronization between client and caregiver patterns of stress. We address the following research questions:

1. Do patterns of physiological stress in clients with SPID and professional caregivers in the 30 minutes preceding an incident of CB differ from control periods of 30 minutes without CB?

2. Do the physiological stress levels of caregivers impact clients' physiological stress levels and vice versa?

We hypothesize that a significant rise in EDA and HR is apparent in both clients and caregivers in the 30 minutes preceding an incident of CB compared to baseline levels when the client does not engage in CB. In addition, we hypothesize physiological synchrony—a mutual change in autonomic nervous system activity—between caregivers and people with SPID and CB. Physiological synchrony has been shown in some interaction partners, including parent-infant dyads [27,28], strangers [29], and romantic couples [30]. However, to our knowledge, physiological synchronization has not been studied before in dyads of professional caregivers and clients with SPID and CB.

Methods

Study Design

A longitudinal design will be performed in 15 single-case studies in which one case is a dyad of one unique client and one unique professional caregiver. More so than randomized controlled trials, multiple single case studies offer opportunities to study underlying processes and perform elaborate analyses on the individual and the environmental level [31]. In addition, people generally respond differently to stressful events and interpret different situations as stressful due to age, gender, experiences, and so on [32], underpinning the usefulness of single-case designs. The study will be performed in Dutch residential care organizations for people with ID. The organizations are part of a knowledge platform (in Dutch: "Kennisplatform EVB") for sharing and developing knowledge regarding people with SPID and CB. This study was approved by the Faculty Ethics Committee of the Radboud University (NL-number: NL71683.091.19) February 12, 2020. Informed consent will be obtained from all caregivers and parent(s) or legal representative(s) of clients.

Sample Size

This study included 15 dyads of a client and a professional caregiver. Due to the exploratory nature of the study, the sample size is not calculated. The sample size of 15 was determined based on feasibility due to the time investment necessary per case and the resources available to conduct this study. Single-case designs have additional sample size factors involved in determining power and accuracy besides the number of participants, including the number of observations [33]. In this study, we use several measurements for each dyad, increasing the power with a relatively small sample size.

Eligibility

Clients will be eligible to enter the study if they meet the following inclusion criteria: (1) adults between 18 and 65 years of age, (2) anticipated to engage in CB regularly (ie, multiple times per week), (3) expected to reside in a designated institute for the upcoming 3 months, and (4) an IQ of 40 or below. Recruited caregivers (1) work a minimum of two days a week with the client and (2) are expected to work with the client for the upcoming 3 months. Clients for whom caregivers, behavioral experts, parents, or legal representatives expect to experience excessive distress from wearing the wearable, or will most likely damage the wearable, are excluded.

Recruitment

Participants will be recruited during a symposium concerning clients with SPID and CB and through invitation letters among the 28 organizations that are part of the knowledge platform. First, the researcher informs interested caregivers about participation in the study via telephone or face-to-face discussions. Second, caregivers will indicate which client is eligible to participate in the study. Third, caregivers will contact clients' parent(s) or legal representative(s) to inform them about the study with an information letter and request for consent to participate. Informed consent will be obtained from all caregivers and legal representative(s) of clients.

Study Procedure

Clients and caregivers will wear the wearable during 20 sessions of 3 to 8 hours. The sessions do not interfere with daily routines and activities. The caregiver will attach the wearable to their own and their client's wrist. Caregivers will follow a protocol developed specifically for clients with SPID and CB to attach the wearable to the client's wrist because the attachment of the wearable may induce stress for both caregivers and clients due to the deviation from the daily routine [5] (see Multimedia Appendix 1). The protocol is personalized per dyad. To minimize the influence of the wearable on stress and behavior, clients and caregivers will wear the wearable prior to the study to familiarize themselves with it. When the wearable no longer induces stress to the client and the caregiver, we will start collecting measurements. The data are saved in the memory of the device and exported into a secured server via USB.

Measures

Physiological Stress

Physiological measures of stress are obtained with the Empatica E4 wristband, a wearable wireless device that measures EDA, blood volume pulse (from which interbeat intervals and HR are derived), body temperature, and movements. This wearable provides advanced data quality compared to other available wearables, including artifact removal technique [34]. Validation studies show promising results [35,36].

HR is determined with a photoplethysmography (PPG) sensor, acquired at a 64 Hz sampling frequency. The amount of light through the skin reflected on the PPG sensor reflects the blood volume changes in the vessels with each heartbeat. HR (beats per minute) is derived from the blood volume pulse. EDA (microsiemens) is acquired at a 4 Hz sampling frequency using two electrodes through which a continuous current flows. When one's sympathetic arousal level increases during stressful events, more sweat is produced, which increases EDA, whereas decreased sympathetic arousal results in a decrease in EDA. The extracted parameters are skin conductance level (SCL) and the number of peaks per minute (PPM). Measures of HR and EDA are corrected for temperature (degrees Celsius) and movement (measured with a 3-axis accelerometer) [34].

Challenging Behavior

For each incident that occurs during the sessions that the E4 wristband is worn, caregivers will report the following: date, time, type and severity of the incident, a description of the incident, whether the incident was expected (yes or no), and location. The incident registration form is based on the Modified Overt Aggression Scale [37]. The incidents are classified as either verbal aggression, aggression against property, auto aggression (ie, self-injury), or physical aggression. The severity of an incident is scored on a scale from 0 (light) to 4 (severe). Examples per type of incident are provided per severity score and personalized per client. Caregivers fill in the incident registration form on paper immediately after the incident has been averted.

Client Mood

Caregivers indicate the client's mood every 15 minutes with green, yellow, orange, and red cubes. The definition of the colors is determined per client with caregivers and behavioral experts by associating each color to specific behaviors. Client mood scales will be based on a daily questionnaire reported in the electronic client record by some organizations. In addition, every organization makes use of a "signaling plan," which includes 4 phases of behavior ranging from 0 (relaxed) to 4 (extremely stressed). The behaviors in these plans are translated into the 4 colors used to indicate mood in this study. To ensure feasibility, caregivers estimate the client's mood throughout the day but only report the client's mood on paper at the beginning of each shift and when the client's mood changes.

Self-Reported Stress

Self-reported caregiver stress in the past month is measured prior to and after participation in the study. Caregivers fill in the 10-items Perceived Stress Scale (PSS-10) [38], which measures the degree to which situations are appraised as stressful on a 5-point Likert scale from 0 (never) to 4 (very often). A sum score between 0 and 40 gives an indication of perceived stress in the last month. Psychometric qualities are good [39]. The Dutch translation of the PSS-10 will be used.

In addition, self-reported caregiver stress in the 30 minutes prior to an incident of CB is measured on a scale from 1 (totally relaxed) to 10 (totally stressed out).

Demographics

The following client characteristics will be collected: sex, age, IQ, history of incidents, diagnoses, and medication. The following caregiver characteristics will be collected: sex, age, education, and work experience.

Statistical Analyses

Descriptive statistics regarding incidents of CB and stress levels will be described in relation to demographic data. As measuring physiological stress in real-life situations results in artifacts (ie, disturbances in the signal due to excessive movements), the data will be visually inspected, and impossible values removed. Subsequently, data will be corrected automatically with a proven method described by Taylor and colleagues [40]. Statistical analyses will be performed in R-4.0.4.

EDA and HR of clients and caregivers in the 30 minutes prior to an incident of CB will be compared with 30 minutes of control periods in which the client did not engage in CB. A multilevel model with repeated measures (level 1) at the incident level (level 2) nested within the person level (level 3) will be used. For the repeated measures (level 1), the 30-minute sessions are divided into epochs of 5 minutes. Separate models for PPM, SCL, and HR will be considered. Covariates in the models include movement, temperature, and gender.

Recurrence Plots (RPs) of the 30 minutes prior to an incident of CB will be made. Cross-Recurrence Quantification Analysis (CRQA) will be performed to determine if patterns of stress in the time series of caregivers are recurring in the time series of clients, and vice versa, in a moment prior, simultaneously, or later in the time series [41]. The Recurrence Rate (RR), a ratio of the number of recurrent points over the total possible number of recurrent points, will be calculated. The RR indicates how often a point in one time series recurs in another time series. Determinism, which is the number of recurrent points that form a diagonal line in an RP relative to the total number of recurrent points, will be calculated. Determinism represents the recurrence of patterns over time, and a high determinism indicates the synchronization of patterns of physiological stress between the caregiver and the client. A diagonal Cross-Recurrence Profile provides insights into who is leading in the pattern of physiological stress prior to an incident. In other words, is the recurring pattern of stress first noticeable in a client and subsequently in the caregiver, or vice versa? CRQA is performed using the R package "crqa" [41].

Results

In total, 15 organizations have declared their commitment to participate in the study. Research findings will be disseminated through peer-reviewed journals, professional networks, conferences, and the website of the knowledge platform concerning people with SPID and CB. The first results are expected in the spring of 2022.

Discussion

Conclusions

This protocol study describes a series of single-case studies assessing stress patterns in professional caregivers and clients with SPID prior to incidents of CB in Dutch residential institutes and the synchronization or desynchronization between these patterns. We hypothesize that a significant rise in EDA and HR is apparent in clients and caregivers in the 30 minutes preceding an incident of CB compared to control periods without CB. In addition, we expect a reciprocal influence of caregivers' and clients' stress levels, meaning an increase in caregiver stress is followed by the rise in client stress and vice versa.

One of the study's strengths is that stress is measured in a real-life setting without interfering with daily routines. While measuring physiological stress in real-life settings results in artifacts, the models in this study will be corrected for movement and temperature. A visual and an automatic correction of artifacts will be performed as well [40]. In an earlier study [22],

a considerable number of artifacts, besides movement and temperature, were found in the data related to the tightness of the wearable on the wrist, which will be addressed when instructing participants. Besides movement and temperature, gender is included as a covariate in the models. Meta-analyses have shown that the associations between physiological measurements and behavior are similar for men and women, but the strength of the associations varies [42-44].

Another strength of this study is that interpersonal variations are accounted for by comparing stress of the same subject in periods prior to CB with control periods without CB. This comparison is important as people have different baseline values of EDA and HR [22]. In addition, the stress of both client and caregiver is assessed in the same time frame. This enables us to study the reciprocity between client and caregivers' stress, which is important as client-caregiver interactions impact the development of stress and CB and are vital to the quality of support caregivers can provide [2,13].

A limitation of the study is that the available resources (eg, time and money) restrict our ability to document fully detailed contextual factors that may affect the outcome. For instance, specific reasons why a caregiver or client is stressed prior to CB remain unaddressed, and variations in physiological stress patterns prior to CB due to other causes of stress that were not assessed remain unknown.

Finally, heart rate variability (HRV) is commonly used as a physiological measure of stress; it is a more sensitive measure for stress when compared to HR, which will be used in this study [21]. However, the amount of participants' movement in real-life settings significantly interferes with the accurate registration of HRV with a PPG sensor [22,45,46]. For this reason, HR will be used as a physiological measure of stress rather than HRV.

Implications for Practice

Stress is common in clients with SPID and CB and the caregivers that support them, and it is often a precursor of CB. Measuring physiological stress is important due to the communicative difficulties associated with the severity of ID and CB, especially in clients with SPID [2], and the reported difficulties of caregivers in interpreting clients'' cues of stress [5]. Measuring physiological stress provides insights into the real-life emotions of those who have difficulties expressing emotions to their caregivers, and it offers a first step in increasing insights into the processes of stress that precede incidents of CB. Eventually, these insights can assist caregivers in recognizing CB by informing them about changes in client stress levels in order to anticipate clients' CB. In addition, caregivers are informed about changes in their stress levels to enable effective stress coping. Insights into the stress of clients and caregivers will contribute to their safety and well-being.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Protocol to attach the wearable to the wrist of a person with severe to profound intellectual disability and challenging behavior [<xref ref-type="bibr" rid="34ref5">5</xref>].
[PDF File (Adobe PDF File), 59 KB - resprot_v10i7e24911_app1.pdf]

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Abbreviations

ASD: autism spectrum disorder
CB: challenging behavior
CRQA: cross-recurrence quantification analysis
EDA: electrodermal activity
HR: heart rate
HRV: heart rate variability
ID: intellectual disability
PPG: photoplethysmography
PPM: peaks per minute
PSS-10: 10-items perceived stress scale
RP: recurrence plot
RR: recurrence rate
SCL: skin conductance level

SPID: severe to profound intellectual disability

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Protocol

Practitioners' and Policymakers' Successes, Challenges, Innovations, and Learning in Promoting Children's Well-being During COVID-19: Protocol for a Multinational Smartphone App Survey

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Abstract

Background: The advent of COVID-19 abruptly thrust the health and safety of children and families into greater risk around the world. As regional and local governments, nongovernmental organizations, communities, families, and children grapple with the immediate public health impact of COVID-19, the rights and well-being of children, especially those who are already marginalized, have been overlooked. Those working with children have likely encountered unprecedented challenges and responded in innovative ways in efforts to address the needs and rights of all children.

Objective: This paper presents a protocol for a large-scale, multinational study using a new smartphone app to capture the real-time experiences and perspectives of practitioners and policymakers supporting children and families during the COVID-19 pandemic around the globe in relation to a children's human rights *4P* framework of protection, provision, prevention, and participation.

Methods: This protocol describes a mixed methods survey utilizing a custom-built iOS and Android smartphone app called the COVID 4P Log for Children's Wellbeing, which was developed in close consultation with 17 international key partner organizations. Practitioners and policymakers working with and for children's well-being across 29 countries and 5 continents were invited to download the app and respond to questions over the course of 8 weeks. The anticipated large amount of qualitative and quantitative response data will be analyzed using content analysis, descriptive statistics, and word frequencies.

Results: Formal data collection took place from October 2020 until March 2021. Data analysis was completed in July 2021.

Conclusions: The findings will directly inform the understanding of the ways in which COVID-19 has impacted practitioners', managers', and policymakers' efforts to support children's well-being in their practices, services, and policies, respectively. Innovative and ambitious in its scope and use of smartphone technology, this project also aims to inform and inspire future multinational research using app-based methodologies—the demand for which is likely to continue to dramatically rise in the COVID-19 era. Mitigating the risks of longitudinal remote data collection will help maximize the acceptability of the app, respondents' sustained engagement, and data quality.

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KEYWORDS

mobile phones; smartphone app; qualitative; mixed method; international; survey; service providers; policy; practice; children's rights; well-being; COVID-19; pandemic; app; mHealth; children

Introduction

Background

The advent of COVID-19 abruptly thrust the health and safety of children and families into greater risk around the world [1-3], with far-reaching consequences for public health, child protection, peace, and justice, globally. While focusing on mitigating the immediate public health and economic impacts of the pandemic, regional and local governments, communities, and families may risk overlooking its acute and long-lasting effects on the rights and well-being of children, in particular, those who are already marginalized [4]. Agencies worldwide have recognized that minimizing the negative impact of the COVID-19 emergency on children—in particular, those related to public health responses—will be critical to protecting children's well-being. This will also be essential to realizing United Nations (UN) Agenda 2030 and Sustainable Development Goals [5].

The distinctive impact of this pandemic on children is vast, and the risks posed to children's rights to survival and development, as well as to their rights to special protection, education, health, and food, have been greatly compounded by COVID-19, and in many cases, by governmental priorities and responses [6-8]. Children's rights to participate in decisions that impact them have also likely been compromised [9,10]. For those children who are in detention, in alternative care, in migration—especially those who are unaccompanied—and living in poverty, this pandemic and related measures of confinement have likely had an even greater impact. A distinctive and well-coordinated response is required by governments, nongovernmental organizations, and local communities to mitigate these impacts [2,11].

Supporting children by implementing policy and practice responses that are focused on distinctly promoting children's well-being will form a part of this necessary response, throughout all stages of this pandemic. In some cases, given the changed nature of their work and the constraints faced by practitioners and policymakers alike, these approaches will need to be innovative and may be unprecedented. A better understanding of these circumstances across cultures, countries, and continents is essential to address the impact on children now and in the medium term [2,3].

Utility of Smartphones for Capturing Critical Information from Hard-to-Reach Groups

The COVID-19 pandemic has posed unparalleled challenges to the conduct of traditional face-to-face research [12]. Harnessing the capabilities of mobile phone devices has become the cornerstone of innovative research methodologies for the remote collection of qualitative and quantitative data, including in low- and middle-income countries, during this time [12].

The use of mobile phones for gathering qualitative and quantitative data across a range of geographical settings has been demonstrated to be feasible and effective [13,14]. Mobile phones are flexible, affordable, and naturalistic devices, which makes them a powerful tool for generating rich, highly contextualized insights, including in hard-to-reach or vulnerable populations [15-18].

Beyond enabling the generation of substantive findings in the health and social sciences, certain mobile methods such as mobile phone diaries and other free-text response formats have shown intrinsic benefits for study participants [14,19]. Examples include increased autonomy, enhanced opportunities for self-expression and reflection, and more acceptable communication of sensitive topics and in high-stress environments [12,14].

COVID 4P Log for Children's Wellbeing Smartphone App for Conducting Global Research

In response to the need to capture vital, time-critical cross-country data in the midst of this global emergency, the research team designed a smartphone app–based survey to explore how children's rights and well-being are being supported in this pandemic. To generate insights that would inform policies and practices during ongoing and future stages of COVID-19 and in preparation for future public health emergencies, we set out to understand effective practices and policies, challenges, innovations, lessons learned, and recommendations for improving practice and policy in relation to the protection, prevention, participation, promotion, and service provision for children's rights and well-being around the globe.

Practitioners and policymakers working with and for children's well-being across 29 countries and 5 continents were invited to download the app and respond to questions over 8 weeks. To do so effectively, we established a broad partnership of 17 international key partners, whose roles span intergovernmental policymaking, child rights advocacy, workforce capacity-building, service delivery, and monitoring roles at UN level. With their active involvement, the team designed a novel fast-capture smartphone app called the COVID 4P Log for Children's Wellbeing [20].

As well as gathering practice- and policy-related data on key aspects of children's lives and rights affected during this pandemic, the daily question schedule and the longitudinal nature of the survey were intended to provide a reflection space for respondents to share their achievements, challenges, and concerns. In addition to the core questions, a series of questions enquires about respondents' own coping and well-being during the pandemic; this component of the survey was influenced by diary-based research, in that it attempted to capture data in the form of intimate reflections or confessionals on these topics, which might be sensitive or difficult to discuss [19]. Engaging in such written reflections may also have intrinsic personal benefits to the respondents, by having the opportunity to share and be heard [19]. In light of the public health containment measures and other mobility restrictions which have been

forcing many professionals into remote lone working, as well as the undue increases in the safety risks and workloads for many frontline workers worldwide, offering professionals a space to share their concerns, successes, and reflections is likely to increase the acceptability and ethical sensitivity of the research [19,21,22].

Aims

The aim of this paper is to provide researchers with insights into the design decisions and approaches undertaken within this project and to contribute to the growing evidence base on the use of fast-capture digital technologies for mixed methods research with hard-to-reach groups.

Methods

Research Design

This project is a mixed methods study utilizing a smartphone app–based survey to enable a fast-capture, contextually aware, and unobtrusive approach to remote data collection.

Research Team

The diverse and complementary expertise of the research team and the relationships with partner organizations and other stakeholders have been critical to the project's success. The research team comprises an international expert in children's rights and well-being, with a wide range of international policy and practice stakeholder collaborations; an expert in human–computer interaction, with experience of user-led app development; a data manager, with experience working with Microsoft Azure databases and app-based research projects; an experienced contracted app developer; a researcher with experience of app-based data collection with hard-to-reach groups; and 2 knowledge exchange administrators and research assistants with communication, visual design, and stakeholder liaison experience.

Sampling and Recruitment

Eligible participants were adults (aged 18 years of age or above) working in a role supporting children's well-being, such as a policymaker, a practitioner, a supervisor, or a manager, in a paid or voluntary capacity, with sufficient English language fluency to engage with the app.

Remote participant recruitment and data collection pose distinct challenges to achieving diverse, representative samples [12]. The pragmatic combination of purposive (maximum variation), convenience and snowball sampling strategies in this study aimed to ensure the efficient collection of rapid, time-sensitive insights from a diverse cohort of professionals amid a global emergency [12,23,24]. Purposive sampling ensured that respondents from a wide range of countries, regions, roles, and areas of work were encouraged to participate. The snowball and convenience sampling approaches relied on the key partners, who assisted with recruitment and follow-up. Snowball sampling was relied upon because study participants, such as supervisors and service managers, were encouraged to disseminate information about the study across their teams, organizations, and sectors.

Each key partner assisted with recruitment by proposing the countries in which their organizational networks had the greatest reach and influence and in which they believed they might be able to recruit at least 50 respondents. In determining the target sample size, we anticipated that achieving this level of representation from all 29 target countries would be challenging and that there would be a reduction in the numbers of participants sustained throughout the 8-week logging period, given the level of participant retention in other surveys [12].

The research team and the key partners promoted the study via social media, the project website, e-newsletters, and videos. Interested participants had the option of visiting the project website or downloading the app directly into their smartphone (Google Play or Apple App Store). Monetary incentives for participation were not offered in order to minimize the risk of coercion and due to the purposive sampling strategy, which mainly relied upon existing networks and relationships.

In the first phase, the Android or iOS app was available for free download to users in the following countries: Australia, Belgium, Canada, Finland, Greece, India, Iraq, Israel, Italy, Jordan, Kenya, Lebanon, Malawi, the Netherlands, New Zealand, Norway, Palestine, the Philippines, Romania, Sierra Leone, South Africa, Sweden, the United Kingdom, and the United States. It was also made available in the Google Play Store's *rest of the world* category in order to recruit app users in Eswatini, Ethiopia, Tanzania, Uganda, and Zambia. The app was only available in English. After consulting with the key partners, it was decided that it would not be made available in Latin America or conflict-affected countries. Furthermore, users with a smartphone having Android versions older than 8.0 (Oreo) or iOS versions that are older than 12.5, and those whose smartphones run on operating systems other than Android and iOS were not able to take part.

The app was available to download for 3 months in its first phase from October 7, 2020 to 5 January 5, 2021, in order to capture data during the pandemic's second wave in many countries [25]. The app was removed from the Google Play and App Stores on January 5, 2021. Because some participants had just begun their 8 weeks of questions at that time, the data collection concluded 8 weeks later on March 9, 2021.

Data Collection

Smartphone App Design

The app was built for both Google's Android (version 8 and above) and Apple's iOS (version 12.5) using React Native (Facebook Inc). The smartphone app was developed in partnership with an independent app developer contracted by the University of Strathclyde, which enabled a flexible tailored approach and delivered a quality product [26]. It is free to download, small in size, and takes little processing and battery power.

To ensure the acceptability and accessibility of the app, an app development steering group was formed, comprising representatives from the key partner organizations. The steering group advised on the app logo, other design features, and the survey questions, as well as taking part in the test flight phase.

Several changes were made as a result of the test flight feedback, including fixing technical issues and adjusting minor aspects of the wording, layout, and flow (sequence of task steps). To increase motivation as well as flow through the app, after submitting a response, a screen was added thanking the participant for completing a response that day, and a certificate of contribution was offered to those who completed questions across all 8 weeks. Consultations with key partners also led to the use of a more vibrant color scheme for the project's visual identity.

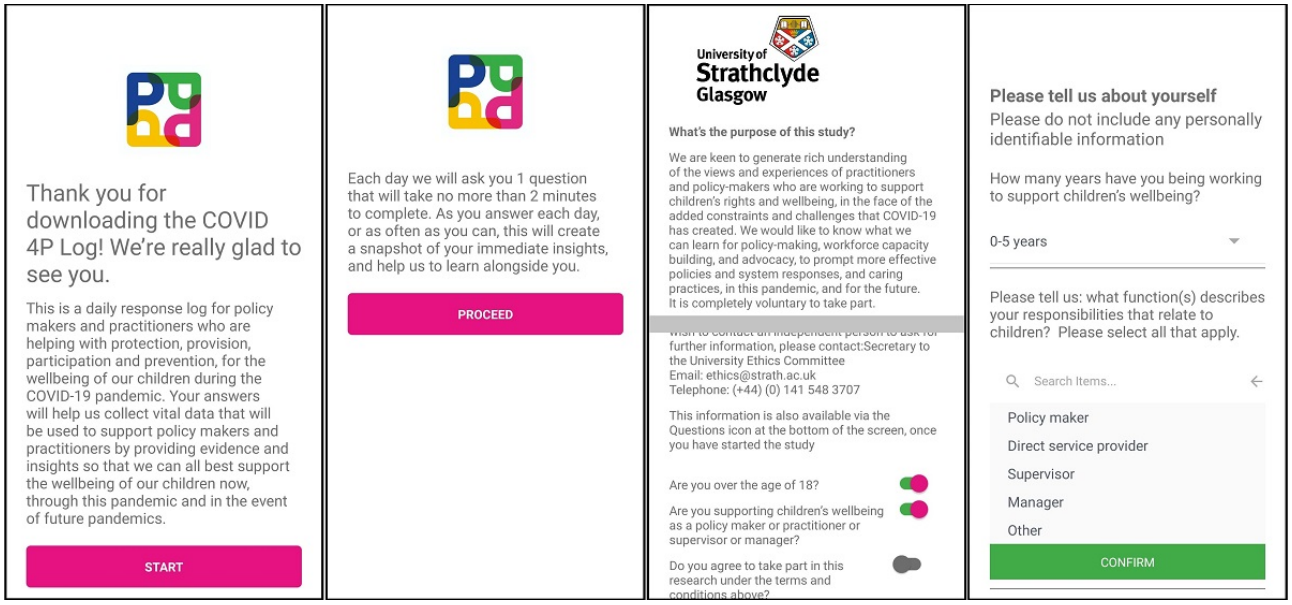
There were 6 main components of the app: Onboarding, Daily Log, Calendar, FAQ (frequently asked questions), Information (about the project), and Settings. Calendar, FAQ, Information, and Settings were all accessible via a navigation bar at the bottom of the app.

Onboarding

Onboarding is typically the process of welcoming a new user and introducing them to how the app works. For our app, after a branded loading screen (Figure 1), the onboarding text (Figure 2) first thanked the person for downloading the app and briefly explained for what it would be used—a daily response log to record policymakers' and practitioners' insights and experiences. The next screen informed the user that they would only be asked 1 question per day, which would take no more than 2 minutes to answer. The user was then provided with an information and consent screen (terms and conditions), which fully explained the design and purpose of the research study, data governance, anonymity, and project partners. To indicate that they consented to taking part, the user was asked to confirm, by tapping on a button next to each statement, that they were over the age of 18, were working in an appropriate role related to children's well-being, and agreed to the above terms and conditions. The subsequent screen was used to record information about the participant's professional role and experience. At the end of onboarding, the participants were taken to their first Daily Log screen.

Figure 1. Loading screen with app logo.

Figure 2. The app onboarding process (from left to right): initial welcome screen, message to user, consent form and agreement indicators, and demographic questionnaire.



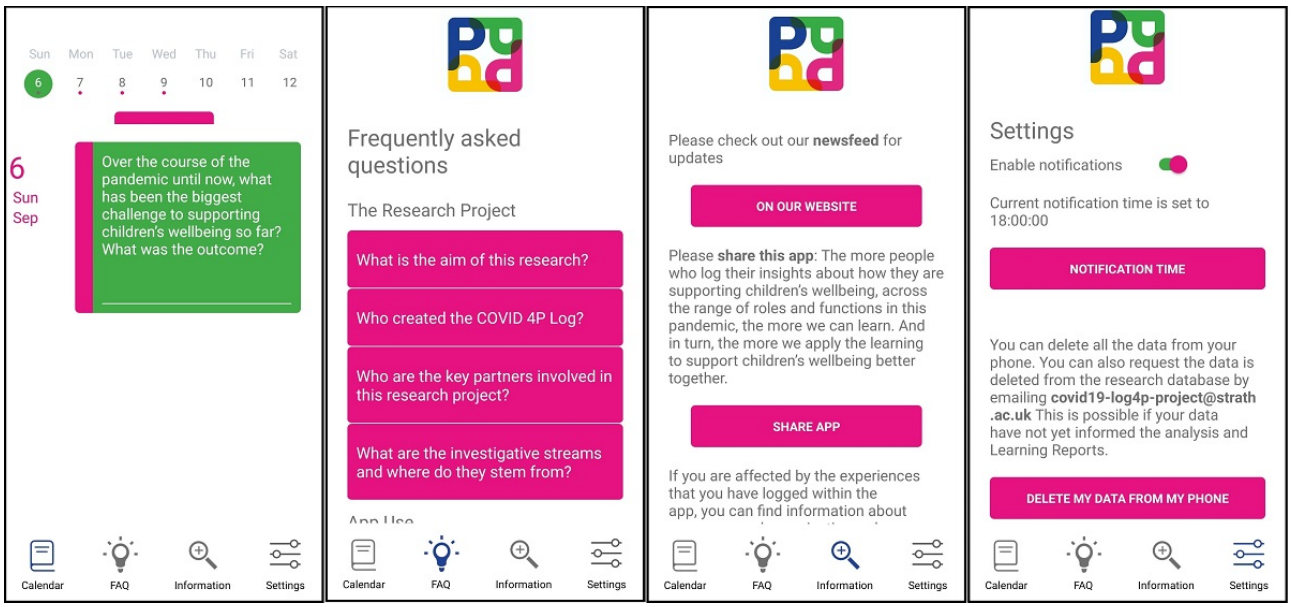
Daily Log

Each day, the app displayed a single Daily Log screen when the participant first opened the app. It showed the question that had been assigned to that particular day and provided a free-text box for the participant to write as much or as little as they wanted. The screen also had an optional question asking the participant if they wanted to provide any general or separate insights or comments. The answers were recorded when the *Submit* button was clicked.

Calendar

Participants were given the ability to revisit answers that they had provided over the previous weeks, in case they wanted to amend what they had said. They were also able to answer the given week's 7 questions at any time, if they did not want to answer daily. The calendar (Figure 3) showed the days of the week at the top of the screen, and each day with a question had a pink dot. By selecting the day, the question and any previous answer were displayed in the lower part of the screen, and these text boxes could be edited to change the answer. Tapping on the pink bar under the days of the week displayed a larger month-long calendar.

Figure 3. Main app screens (from left to right): Calendar, FAQ (frequently asked questions), Information, and Settings.



FAQ

The FAQ screen (Figure 3) provided information about the research project, how to use the app, data protection, investigator contact details, and terms and conditions.

Project Information

This screen provided a link to the main project website, a button to share a link to the app and project information videos via social media platforms, and links to country-specific resources

and organizations, should they wish to seek help for a child or if they were emotionally affected as part of their involvement in the project.

Settings

The Settings screen allowed participants to enable or disable notifications and set the time at which the Daily Log reminder notification was sent to them. For privacy and data governance reasons, it also contained a button that would delete all the data they had provided stored locally on the device. If they wished to have their data removed from the main research database, they could request this via a project email address.

Survey Development

The survey was informed by 8 investigative streams, and a new set of questions corresponding to each investigative stream was introduced each week (Table 1). These streams were shaped by a 4P (protection, provision, prevention, and participation) children's human rights framework designed to better understand the ways practitioners and policymakers were able to protect children, provide for their unique needs, enable their participation in decisions that affect them, and prevent harm in this pandemic context. While limited in specificity, the 4Ps nevertheless offer accessible framing of the rights most closely corresponding to aspects of children's well-being that are the focus of this study. The benefits and drawbacks of both human rights and well-being approaches were considered by the key partners [27]. Both rights and well-being were chosen in order to most effectively address the wide range of interests that shape the key partners' varied work.

The survey questions were drawn from a wide range of mainly COVID-related multidisciplinary international policy- and practice-focused English-language publications, particularly those issued by established international institutions concerned with children, including UNICEF [28], the UN Committee on the Rights of the Child [29], and the Pathfinders for Peaceful, Just, and Inclusive Societies [30]. These publications are mainly grey international policy and practice literature, where concerns about children during COVID-19 were shared earlier in the pandemic than they were in the peer-reviewed academic literature.

In focus groups, key partners contributed their feedback on selected questions across the investigative streams, reflecting on clarity, situational and cultural relevance, sensitivity, and overall acceptability of the questions. In addition, individual key partners identified specific aspects of children's lives for inquiry relevant to their organizational focus. In some cases, specific questions were drafted, shared, and further adapted in partnership. Additionally, an international group of child researchers involved in advising the Life under Coronavirus international peer research project [31] met as a focus group to directly advise the research team on a specific set of questions to inform to the investigative stream on children's participation.

Table 1. Survey schedule.

Topic (investigative stream)	Example survey question	Survey items, n
Week 1		
Onboarding (demographic and work-related) questions	What best describes what you do in relation to children?	11
Learning from the pandemic so far	What has gone well in your sector's support of children's well-being during COVID-19?	14
Week 2		
Protection: Ending violence against children	Has your sector experienced challenges in protecting children from violence during COVID-19?	21
Respondents' coping and well-being	On a scale of 1-5, how stressed and anxious have you been feeling in the past week?	5
App evaluation	How would you describe your overall experience of taking part in this study so far?	5
Week 3		
Provision: Access to food, health, education	How have you changed what you do in your work because children have had more restricted access to basic needs, eg, food, education and health care, during COVID-19?	21
Week 4		
Collaborations, flexibility, transparency, and trust: Applying evidence from past emergencies to COVID-19	In past emergencies around the world, government actions that facilitate trust, connections and collaborative working between government, across sectors and within communities, have been found to be important for recovery from the emergency. Have you seen these actions by your government(s) in this pandemic?	17
App evaluation	Has taking part in this study had an impact on your work?	4
Week 5		
Prevention: Children's social and emotional well-being	Have you found that children have experienced mental health issues during COVID-19?	17
Week 6		
Special considerations - Access to justice, alternative care, disabilities	Children in detention are likely to be in poorer health than those who are not. The COVID-19 outbreak exacerbates the challenges these children face. Have children been released from detention so that they can return to their families and self-isolate?	15
App evaluation	What has been motivating you to continue taking part in this project?	4
Week 7		
Children's participation	During COVID-19, have children's views been sought about policy or practice decisions that affect their lives?	21
Week 8		
Preparing to rebuild post–COVID-19	What are the priorities for children that should be emphasized following the first phases of COVID-19? Please tell us more.	15
App evaluation	If you could, would you want to keep using an app of this sort as an ongoing part of your day-to-day work?	7

Survey Structure

App respondents were asked a total of 177 questions over a period of 8 weeks (Table 1). On average, 1 main open-ended question with 3 follow-up questions (open or closed-ended) were asked each day. Week 1 began with a series of onboarding questions about respondents' demographic and work-related information such as gender, country and region of work, years of experience, professional role, and sector. In addition to questions related to the investigative streams, a series of questions was also asked about respondents' own coping and well-being, as well as about their experience with the app.

As soon as questions were completed, they were automatically uploaded to the cloud server when Wi-Fi or mobile data were available. At the conclusion of participants' 8 weeks of responses, the app provided them with a project email address and offered the opportunity to give theirs, if they wished to stay in touch with the project and receive updates.

Data Management

A data management plan was completed in line with university standards, and the data manager ensured compliance with the plan. The project data (survey responses) were transmitted to a dedicated, European Union–based cloud-hosted database at OVHCloud (OVH Groupe SAS); this occurred when the research participants submitted their responses as soon as Wi-Fi or mobile data access was available. The data were then accessed with DBeaver (open source) database management software and extracted as a .csv file. Data were stored on the university's internal systems and were clearly versioned. The data were secured by having a passkey and by only being accessible from specified IP addresses.

After data were extracted from the database in .csv format, they were stored in the university's internal networked storage in a location only accessible to the research team. The data manager produced a script in Excel using Visual Basic script (Microsoft Inc) to transform the data into a usable format. This was necessary to overcome the challenges of working with large amounts of data.

All participant data were strictly anonymous. There were no personally identifiable data collected within the app by default, and users were given instructions not to provide any personally identifiable information within the open-text responses. Prior to data analysis, the data manager screened the data to ensure that no personally identifiable information had inadvertently been provided. All such data were anonymized; access to the raw data was restricted to the research team. All data are stored on Azure cloud storage (Microsoft Inc) in full compliance with the General Data Protection Regulation legislation.

Data Analysis Plan

The open-ended survey response data will be analyzed using qualitative content analysis, which involves open coding, grouping, categorization, abstraction, and conceptual mapping [32]. The coding strategy will involve both structural and data-driven (inductive) approaches [33,34]. The structural coding will be based upon the investigative streams underpinning this study, as well as upon the survey questions. The responses to the closed-ended survey questions will be analyzed using descriptive statistics. Cross-tabulation will be performed to compare participants' responses according to sociodemographic characteristics such as country, professional role, gender, experience level, and others.

The qualitative data analysis software, NVivo (version 12; QSR International), will be used to assist with the data analysis. NVivo enables the efficient and systematic storage, management, analysis, and sharing of large amounts of qualitative and quantitative data [35-37]. Various data visualization, coding, and text mining features—such as word clouds, word frequency queries, text search queries, word trees, coding context, and matrices—will be used to facilitate the efficient generation of rich insights from the data [36].

Throughout this process, the researchers will keep a research diary containing both methodological and analytic memos [32]. Regular team meetings will be conducted to conduct formal and informal coding comparisons, discuss emerging codes and themes, clarify ambiguous or unclear datapoints (such as professional jargon, abbreviations and vernacular), and help minimize personal and professional biases that could inadvertently affect the analysis [38].

Research Advisory Group

After data collection, the key partners will be invited to a research advisory group, which is intended to comprise a representative sample of stakeholders including policymakers, child rights advocates, and service providers who will be asked to comment on an accessible summary of the anonymized findings. Their input will help articulate the implications of the findings for policy and practice. Additionally, Life under Coronavirus child researchers will be invited to reflect with the research team on the study's conclusions. This approach to member checking will enhance the credibility and trustworthiness of the findings [39].

Ethical Considerations

Conducting research that targets at-risk or hard-to-reach groups, including those working in high-stress environments, during a global pandemic raises acute ethical concerns [12]. In this study, the potential risks of participation—such as the undue time and emotional commitment required and the loss of privacy—were evaluated in light of the considerable expected benefits of promoting child welfare and informing policy and practice worldwide. Several procedures, outlined below, were undertaken to minimize the risks for and burden on study participants and to promote their engagement.

Information on how data are gathered and used during the project was provided to participants on Participant Information and Consent Form pages, to which respondents were required to agree prior to accessing the app questions. This was also available within the FAQ pages in the app itself and on the project website (a link was provided in the Information section). Participants were able to withdraw from the study by stopping participation and removing the app from their mobile phone or by contacting the study administrator by email (which was explained in the Information section of the app). They could remove any data stored on the phone via a button in the Settings or by deleting the app from their phone.

There was concern about the risk of financial costs incurred as a result of using a smartphone app, especially given that participants from low-income countries were involved in this study. The app would have been fully free for the participant to use if they used a Wi-Fi connection for which they were not financially liable (eg, public or workplace) or that had an unlimited data allowance. Users who relied upon mobile data connections or personal Wi-Fi with a data usage cap, however, may have incurred a personal cost for taking part. All efforts were made to minimize the size of the app download; it requires 37.6 MB (Android) or 21.1 MB (iOS) of data for initial download. When bugs needed to be fixed, however, some participants would have been required to download updates of a similar size.

The risk of placing undue demands on participants was addressed in the design of the app and the survey. The app promoted autonomy by allowing participants to initiate the

activity themselves, to determine when and if they wished to be notified by the app to complete the daily question, and to decide if they preferred to complete more than 1 daily question at a time by using the Calendar setting. Participants could also choose to not answer questions. There was a voice-to-text option for those who preferred to speak (and amend) rather than type their responses. Participants could begin and end their participation at a time that suited them.

It is important that the study upheld a duty of care to participants, within the bounds of an anonymous study, as the questions explored how policies, services, and professional practice might or might not be meeting children's needs. It was anticipated that some participants might experience or would express concerns about, increased risks of harm to children; therefore, the app directed participants to information on the project website about where in their country they could seek support for their concerns about a child or for their own mental health.

Results

The study was initiated in April 2020, and the research team began liaising with key partners in May 2020. App development and initial testing were undertaken between June and August 2020. The test flight process began in August 2020, and the app and the majority of questions were finalized in September 2020. Data collection was undertaken between October 2020 and March 2021. Data analysis was completed in July 2021. Dissemination to policy and practice audiences, as a first priority, and to others, later on, will be planned with key partners, given the time-sensitive nature of the findings and the urgency of the issue of children's well-being. Learning reports will be published from June 2021 onward. Key partners will play a further and pivotal role throughout the dissemination stages.

Discussion

General

This paper presents the protocol for a smartphone app–based survey with a distinctive global scope, a participatory approach to survey development involving a diverse group of partner organizations, and a time-sensitive focus on practitioners and policymakers working across a range of settings, countries, continents, and cultures during the COVID-19 pandemic. Ultimately, this study aims to explore a range of concerns at practice, service, and policy levels that reflect the complexity of children's lives and the profound implications of this global emergency.

The role and commitment of the key partners to this project have made a central contribution to its reach, inclusivity, and rigor. Their involvement has been underpinned by goodwill, positive relationships with the research team, and a collective sense of urgency about the issues facing children at this time.

Study Limitations and Risks

There are a number of risks and limitations in this study [12,18].

Linguistic and Cultural Accessibility

The app was only available in English. This likely posed challenges to the engagement of persons with low literacy levels or lack of fluency in English. Crucially, study participation was contingent upon smartphone ownership and the availability of Wi-Fi smartphone devices; it was not feasible to provide data packages.

Data Integrity and Quality Risks

We anticipate typing errors and single-word responses, ambiguous vernacular, unwillingness to enter long responses, and difficulties using the voice-to-text feature. Some responses will thus lack sufficient context or elaboration. Additionally, due to the inherent limitations of anonymous survey designs, we were unable to ask participants to elaborate or clarify responses. Conversely, participants were not able to clarify any questions via the app.

Ensuring data integrity is another challenge of using an anonymous survey format. Because we were not able to ascertain how many users were actively using the app, it was difficult to ensure that all data were being accurately received. To address this, during the beta testing phase and periodically during the early live run of the app, specifically identified researchers and partners filled in the responses using only their initials, allowing the data manager to check to ensure data were being received as expected.

Participant Attrition, Engagement, and Motivation

Some general challenges related to the use of a longitudinal smartphone app survey warrant discussion. Participants may have forgotten to answer the daily questions or lost motivation over the 8-week period. The high burden of participation (177 questions asked over 8 weeks) is likely to have increased attrition. In addition, the relevance of the questions to participants may have varied between investigative streams, given the range of participants' roles, experience, and knowledge, which may also have contributed to attrition. And, due to the nature of their work, participants may have lacked the time or the privacy to sustain detailed daily responses. The resulting attrition may have led to survey questions in the latter weeks of the study being insufficiently addressed. Furthermore, despite anonymous data collection, some prospective participants may have concerns regarding data privacy and anonymity. The remote and anonymous recruitment and data collection will make it more challenging to establish rapport; this may have contributed further to attrition and to reduced respondent motivation.

Technological Risks

The creation of an entirely new app, over an established app service, introduces potential risks such as technical malfunctions and compatibility issues across devices. Technical malfunctions can hinder a user from being able to use the features of the app as intended, which could lead to (among other issues) loss of data, if there are data entry or upload malfunctions; inaccessible information or confusion about how to use the app, if the FAQ or Information sections malfunction; and reduced trust and increased frustration with the app and project, leading to reduced use of the app or even removal of the app from the user's phone.

Risks to the Transferability of the Study Findings

Snowball and convenience sampling strategies in this project have likely resulted in nonrepresentative samples [12]. The sample was purposefully restricted to a set of target countries that did not include humanitarian or conflict settings or countries in fragile states. Furthermore, there may be vast differences among the response rates by individual participants. This may also negatively impact data transferability.

Conclusion

The findings of this global smartphone app–based survey study will directly inform understanding of the ways COVID-19 has impacted practitioners', managers', and policymakers' efforts to support children's well-being in their practices, services, and policies, respectively. This knowledge will be critical to leveraging learning and innovations to better protect children, provide for their unique needs, prevent negative long-term impacts of the pandemic on their well-being, and enable their participation in decisions that affect them. The project also aims to inform the development of a range of publications, best practice guidelines, and other outputs focused on improving pandemic-related professional practices, child rights–oriented policies, and future applications of a smartphone app methodology for real-time responses. Mitigating the risks of longitudinal remote data collection will help maximize the acceptability of the app, respondents' sustained engagement, and data quality.

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Authors' Contributions

JCD, DK, and GW designed the study and wrote the manuscript. JCD is the principal investigator.

Conflicts of Interest

None declared.

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Abbreviations

4P: protection, provision, prevention, and participation
FAQ: frequently asked questions
UN: United Nations

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Early Report

Digital Health Interventions in Physiotherapy: Development of Client and Health Care Provider Survey Instruments

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Abstract

Background: The advancement of digital health has widened the scope of technology use across multiple frontiers of health care services, including personalized therapeutics, mobile health, eHealth record management, and telehealth consultations. The World Health Organization (WHO) responded to this in 2018 by publishing an inaugural broad classification framework of digital health interventions (DHIs) used to address contemporary health system needs.

Objective: This study aims to describe the systematic development of dual survey instruments (clinician and patient) to support data collection, administered in a physiotherapy setting, about perceptions toward DHIs. This is achieved by adapting the WHO framework classification for DHIs for application in real-world research.

Methods: Using a qualitative item review approach, WHO DHI descriptors were adapted and refined systematically to be used in a survey form. This approach was designed to align with the processes of delivering and receiving care in clinical practice, using musculoskeletal physiotherapy as a practical case scenario.

Results: Complementary survey instruments (for health care providers and clients) were developed by adapting descriptor items. These instruments will be used in a larger study exploring the willingness of physiotherapists and patients to use digital technologies in the management of musculoskeletal conditions.

Conclusions: This study builds on the WHO-standardized DHI framework. We developed dual novel survey instruments by adapting and refining the functions of DHIs. These may be deployed to explore the perceived usefulness and application of DHIs for different clinical care functions. Researchers may wish to use these survey instruments to examine digital health use systematically in a variety of clinical fields or technology scenarios in a way that is standardized and generalizable.

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KEYWORDS

digital health interventions; surveys and questionnaires; World Health Organization; physiotherapy; physical therapy; musculoskeletal; mobile phone

Introduction

Background

Digital health interventions (DHIs) are increasingly being considered for integration into standard clinical care; in community, primary care; and in hospital settings. This has been accelerated in recent months due to the necessity and urgency to take up DHIs in light of health care pressures and physical distancing necessitated by the COVID-19 pandemic [1-3]. These DHIs may include internet and web-based patient portals, smartphones and apps, electronic health records, decision support tools, wearables, social networks, telehealth consultations, and others [1,4-6]. DHIs appear to offer the possibility of "...effective, cost-effective, safe, and scalable interventions to improve health and healthcare" [4]. Face-to-face or remote models of clinical care may benefit from integrating many varied DHIs to support data collection and analytics of patient examination records, remote monitoring of clinical progress, health status change alerting, delivering teleconsultation, providing web-based education, aiding clinical decision support, or enabling professional-to-professional communication (among others).

DHIs and Physiotherapy

In the case of physiotherapy (physical therapy) care, routine management of patients presenting with musculoskeletal (MSK) conditions (muscles, ligaments, tendons, joints, nerves, or bones) follows a complex iterative feedback loop of assessment and treatment strategies that generate and test clinical hypotheses and support diagnosis and treatment planning [7,8]. In practice, a physiotherapist collects and analyzes several variables subjectively (qualitative) and objectively (quantitative) about a patient's presentation to formulate decision-making about treatment strategies and planning [9,10]. In real-world practice, it can be a challenge for physiotherapists and patients to capture and synthesize subjective (qualitative) and objective (quantitative) data consistently and reliably. In this regard, DHIs offer potential in physiotherapy and have garnered increased attention [11]. They offer physiotherapists and patients tremendous potential to streamline and automate data collection, remotely monitor health status, alert and prompt, signal care progress or outcomes, and deliver consultations [4,12,13].

Digitally supported care has great potential to positively impact patient management, health behaviors, and treatment satisfaction, which contribute to better health outcomes and improve health system performance [14]. DHIs that are scalable can also overcome barriers to access or cost and may be individualized to meet patient and clinician needs and expectations [4,6]. Nonetheless, evidence about DHI acceptance, uptake, and efficacy remains limited [15], partly because DHIs are complex and multifaceted and because of the lack of a standardized DHI classification system that is easily grasped by both patients and health care providers (HCPs) [4]. Furthermore, although research investigating the acceptance of DHIs exists, assessment of engagement with digital health requires more diverse and comprehensive measures of evaluation than those that currently exist [4,6,15].

Digital Health Classifications

In 2018, the World Health Organization (WHO) released the *Classification of Digital Health Interventions v1.0* [5]. This framework provides a way to describe and classify how digital health technologies are being leveraged by stakeholders across health systems. Inherently, the framework offers a mechanism for stakeholders (such as researchers, HCPs, clients [patients], vendors, and policy makers) to describe the numerous functions of digital health. The WHO's DHIs framework spans a repertoire of mobile health, eHealth, and emerging technological capabilities, which may be used to address health system challenges. Each intervention is paired with associated synonyms and illustrative examples of digital health use. The DHIs are also grouped and mapped to functions relevant to each of the 4 targeted primary user groups (clients, HCPs, health system or resource managers, and data service users) [5]. This framework, which describes DHIs in a common uniform language, is a major advance toward supporting the standardized, accurate, and reliable reporting of DHIs in scientific research, in clinical record-keeping and communications, and in service improvement projects [5,16].

There are, however, potential barriers to the broader application of the DHI framework. These include its predominant focus on public health, as attested to by the WHO [5]. It may not adequately take into account health care delivered in private sector settings. The language used to describe various functions of digital health is arguably technical, and the terminology appears framed more for the health informatics community rather than a clinical community that may possess less advanced digital health competency. Tensions around language and vocabulary used in health informatics continue to be discussed and have been the focus of debate in the scholarly community for some time [17,18]. Thus, the framework in its current form may be most accessible to those with specific backgrounds in digital health and informatics, limiting its potential broader application among HCPs and clients directly involved in clinical care. For example, the language used to describe digital health use by HCPs around structured versus unstructured records may not be easily understood. The following examples come from the WHO classifications of DHIs for HCPs:

2.2.2 Manage a client's structured clinical records

2.2.3 Manage a client's unstructured clinical records

Using a less formal, discipline-specific language might help individuals to understand or quantify the unique meaning of discrete functions of digital health. Furthermore, augmenting this work with a view toward supporting data collection to gather individual perceptions about DHIs may allow increased real-world adoption of the WHO framework in clinical research. In addition, this provides a way to not only view DHIs through the lens of a taxonomy but also to quantify engagement with digital health.

Hence, the objectives of this paper are to develop dual (clinician and patient) survey instruments that support data collection about perceptions toward willingness to engage with DHIs, administered in a physiotherapy setting as a case study. This was achieved by adapting the WHO's framework classification for DHIs. This work may support the increased real-world

adoption of the WHO framework in further clinical research settings.

Methods

Clinical Case Study in Physiotherapy: Developing New Survey Instruments

Our case study setting applies the translated DHI functions to a pair of surveys developed for use within the context of physiotherapy (physical therapy) and MSK health conditions. MSK conditions are health problems related to muscles, ligaments, tendons, joints, nerves, or bones. This realm was identified as a suitable case study because it is the professional background of 3 of the chief investigators (MM, RSH, and BJL); their reputations and networks increased the likelihood of being able to recruit participants in phase 4. The survey instruments were designed to measure *willingness* of clients and physiotherapists to engage with DHIs in real-world scenarios.

Qualitative Item Review of WHO Framework Items to Inform Survey Instruments in a Physiotherapy Setting

Overview

The *Results* section provides a rationale for the use of qualitative item review (QIR) [19] to adapt the WHO DHI items for inclusion in a pair of surveys. The authors followed widely accepted systematic steps in developing the survey tools, as detailed in previous well-regarded and highly cited papers [20,21]. Furthermore, we highlight select target end user feedback to support the refinement of the final items to be included in the survey instruments. Ethical approval was granted by the Human Research Ethics Committee of the University of Melbourne (study ID 2056217.1).

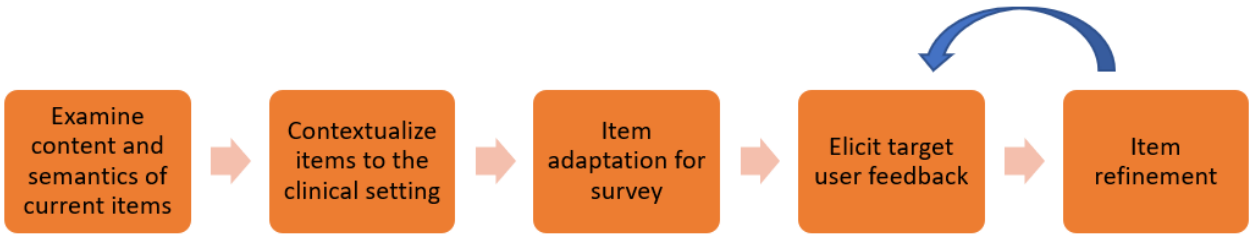
Rationale

The method used to adapt and refine descriptor items in the WHO classification of DHIs framework leverages QIR. We used an MSK physiotherapy case study example to outline the process. This is based on previous work by the authors published in this journal [22], the authors' clinical profiles, and their informatics research backgrounds. QIR has previously been used by the National Institutes of Health in their Patient-Reported Outcome Measurement Information System to develop several patient-reported outcome measure item banks to create standardized patient-reported outcome measure surveys for research across various health areas [19]. The QIR method is appropriate as it allows for the identification and scrutiny of items, which are further optimized by expert review and through the elicitation of target end user feedback [22].

Procedures

The QIR method was applied to the original set of WHO DHI Clients 1.0 and Health care Providers 2.0 items. An iterative approach over five phases was conducted, led by 2 of the primary study authors (Figure 1). This was reviewed by the rest of the research team to verify the accuracy and alignment against the original WHO framework, until consensus was reached on the final item for inclusion in our survey. The phases were as follows: (1) examine the connotations of the original top-level DHI function and consider the semantics of each item's wording, (2) contextualize items to the clinical setting, (3) adapt item wording into a survey instrument format, (4) elicit target end user feedback, and (5) final refinement of survey item.

Figure 1. A systematic approach to qualitative item review and adaptation of items in the World Health Organization Classification of Digital Health Interventions v1.0.



A tracking system was developed to record any adaptations made to items using a Microsoft Excel spreadsheet defined by a data coding version (iteration) number. All coauthors have professional backgrounds in either the allied health clinical sciences and clinical informatics (eg, physiotherapy, speech pathology, health science, and health informatics). Furthermore, all coauthors have extensive prior research experience in the development of survey instruments for HCPs and clients.

Phases 1 and 2

During the first two phases, the content and semantics of each existing WHO DHI descriptor were assessed, contextualized, and adapted where deemed appropriate by 3 authors separately and then together (including the primary author), to reflect the specific nature of patient care in the clinical context (eg, MSK physiotherapy). Original descriptor domains were rephrased in lay terms in an attempt to describe the various functions of DHIs to support care (ie, HCPs delivering care vs clients or patients managing conditions). There were 10 HCP functions, with 32 items to examine, and 7 client functions, with 16 items to examine. The rest of the research team discussed the appropriateness and interpretation of the revised DHI functions for fit until an intercoder agreement for each descriptor was established.

Phase 3

During phase 3, 2 authors (including the primary author) transformed items into survey instrument question stems that framed items to assess *willingness* to use the DHIs for various purposes, as categorized in the WHO framework. The result is the direct product of adapting the WHO framework items into a question form, not from some preexisting questionnaire.

Phases 4 and 5

In phase 4, a convenience sample of target end users (9 physiotherapists [HCPs]) working in MSK clinical practice and 11 physiotherapy service users (clients) were invited to review the adapted survey items and provide feedback on their clarity, comprehension, and validity for final inclusion in the survey instruments. Participants' demographic characteristics are provided in Multimedia Appendix 1. These participants were invited to provide written free-text comments about their ability to interpret the survey items and language used. Three authors (including the primary author) collated, analyzed, and discussed the feedback. This process allowed for a consensus about any items requiring further revision. Items were then further revised in a final iteration during phase 5, which were revisited with the target users to confirm the fit for survey instrument readiness.

Results

QIR of WHO Framework Items to Inform Survey Instruments in a Physiotherapy Setting

Phases 1 and 2

Tables 1 and 2 show the original and adapted versions of the WHO framework items for surveying clients and HCPs, respectively. The full refinement process and all item revisions are presented in Multimedia Appendices 2 and 3. All the 16 items of the WHO *Clients* section of the framework were adapted from their original wording. On average, each item was revised 3.3 times before inclusion in the survey.

Of the 32 items in the WHO *Health care Providers* section of the framework, only 1 item (*2.10 Laboratory and Diagnostic Imaging* category—*Capture diagnostic results from digital devices*) was not adapted from its original. On average, the remaining items were revised 3.2 times.

Table 1. Final adaptation of the World Health Organization classification items-clients.

Original		Adapted	
Digital health intervention category	Item	Digital health intervention category	Item after QIR[a]
1.1 Targeted client communications	Transmit health event alerts to specific population groups	1.1 Targeted communications	Send me urgent health alerts that people living with my condition need to know (eg, medication product recalls, etc)
N/A[b]	Transmit targeted health information to clients on health status or demographics	N/A	Send me health information of interest to people living with condition (eg, about new treatments, research, etc)
N/A	Transmit targeted alerts and reminders to clients	N/A	Send personalized alerts and reminders relevant specifically to me (eg, about services I've booked or have coming up)
N/A	Transmit diagnostic results, or availability of results to clients	N/A	Sends me health test results, or tells me results are available
1.2 Untargeted client communication	Transmit untargeted health information to an undefined population	1.2 General communications	Send me general news or information about good health or healthy living
N/A	Transmit untargeted health event alerts to undefined group	N/A	Send me general health alerts (eg, about environmental factors impacting my ability to exercise-weather, air quality, etc)
1.3 Client to client communication	Peer group for clients	1.3 Person to person communications	Communicate online with other peer groups of people living with my condition
1.4 Personal health tracking	Access by client to own medical records	N/A	Access my own medical records
N/A	Self-monitoring of health or diagnostic data by clients	N/A	Self-monitor my condition or diagnosis-related information
N/A	Active data capture/documentation by clients	N/A	Actively collect information about my condition or injury status and record it
1.5 Citizen-based reporting	Reporting of health system feedback by clients	N/A	Allow me to collect and provide feedback about the health system
N/A	Reporting of public health events by clients	N/A	Allow me to report urgent public health events/issues that people living with my condition need to know
1.6 On-demand information services to clients	Client look-up of health information	1.6 Information when I need it	To look up health information
1.7 Client financial transactions	Transmit or manage out of pocket payments by clients	1.7 Financial transactions	Send or manage any "out of pocket" payments I may need to pay
N/A	Transmit or manage vouchers to clients for health services	N/A	Send or manage vouchers/coupons I might have for health services (eg, travel vouchers)
N/A	Transmit or manage incentives to clients for health services	N/A	Send or manage rewards or incentives I have to use health services

[a]QIR: qualitative item review.

[b]N/A: not applicable.

Table 2. Revision of the World Health Organization classification items-health care providers.

Original		Adapted	
Digital health intervention category	Item	Digital health intervention category	Item after QIR[a]
2.1 Client Identification & Registration	Verify client unique identity	2.1 Patient identification & registration	Verify a patient's personal details (eg, new patient registration)
N/A[b]	Enrol client for a health service or care planning activity	N/A	Make a clinical appointment
2.2 Client Health Records	Longitudinal tracking of client's health status & services	2.2 Patient Health Records	Track a patient's condition and/or clinical service use over time
N/A	Manage the client's unstructured clinical records	N/A	Enter a patient's free-text clinical progress notes
N/A	Manage the client's structured clinical record	N/A	Record or code a patient's condition using standardized coding, checkboxes, and dropdown menus
N/A	Routine health indicator data collection & management	N/A	Record and/or flag indicators of change in a patient's condition
2.3 Healthcare Provider Decision Support	Provide prompts and alerts according to a specific protocol	2.3 Clinician Decision-Support	Prompt my thinking using software that supports clinical decision-making
N/A	Provide a checklist according to a specific protocol	N/A	Provide me a digital checklist of clinical procedures to follow
N/A	Screen clients by risk or, other health status	N/A	Screen my patients
2.4 Telemedicine	Consultations between remote client and healthcare provider	N/A	Conduct remote consultations
N/A	Remote monitoring of client health, or diagnostic data by healthcare provider	N/A	Remotely monitor or track a patient's condition
N/A	Transmission of health-related data to healthcare provider	N/A	Send me data about my patient's condition
N/A	Consultations for case-management between healthcare providers	N/A	Conduct case consultations with other clinicians
2.5 Healthcare Provider Communication	Communication from healthcare providers to supervisor	2.5 Clinician communications	Communicate with a manager or supervisor
N/A	Communication and performance feedback to healthcare providers	N/A	Provide me with feedback about my clinical performance
N/A	Transmit routine news and workflow notifications to healthcare provider	N/A	Send me routine updates and workflow notifications
N/A	Transmit non-routine health event alerts to healthcare providers	N/A	Send non-routine or unexpected health event alerts about a patient
N/A	Peer-group for healthcare providers	N/A	Utilise online peer communication groups for clinicians
2.6 Referral Coordination	Coordinate emergency response and transport	N/A	Coordinate emergency responses and/or transport for a patient
N/A	Manage referrals between points of service with health sector	N/A	Manage health services referrals or reports (eg, to other clinicians)
N/A	Manage referrals between health and other sectors	N/A	Manage referrals or reports to external bodies eg, government services
2.7 Health Worker Activity Planning & Scheduling	Identify clients in need of services	2.7 Clinician workflow coordination	Identify patients in need of a health service
N/A	Schedule healthcare provider's activities	N/A	Schedule my clinical activities
2.8 Healthcare Provider Training	Provide training content to healthcare providers	2.8 Clinician training	Provide me with training or educational content
N/A	Assess capacity of healthcare providers	N/A	Assess my clinical capacity, or performance

Original		Adapted	
Digital health intervention category	Item	Digital health intervention category	Item after QIR[a]
2.9 Prescription & Medication Management	Transmit or track prescription orders	N/A	Track prescription orders
N/A	Track clients' medication consumption	N/A	Track patient's medication consumption
2.10 Laboratory & Diagnostic Imaging Management	Report adverse drug events	2.10 Pathology & Imaging Management	Report adverse medication events
N/A	Transmit diagnostic result to healthcare providers	N/A	Send me diagnostic imaging results (eg, scans)
N/A	Transmit and track diagnostic orders	N/A	Track diagnostic imaging orders
N/A	Capture diagnostic results from digital devices	N/A	Capture diagnostic results from digital devices
N/A	Track biological specimens	N/A	Track pathology eg, blood tests

[a]QIR: qualitative item review.

[b]N/A: not applicable.

Phase 3

As previously outlined, 2 authors transformed individual items based on their suitability to interpret them in a survey to assess the willingness to use DHIs. Survey questions were framed from the question stem, "How willing are you to use digital technology to..." Response options were provided using a 5-point Likert scale ranging from *not at all willing* to *very much willing*.

Phases 4 and 5

Target end user feedback revealed that 14 items—that is, 25% (8/32) of *health care provider* items and 38% (6/16) of *client* items—were flagged by participants as most difficult to interpret. Participants noted challenges in interpreting the meaning of the item in question and issues with the chosen language. In the client items, these were mostly related to domain 1.1: *Targeted communications* and domain 1.2: *General communications* (Table 1). In the HCP items, there were no particular domains (other than domain 2.2: *Client health records* and domain 2.3: *Health care provider decision support*) where difficulties were more commonly reported (Table 2). On the basis of the summative feedback, clients preferred more person-centric language to be used (eg, changing *1.4: Access by client to own medical records* to *Access MY own medical records*), whereas HCPs preferred language to be more clinically focused. These end users preferred *health care providers* to be referred to as *clinicians* and *clients* to be described as *patients*. Furthermore, based on feedback, examples were added to select items (Tables 1 and 2) to provide greater context and to assist with interpretation.

Samples of both the refined client and HCP instruments are shown in Figures 2 and 3, respectively. The dual survey instruments were named (1) Digital Health Intervention Willingness-Client (DHIW-C; Figure 2) and (2) Digital Health Intervention Willingness-Health care Provider (DHIW-HCP; Figure 3) in the spirit of the original WHO classifications. Both instruments are available in their entirety in Multimedia Appendices 4 and 5. Furthermore, both instruments (Figures 2 and 3) contain person-centered language, such as "How willing are 'you'..." and "...send 'me' urgent..." In both instances, this language refers to the respondent and is deliberately framed in this way to avoid diverging too far from the original WHO framework items. This phraseology was not identified as problematic during piloting, with participants readily identifying "you" and "me" as the same person.

Figure 2. Excerpt from the Digital Health Intervention Willingness-Client survey.

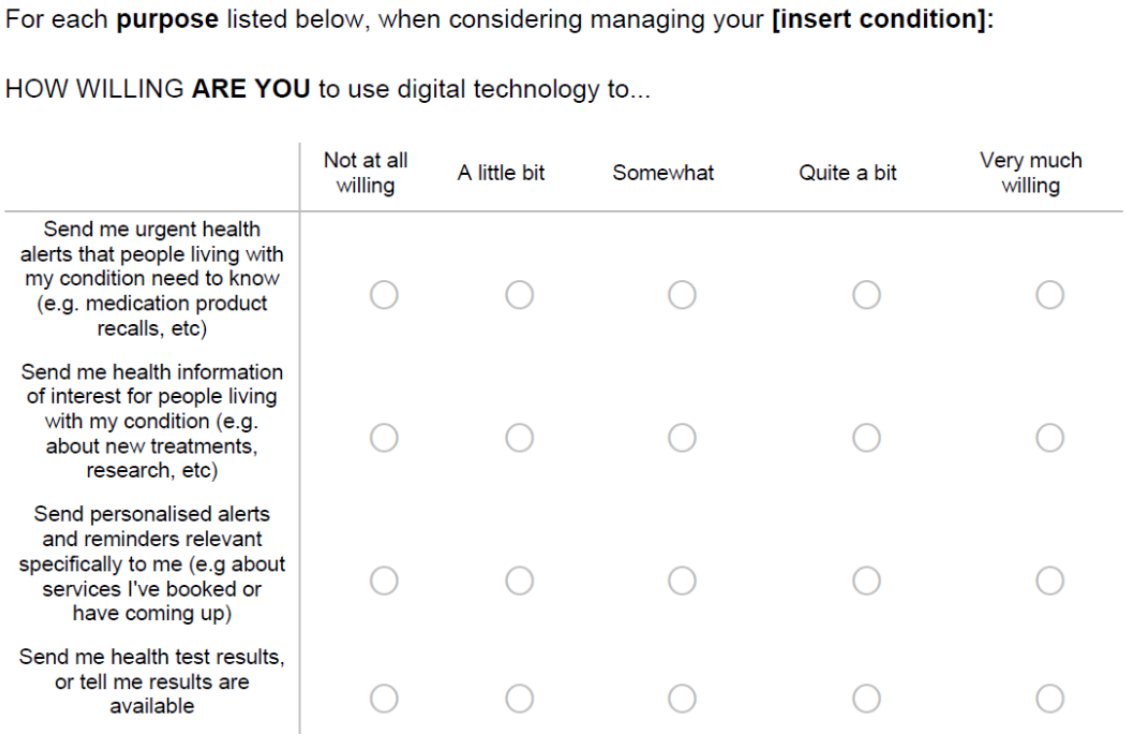
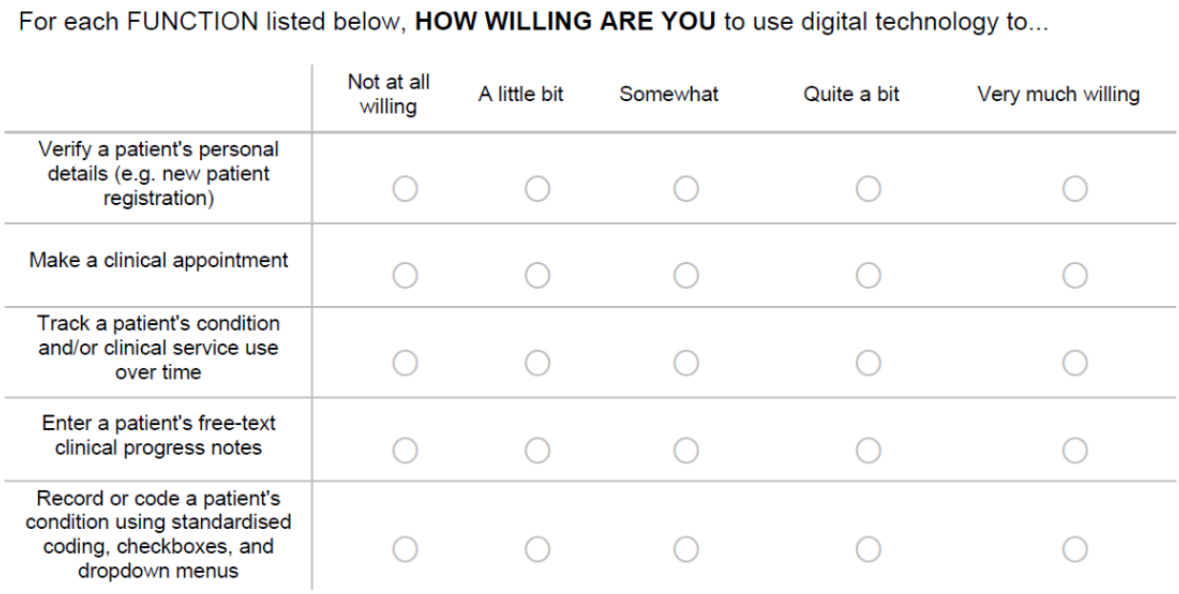


Figure 3. Excerpt from the Digital Health Intervention Willingness-Health care Provider survey.



Discussion

Principal Findings

This study describes an iterative, phased process undertaken to build on work that classifies DHIs, by adapting items from the WHO classification of DHIs v1.0 for use in dual survey instruments [5]. To our knowledge, this has not been done previously. Findings from this study highlight the complexities of knowledge representation within digital health taxonomies and in the digital health environment. Riaño et al [23] suggested that knowledge representation in health is a complex area, particularly as the domain evolves in the face of advances in technology, such as artificial intelligence. The WHO's DHI framework is a significant contribution to digital health and informatics research and practice reporting, via its conceptualization of the various functions of DHIs for reporting purposes [5]. We have outlined our approach to build on this and adapt DHI classification items into survey instruments that enable collection of data about willingness to use various functions of digital health. Our aim was to make the various functions of DHIs more clinically applicable in real-world settings for individuals with less advanced knowledge of the digital health ecosystem. This includes both HCPs and consumers as well as clinical researchers wanting to build

insights into the use of DHIs from a more evidenced-based perspective.

Scalable Assessment of Digital Health

Research in the realm of digital health uptake and acceptance suggests that stakeholders in digital health (ie, HCPs, clients, and researchers) recognize the importance of digital health but require more consistent and reliable methods of reporting and evaluating engagement with digital health initiatives [6,15,16]. Various digital health survey instruments exist to examine users' perceptions of digital health. However, many tend to focus more explicitly on quality and the disparate functions of DHIs. For example, the DISCERN instrument assesses the quality of web-based health information, and the health on the net code is a checklist used to signal quality-controlled health website content (such as web-based patient education materials) [24,25]. Comparably, the Mobile App Rating Scale is specific to surveying and rating mobile apps [26]. In a similar vein, our newly developed surveys (DHIW-C and DHIW-HCP) fill a unique gap that allows examination of user engagement with the various *functions* of digital health, rather than focusing on a single specific category of technology or technological tools.

Clinical Implications

This study has several clinical implications. First, the corresponding survey instruments may help bridge the current evidence gaps in the reporting of DHIs. Murray et al [4], in their seminal piece on DHI evaluation, stated that DHIs have tremendous potential in terms of scalability for improving health. However, the authors contended that DHIs are complicated to examine and that a stronger, more reliable evidence base is needed to report such interventions [4]. A recent systematic review assessing the efficacy of DHIs to improve health outcomes in the workplace found a modest net effect of DHIs. However, the authors noted the continued highly heterogeneous nature of digital health research as well as difficulties in examining digital health use because of the lack of standardized measures for reporting on key active components of DHIs [27]. The authors concluded that focusing on engagement with DHIs and using standardized measures for describing DHIs will benefit future research and possibly provide greater opportunities for meta-analyses of DHI outcomes [27]. This is further supported by Zanaboni et al [28], who advise that to build a reliable evidence base about digital health use and health outcomes, greater focus needs to be placed on clinical research in the form of high-quality randomized controlled trials. Blandford et al [29] propose that the evaluation of DHIs in research requires flexibility and adaptation of traditional health research methods. For instance, randomized controlled trials investigating DHIs should look to move away from the current approach of assessing the technology *features* (which may be outdated by the time the research is complete) and instead focus on the digital health *principles* latent in the intervention [29]. Our novel measures support this notion, by providing a way to measure perception toward the *functions* of DHIs that lie at the heart of any digital intervention. Furthermore, as seen in the structure of the DHIW-C and DHIW-HCP instruments (Figures 2 and 3), the measures are readily transferrable to a variety of clinical health contexts or specialty areas and conditions, which also allows for comparing and contrasting DHIs.

Limitations

This study had some limitations. First, the process undertaken using a single discipline case study pertains to a narrow subset of clinical informatics research, limiting its generalizability (ie, a study of DHIs in an MSK physiotherapy context). Other health care professionals and clients with different health problems may have had alternative views on the wording of the items in our surveys. Second, we piloted survey items in phase 4, once items had been adapted, refined, and placed in a question format. It is possible that if target users reviewed items during the earlier phases, opinions may have differed. Involving the target users in phase 4 may be a limitation, rather than involvement in phase 1. However, we felt it prudent to first examine the items and place them in a format that would be meaningful to end users. As their primary input was to comprehend the questions in the surveys, we felt this was the most methodologically sound time to involve them. Furthermore, this study did not aim to assess the psychometric properties of the developed survey instruments. Future research is warranted to assess the instruments' psychometric properties. Finally, our instruments are presently available only in English, potentially limiting wider global use. However, pending future adaptation and psychometric testing, future research to translate the DHIW-C and DHIW-HCP may be a useful undertaking.

Conclusions

This study has detailed the systematic development of dual (patient and clinician) survey instruments (DHIW-C and DHIW-HCP) to support data collection about perceptions toward DHIs administered in a physiotherapy setting. This was achieved by adapting the WHO framework classification for DHIs for application in real-world research. It also highlights the applicability of the WHO's standardized DHI framework in digital health research. With further research, using our surveys as the foundation, future surveys may be developed across a range of health care and technology contexts to examine user perceptions toward willingness to engage with DHIs. As DHIs continue to evolve and their omnipresence grows in research and practice, standardized surveys may be helpful by allowing users to capture information about a broad spectrum of DHI functions that are increasingly prevalent in clinical practice.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Pilot participants' characteristics.
[PDF File (Adobe PDF File), 103 KB - resprot_v10i7e25177_app1.pdf]

Multimedia Appendix 2
Data recoding the World Health Organization classifications for survey-client.
[PDF File (Adobe PDF File), 115 KB - resprot_v10i7e25177_app2.pdf]

Multimedia Appendix 3
Data recoding the World Health Organization classifications for survey-health care professional.
[PDF File (Adobe PDF File), 155 KB - resprot_v10i7e25177_app3.pdf]

Multimedia Appendix 4
Digital Health Intervention Willingness-Client.
[PDF File (Adobe PDF File), 173 KB - resprot_v10i7e25177_app4.pdf]

Multimedia Appendix 5
Digital Health Intervention Willingness-Health care Provider.
[PDF File (Adobe PDF File), 190 KB - resprot_v10i7e25177_app5.pdf]

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Abbreviations

DHI: digital health intervention
DHIW-C: Digital Health Intervention Willingness-Client
DHIW-HCP: Digital Health Intervention Willingness-Health care Provider
HCP: health care provider
MSK: musculoskeletal
QIR: qualitative item review
WHO: World Health Organization

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Proposal

Safety and Acceptability of a Natural Language Artificial Intelligence Assistant to Deliver Clinical Follow-up to Cataract Surgery Patients: Proposal

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Abstract

Background: Due to an aging population, the demand for many services is exceeding the capacity of the clinical workforce. As a result, staff are facing a crisis of burnout from being pressured to deliver high-volume workloads, driving increasing costs for providers. Artificial intelligence (AI), in the form of conversational agents, presents a possible opportunity to enable efficiency in the delivery of care.

Objective: This study aims to evaluate the effectiveness, usability, and acceptability of Dora agent: Ufonia's autonomous voice conversational agent, an AI-enabled autonomous telemedicine call for the detection of postoperative cataract surgery patients who require further assessment. The objectives of this study are to establish Dora's efficacy in comparison with an expert clinician, determine baseline sensitivity and specificity for the detection of true complications, evaluate patient acceptability, collect evidence for cost-effectiveness, and capture data to support further development and evaluation.

Methods: Using an implementation science construct, the interdisciplinary study will be a mixed methods phase 1 pilot establishing interobserver reliability of the system, usability, and acceptability. This will be done using the following scales and frameworks: the system usability scale; assessment of Health Information Technology Interventions in Evidence-Based Medicine Evaluation Framework; the telehealth usability questionnaire; and the Non-Adoption, Abandonment, and Challenges to the Scale-up, Spread and Suitability framework.

Results: The evaluation is expected to show that conversational technology can be used to conduct an accurate assessment and that it is acceptable to different populations with different backgrounds. In addition, the results will demonstrate how successfully the system can be delivered in organizations with different clinical pathways and how it can be integrated with their existing platforms.

Conclusions: The project's key contributions will be evidence of the effectiveness of AI voice conversational agents and their associated usability and acceptability.

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KEYWORDS

artificial intelligence; natural language processing; telemedicine; cataract; aftercare; speech recognition software; medical informatics; health services; health communication; delivery of health care; patient acceptance of health care; mental health; cell phone; internet; conversational agent; chatbot; expert systems; dialogue system; relational agent

Introduction

Background and Rationale

Clinical Problem

In the United Kingdom, aging population is causing an increased demand for health care services that is exceeding clinical capacity [1]. With staff pressured to deliver high-volume workloads, the resulting burnout crisis is increasing costs for health care providers. Demand has been further exacerbated by the COVID-19 pandemic, as the widespread cancelation of elective care has created a large backlog of clinical work [2]. However, a large proportion of this clinical work is taken up by highly repetitive and low-skill tasks, preventing staff from working *at the top of their license*. Therefore, there is a need to improve the efficiency in the delivery of care and to collect data that can be analyzed to support routine improvement and optimization through the automation of routine clinical interactions.

One area of care where improved efficiency is urgently needed is cataract surgery. Cataract surgery is the most common operation in the National Health Service (NHS), with approximately 450,000 procedures conducted per year [3]. COVID-19 has caused record delays in receiving planned surgeries [4], and the average wait time for cataract surgery was approximately 2.5 months [5]. The aging population will also have a significant impact on the number of patients with cataracts, which is expected to double between now and 2050 [6]. The cataract pathway is also an ideal case for optimization because there is little variability and high levels of patient safety; the most significant complication (endophthalmitis) occurs in fewer than 1 in 1000 cases [7]. To address this clinical need, this study aims to collect data on the effectiveness, usability, and acceptability of an artificial intelligence (AI) natural language assistant for delivering cataract surgery follow-up checks.

Current System and Its Limitations

Similar to most operations, cataract surgery requires a postoperative check to monitor for complications and assess success. This has historically been performed with a face-to-face visit; prior to the COVID-19 pandemic, this was the standard procedure for 72% of NHS Trusts [8]. However, this postoperative system has a high operational demand and is not always necessary; a recent ophthalmology Getting It Right First Time (GIRFT) report stated that a hospital review of cataract surgery patients is not required, as long as follow-up arrangements are in place [8]. In the current context of the COVID-19 pandemic, face-to-face visits also pose a high risk for virus transmission due to the proximity of patients and clinicians.

Although this project focuses on cataract surgery follow-up, the underlying platform will be applicable to a wide range of routine clinical tasks. The need for an effective automated tool is especially great, as a *new normal* of widespread remote clinical care has been established in the wake of COVID-19.

User Needs

Using AI-enabled automation is a novel approach for patient care, and patient perspectives are mixed [9,10]. Research on cataract surgery patients during the development of this solution found that although many patients stated that they would prefer a clinician to provide follow-up, this opinion was contingent on the quality of the system and service [11]. Most patients rated the solution highly on simplicity and ease of use and expressed appreciation for the additional convenience of a telephone follow-up [11].

The patients also suggested that the AI system might be less rushed than a clinician and would have the benefit of freeing up nurses' time for other clinical work. This is supported by internal company research on the clinical outcomes of 300 cataract surgery follow-up calls, which identified that only 10% (30/300) of patients telephoned by expert clinicians were determined to need a face-to-face review. Therefore, an automated telephone follow-up could significantly reduce the number of clinical appointments necessary to deliver postoperative care.

Solution Overview

General Description

The solution developed to improve clinical efficiency for cataract surgery follow-up is a natural language, voice telemedicine conversation delivered to patients via telephone calls. For the patient, this is intended to be no different than a regular telemedicine consultation with a doctor or nurse; it does not require the download of an app, the provision of a device, or any training. This is important because the populations that consume the majority of health care services (older adults and socioeconomically disadvantaged populations) tend to be relatively more digitally disenfranchised.

The solution, a natural language AI assistant called Dora agent: Ufonia's autonomous voice conversational agent, has been developed by Ufonia Limited. By the start of the clinical testing described in this proposal, validation with Ufonia's development partners at Buckinghamshire Healthcare NHS Trust will be complete, and Dora will be at Technical Readiness Level (TRL)5. By the end of this study, the solution will be at TRL6, which has been demonstrated in a relevant clinical setting.

Key Features

Dora uses a variety of AI technologies to deliver the patient follow-up call, including speech transcription, natural language understanding, a machine learning conversation model to enable contextual conversations, and speech generation. Together, these technologies cover the input, processing and analysis, and output needed to maintain a natural conversation. Dora is

currently delivered via a telephone connection as a real-time, stand-alone system.

Benefits of Proposed Solution

For Digitally Enabled Care

The solution is aligned with the aims of NHS to improve efficiency and increase digitally enabled care [8,12]. Cataract surgery follow-up provides a good launching point for further development of digital solutions, as it typifies many routine telemedicine care processes that could be similarly automated.

For Health Care Staff

The solution is expected to have significant benefits for health care staff by reducing their clinical burden. Preliminary company research suggests that Dora will reduce the number of patients who require follow-up with a clinician by approximately 80%. This reduces the type of high-volume, repetitive task that contributes to burnout and allows clinicians to be redeployed to higher-value activities, where their skills, insight, and empathy can be best used. In addition, telephone follow-up reduces the risk of COVID-19 transmission and frees up hospital space to help meet the increasing patient demand.

For Patients

The system also has several benefits for patients. Dora will provide a reliable and consistent safety net after surgery. Patients will be able to ask questions about their recovery (such as when to drive, swim, and stop taking eye drops) just as they would with a human clinician. The system is convenient because it does not require them to travel to the hospital and can take place at the time or duration that suits them. Reducing the number of in-person follow-ups will allow clinicians to perform other clinical activities, making patients more likely to receive timely care for their initial cataract surgery or for other conditions. This will be evaluated as part of the study by examining the number of surgeries conducted.

Aims and Objectives

The purpose of this study is to evaluate the evidence for clinical safety, study design feasibility, usability, acceptability, satisfaction, appropriateness, and cost-effectiveness of the autonomous cataract follow-up call system (Dora) for detecting patients that require further assessment. The primary aims are to establish preliminary evidence that Dora is safe, to evaluate its sensitivity and specificity, and to determine what can be learned to improve its design for future studies.

To achieve these aims, there are 5 key objectives:

1. To establish baseline rates of efficacy for Dora's detection of patients requiring further assessment
2. To evaluate patient acceptability of an autonomous call in comparison with existing standards of care
3. To evaluate the cost-effectiveness of autonomous calls in comparison with existing standards of care
4. To capture conversational data to train future versions of the system
5. To capture data and assess study feasibility to inform the development of future trials

Research Questions

On the basis of these aims and objectives, 4 main research questions were defined to guide the project:

1. What are the factors impacting the effectiveness of Dora's conversational call follow-up to determine patients who require further assessment?
2. Can Dora sufficiently support conversation and patient engagement to collect the data needed to allow Dora's computational capabilities to perform an accurate assessment?
3. What are the perceived benefits and barriers of using conversational agents for patient follow-up?
4. Is Dora more cost-effective than existing standards of care?

Methods

Study Design

Using an implementation science construct, the study will be a phase 1 pilot study to develop evidence regarding the feasibility, acceptability, and potential effectiveness of Dora and to identify factors influencing effectiveness. The study will last for 18 months: 6 months of evaluation and intervention refinement, 9 months of implementation and follow-up, and 3 months of postevaluation analysis and write-up.

Research Participants

The study population will incorporate two clinical sites: the Imperial College Healthcare NHS Trust and the Oxford University Hospitals NHS Trust. The population at the Imperial College site is drawn from the North West London Collaboration of Clinical Commissioning Groups (CCGs) and is densely populated, highly diverse, highly mobile, and relatively young [13]. Black, Asian, and other minority ethnic groups make up 37% of the resident population in the West London CCG [14], and 20% of London residents do not speak English as their first language [15].

In contrast to London, the Oxfordshire population is less diverse but more rural [16]. Although it is growing in ethnic diversity, residents are primarily of a White British background; in 2011, approximately 84% of Oxfordshire residents identified as White British (compared with the national average of approximately 80%) [17]. It was also found that 16% of the Oxfordshire population did not speak English as their main language (compared with the national average of 8%) [18]. In terms of age, the population of Oxfordshire is similar to the national profile, particularly for older ages [19].

Recruitment

Recruitment will take place at sites in the Imperial College Healthcare and Oxford University Hospitals NHS Trusts that conduct cataract surgeries. Study information will be shared with cataract surgery patients at their initial visit (and via post or telephone call for patients who are delayed by COVID-19 or cannot visit in person). Informed consent will be obtained at the time of preassessment (in-person or virtually depending on the current COVID-19 guidelines). In the discharge lounge following surgery, patients who have consented to participate will be given further information to remind them about the call

from Dora. This work will be performed by a dedicated research nurse at each site.

Study Duration and Follow-up

This study will conduct telemedicine calls with patients in addition to their standard of care. Patients will receive their call from Dora between 25 and 27 days post surgery. The evaluation of Dora in two different NHS Trusts will help demonstrate that Dora can be integrated into different pathways. It will also provide a range of sensitivities to input into the health economic models to determine whether Dora provides cost-effectiveness in different settings.

Procedure

Overview

Although patients typically have cataracts in both eyes, procedures are typically performed on one eye at a time in the United Kingdom. As this is a pragmatic study, patients undergoing either first or second eye surgery will be recruited. This should be in a balanced proportion due to the random nature of operating timing, but differences between groups will be examined in the posthoc analysis. Given that the usual interval between cataract surgeries is more than 6 months, it is unlikely that the same patient will be recruited twice in the study. If there are any cases where the same patient is recruited, they will be excluded from participating for the second time.

Dora Call

The call that patients will receive from Dora will include several conversational elements:

- Greeting and introduction
- Identification of patient
- Cataract follow-up questions
- Patient's queries
- Decision
- Questions about acceptability
- Closure of call

The entire conversation will be supervised by an expert clinician (an ophthalmology research fellow). This clinician will be able to interrupt the call at any point if the system fails, the patient struggles to interact with it, or Dora does not collect sufficient information from the patient.

The cataract follow-up questions will classify 5 key symptoms: redness, pain, reduced vision, flashing lights, and floaters. Both Dora and the supervising clinician (masked to each other) will independently indicate for each symptom, whether the symptom is:

1. Absent (eg, no pain)
2. Present but not clinically significant (eg, mild gritty sensation)
3. Present and clinically significant (eg, deep and persistent pain)
4. Insufficient information for classification

Issues identified in response to any of these questions will prompt the need for a face-to-face review. The complexity of the model comes from evaluating the exact nature of these symptoms, for example, distinguishing between improving redness in the corner of the eye (due to the local anesthetic injection) and widespread redness that has progressed, which may represent infection. The conversational nature of the model enables it to ask patients further questions to clarify their responses and assess the significance of the reported symptoms.

If clarifying points are necessary for the clinician to make a decision, Dora will enable the clinician who will ask the necessary questions, and then record updated assessments for symptoms and overall management before handing back to Dora for frequently asked questions and patient evaluation.

If the call is uninterrupted, Dora will make a decision about the patient's management plan. Once the cataract follow-up questions have been completed, the clinician will also set their own decision, masked to the decision made by the system (Table 1). For this project, the supervising clinician's decision, which is made based on the information from the call with Dora's decision masked, is considered the gold standard for evaluation. For each patient, the final decision regarding the management plan can be as follows:

1. Discharge (and/or add to waiting list for second eye cataract surgery and/or continue follow-up as previously planned in the ophthalmology clinic)
2. Eye casualty review within 1 week
3. Same day eye casualty review

Table 1. Outcome communicated to the patient at the end of the call depending on the blinded decision of Digital Online Recording Automation agent: Ufonia's autonomous voice conversational agent and the clinician.

Clinician decision	Outcome
Does not need review	No review
Needs review	Review
Insufficient information	Interrupt call

If the patient needs review, they will either be seen at the scheduled appointment the following day or by the clinical fellow the following day, if an appointment is not scheduled (at Oxford or if pathways change due to COVID-19). If they are found to have a complication, they will enter the existing NHS care pathways as they would with typical care. If the complication is deemed urgent by the clinician, the patient will be seen the same day.

Theoretical Framework

The evaluation of baseline efficacy, sensitivity and specificity, feasibility of study design, acceptability, and usability shall be

conducted using the following scales and theoretical models and frameworks:

1. The system usability scale [20]
2. Assessment of Health Information Technology Interventions in Evidence-Based Medicine Evaluation Framework [21]
3. The telehealth usability questionnaire [22]
4. Long-term adoption and suitability for further trials will be evaluated using the Non-Adoption, Abandonment and Challenges to the Scale-up, Spread, and Suitability framework [23]

Data Collection

The key element of the conversation that this study will assess is Dora's ability to make *correct* decisions about whether review is necessary. For this project, the correct decision is that which the supervising clinician makes based on the information they hear. Therefore, the key data to be collected are Dora's and the clinician's decisions.

The call will also collect data about the individual patient's condition. The follow-up questions are aligned with existing cataract patient-reported outcome measures so that they meet the needs of responsible clinicians and can be used to populate the National Ophthalmology Database [3].

The usability and acceptability of the system will be assessed through automated questions at the end of each call. In addition, a sample of patients with good and poor experience will be approached to have a more in-depth interview (as detailed in the *Ethics* section).

Data Analysis

The primary analysis will be the calculation of a kappa statistic of interobserver (Dora and clinician) reliability of the decision made. In addition, the outcome of the assessment will be compared with the *real* complication rate determined by any face-to-face assessments. This will be established by the identification of any patient presentation within 60 days after the last call. Given the specialist nature of ophthalmology services, it can be assured that patients will present through the eye casualty services offered by each site. This analysis will provide baseline sensitivity and specificity data for use in preparing subsequent evaluations of efficacy.

The usability and acceptability questions delivered at the end of the call will be analyzed quantitatively based on the scales' scoring criteria; for instance, a score above 80 on the system usability scale is generally considered to indicate an above average user experience [24]. The interview recordings will be transcribed and assessed using thematic analysis.

Bias

To prevent participation bias, there will be no exclusion of participants who are willing to participate in the study, unless they have a relationship with any of the researchers associated with the study (to avoid conflicts of interest). To address unconscious bias or other forms of interview recruitment issues, interview participants will be selected randomly by a computer script of consented participants. A quantitative analysis of the use experience will include all participants to avoid recruitment bias. Participants' levels of education will be recorded to note possible ways in which education impacts intervention use.

It is vital to maintain the integrity of the study and avoid any commercial influence on the results. Therefore, a research contract will be established between Ufonia and the academic research partners, enabling unrestricted right of publication of nonconfidential information and independence of study implementation.

Risks

The COVID-19 pandemic has raised potential issues for recruitment for the study. To address this risk, an ethics submission will enable remote informed consent if restrictions prohibit face-to-face contact.

Risks regarding the system include it failing to detect patients who require urgent clinical review, which will be mitigated by having an expert clinician supervise the call in real time and intervene if needed. The risk of lack of trust in the system has been mitigated by an extensive cocreation process for Dora, which focuses on user-centered design.

The interviews are scheduled to take place for 40 to 60 min, to mitigate time risk to participants. The nature of interview questions avoids areas of cultural or psychological sensitivity and is purely focused on the impact of the intervention. To control any potential perceived issues in this area, participant confidentiality is protected using data protection procedures that are compliant with the General Data Protection Regulation (GDPR) [25].

Ethical Considerations

Study Governance

Research Ethics Committee permission has been granted. This manuscript provides an overview of the study approach, but it will be subject to further revision before ethical submission. An independent study steering board composed of the academic principal investigator (PI), co-academic PI, a study researcher, a member of the public, and an external researcher will meet every 2 months to review progress against the study plan and to assure study ethics are being followed. Reports shall be distributed for review by the project team for action. To ensure the validity, reliability, and transferability of the study findings, the Consolidated Standards of Reporting Trials, Standard Protocol Items: Recommendations for Interventional Trials, and Consolidated Criteria for Reporting Qualitative Studies guidelines, including additional AI-related extensions, will be followed and recorded in the study protocol.

Informed Consent

British educational research association guidelines have been followed for voluntary informed consent, use of methods, and university policies in the event that there are issues in delivery [26]. Before completing informed consent, participants will be given information that fully describes the process of the study, including why their participation is necessary, how their data will be used, and who the results will be reported to. As many patients are understandably concerned about how their data will be used, data management will be explained in detail as part of

the consent process. It will also make clear their right to withdraw from the study at any time and have their data destroyed. Patients will also be asked to separately consent for their data to be used to further train the conversational systems. Declining to share this conversation data will not affect patients' participation in the study or their clinical care.

Data Management

The Ufonia system stores patient identifiable data as part of the clinical record. Explicit consent is obtained from patients to use these data in ongoing development. The solution is in compliance with the GDPR [25] and is being built to meet specific NHS regulations. For the proposed study, the organizations involved (including each Trusts' Data Protection Officer and Caldicott Guardian) will undertake a Data Protection Impact Assessment and, where needed, create information sharing agreements to ensure compliance with relevant data protection regulations. Ufonia will act as the data processor, and individual hospitals will remain the data controllers.

During the study implementation, each participant will be given a unique identifier. The primary key between the unique ID and participant will be securely held and given to the participant as a reference ID. Data will be analyzed using the unique IDs; the primary key is only maintained to enable participants to withdraw their data from the study. If such a request is made before data aggregation or publication, all of their corresponding data and files will be destroyed.

Audio recordings, transcriptions, and metadata about the calls will be securely stored in UK datacenters with strict role-based access control. The transcription service will only have reference to the unique IDs, and the audio recording will be reviewed by the PI to remove any identifying information before being shared. Patient identifiable data will not be sold to any other party and will not be shared with any organization unless they are a partner in the study and have an appropriate information sharing agreement in place. In accordance with GDPR requirements, records of consent will be kept for 3 years after the publication of the final study results [25].

Results

The evaluation is expected to show that conversational technology can conduct an accurate assessment and that it is acceptable to different populations with different backgrounds. In addition, the results will demonstrate how successfully the system can be delivered in organizations with different clinical pathways and can integrate with their existing platforms.

Discussion

Overview

This project will establish a strong foundational evidence for the use and wider deployment of a novel application of AI technologies. The platform has the potential to transform the delivery of care across multiple clinical pathways by reducing costs, increasing capacity, and improving the convenience and experience for patients and professionals.

The key outputs from this project will provide the following:

1. Safety and preliminary efficacy data for regulatory approval.
2. Proposed structure and implementation model for further clinical trials.
3. Health economic data to support wider roll-out and ongoing evaluation.
4. Results submitted for peer-reviewed publication.

Limitations

A limitation of Dora is that, at present, patients with cognitive difficulties or hearing impairment or non-English speakers will not be able to use the system, facing the same limitations they currently do with human telemedicine services.

A limitation of the study is that a direct comparison of the number of issues identified during routine follow-up cannot be made between the Oxford and Imperial sites. This is because the Oxford University Hospitals NHS Trust does not proactively review patients, instead relying on them to present themselves to their eye casualty service. This introduces a potential risk for missed complications if Dora does not decide that a review is needed. However, this risk is minimized by expert clinician oversight and is a part of the current standard of care at the Oxford University Hospitals NHS Trust.

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Authors' Contributions

NP conceived the study topic and designed and drafted the proposal. GM, EL, MM, EN, and KX contributed to drafting and revising the proposal. Final revision was conducted by EM.

Conflicts of Interest

EL, NP, and GM are all employees of Ufonia Limited, a voice AI company. NP is employed part-time by Oxford University Hospitals (OUH) NHS Trust and is responsible for the development of innovation. His work for Ufonia has been approved by his line manager (Chief Digital and Partnerships Officer) and declared in the Trust's register of interests. None of the resources

he is responsible for within the Trust are used to support the project. GM is employed by Oxford University Hospitals and his work at Ufonia is declared in the Trust's register of interests.

Multimedia Appendix 1
Peer-review feedback from NHS.
[PDF File (Adobe PDF File), 715 KB - resprot_v10i7e27227_app1.pdf]

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Abbreviations

AI: artificial intelligence
CCG: Clinical Commissioning Group
GDPR: General Data Protection Regulation
NHS: National Health Service
OUH: Oxford University Hospitals
PI: principal investigator
TRL: Technical Readiness Level

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Protocol

Integrated Smoking Cessation for Smokers With Serious Mental Illness: Protocol for a Convergent Mixed Methods Implementation Evaluation Study

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Abstract

Background: Tobacco smoking is associated with significant morbidity and premature mortality in individuals with serious mental illness. A 2-year pragmatic clinical trial (PCORI PCS-1504-30472) that enrolled 1100 individuals with serious mental illness in the greater Boston area was conducted to test 2 interventions for tobacco cessation for individuals with serious mental illness: (1) academic detailing, which delivers education to primary care providers and highlights first-line pharmacotherapy for smoking cessation, and (2) provision of community health worker support to smoker participants. Implementing and scaling this intervention in other settings will require the systematic identification of barriers and facilitators, as well as the identification of relevant subgroups, effective and unique components, and setting-specific factors.

Objective: This protocol outlines the proposed mixed methods evaluation of the pragmatic clinical trial to (1) identify barriers and facilitators to effective implementation of the interventions, (2) examine group differences among primary care physicians, and (3) identify barriers that stakeholders such as clinical, payor, and policy leaders would anticipate to impact the implementation of effective components of the intervention.

Methods: Qualitative interviews will be conducted with all study community health workers and selected smoker participants, primary care providers, and other stakeholders. Measures of performance and engagement will guide purposive sampling. The Consolidated Framework for Implementation Research will guide qualitative data collection and analysis in accordance with the following framework approach: (1) familiarization, (2) identifying a thematic framework, (3) indexing, (4) charting, and (5) mapping and interpretation. Joint display analyses will be constructed to analyze and draw conclusions across the quantitative and qualitative data.

Results: The 3-year cluster-randomized trial has concluded, and the analysis of primary outcomes is underway. Results from the pragmatic trial and this mixed methods implementation evaluation will be used to help disseminate, scale, and expand a systems intervention.

Conclusions: The results of this mixed methods implementation evaluation will inform strategies for dissemination and solutions to potential barriers to the implementation of interventions from a smoking cessation trial for individuals with serious mental illness.

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KEYWORDS

mixed methods implementation evaluation; pharmacotherapeutic smoking cessation aids; serious mental illness; smoking cessation; tobacco

Introduction

Tobacco smoking is associated with significant morbidity and premature mortality in individuals with serious mental illness. People with serious mental illness in the United States have physical diseases at a young age and die approximately 28 years earlier than those without mental illness, primarily from diseases that are directly attributable to tobacco smoking [1,2]. Premature mortality among individuals with serious mental illness is the largest lifespan disparity in the United States [3,4]. Recent estimates indicate that 64%-79% of individuals with schizophrenia spectrum disorders smoke tobacco regularly [5,6], as do 44%-71% of those with bipolar disorder [5-7] and 43% of those with major depressive disorder [8]. Most people with serious mental illness state that they would like to quit smoking but have not been offered smoking cessation treatment [9-11]. People with serious mental illness appear to be less likely to quit smoking [12] and more likely to experience relapse without pharmacotherapeutic smoking cessation aids [13], yet few are prescribed proven effective tobacco dependence pharmacotherapies together with behavioral treatment [14,15].

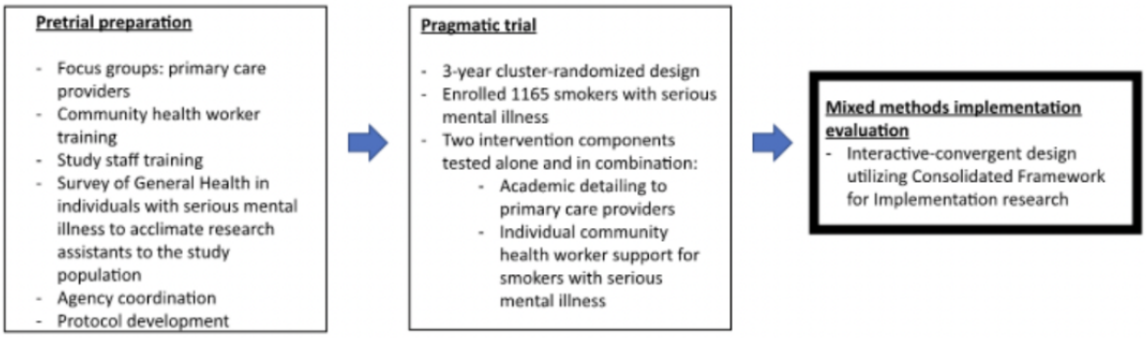
In a pragmatic clinical trial (PCORI PCS-1504-30472) conducted from November 2016 to February 2020, our research group tested the effectiveness of a 2-year intervention that involves (1) academic detailing, which involves the delivery of targeted smoking cessation education to primary care physicians and (2) community health worker support for tobacco abstinence among those with serious mental illness. Over 1100 smokers with serious mental illness—hereinafter referred to as "smoker participants"—enrolled in the trial in 2016. Primary quantitative analysis of study outcomes is underway.

Academic detailing is a provider-level educational intervention in the form of targeted, practical, action-oriented information, which is designed to educate providers on current best practices in a particular area. During this intervention, education is provided to primary care providers by doctoral-level (MD and PhD) study staff who are focused on the safety and tolerability of first-line pharmacotherapy for smoking cessation treatment in those with serious mental illness. The impact of academic detailing on the provision of smoking cessation pharmacotherapy to providers, and the resulting cessation outcomes, has not been studied.

Community health workers assist patients with accessing services and provide health education and outreach in their communities. Utilization of community health worker support has been demonstrated to be useful in reducing the length and number of hospitalizations, improving posthospitalization follow-up, and improving mental health in the general medical setting [16,17]. To date, interventions for community health workers have not been studied among those with serious mental illness or those specifically targeting smoking cessation. In this pragmatic clinical trial, we tested the provision of community health worker support to patients with a defined role and focused on promoting smoking cessation.

Figure 1 shows a procedural diagram of trial development, the trial, and the posttrial mixed methods implementation evaluation, the latter being the subject of this protocol.

Figure 1. Overview of the pretrial preparation and the pragmatic trial leading to the mixed methods implementation evaluation in this study.



Dissemination, scaling, and expansion of a systems intervention in a pragmatic clinical trial to other settings is greatly aided by the systematic identification of barriers and facilitators to implementation, and identification of relevant subgroups, effective and unique components, and setting-specific factors [18,19]. This mixed methods evaluation [20] will use categorical measures of engagement and performance (none or low, moderate, or high) to stratify subgroups of community health workers, smoker participants, and primary care providers to allow the analysis to be tailored and differentiated by group. Additionally, obtaining a deeper understanding of the 2 main intervention components, academic detailing and the community health worker services, will inform future health interventions for both those with serious mental illness and the general population. The complementary nature of quantitative and qualitative data will be leveraged to maximize our capacity to assess a broader range of contextual factors, generating data that are richer and more robust and actionable than either method alone [21]. This evaluation is additionally informed by implementation science, a field of methods and approaches that

addresses challenges to the implementation of health interventions in usual practice settings [22].

We aim to conduct a mixed methods evaluation of the aforementioned pragmatic clinical trial to (1) identify barriers and facilitators to effective implementation of the interventions described by community health workers, smoker participants, and primary care providers in qualitative interviews; (2) examine how primary care providers, grouped at the clinic level, differ by quantitative performance and engagement level and how their experiences with the intervention components, barriers, and facilitators compare across these groups; and (3) identify barriers that stakeholders such as clinical, payor, and policy leaders would anticipate to impact the implementation of effective components of the smoking cessation intervention tested.

Methods

Design: Mixed Methods Intervention Evaluation Utilizing an Interactive Convergent Design

We propose a mixed methods evaluation [20] utilizing an interactive convergent design [23,24], which implies that qualitative and quantitative data are analyzed in tandem. As we code and analyze data, the emerging qualitative and quantitative findings will "talk" with each other so that the findings of each will inform additional analyses (Figure 2). This "iterative approach" denotes how the ongoing findings from each "strand"—that is, the qualitative or quantitative component of the inquiry in a mixed methods study [25]—will inform data collection of the other strand. We anticipate that findings from the qualitative data will yield hypotheses that will be examined quantitatively to further a comprehensive understanding of barriers and facilitators. Likewise, quantitatively derived findings will be enhanced by providing qualitative examples to potentially enhance the understanding of context and to validate the findings.

The Consolidated Framework for Implementation Research provides a basis for qualitative data collection and analysis [26]. This "meta-theoretical" framework, generated specifically for health care research, suggests that barriers are present at several levels, including organizational-level barriers (eg, lack of time and funds), provider-level barriers (eg, perceptions of academic detailing and the use of first-line pharmacotherapy in this population), and patient-level barriers (eg, stigma and knowledge of availability and accessibility resources and treatments). The Consolidated Framework for Implementation Research draws upon 19 different implementation models to create a typology of constructs to guide different phases of implementation studies and has been adapted for this study (Figure 3). Constructs of the Consolidated Framework for Implementation Research have been extensively utilized across settings and populations and provide a practical guide for the systematic assessment of barriers and facilitators when implementing interventions [26,27]. Specific variables that have previously been shown to impact the successful integration of evidence-based treatments and those that have been barriers to and facilitated future scale-up and dissemination strategies will be employed in this study [28,29].

Figure 2. Mixed methods intervention evaluation utilizing interactive convergent design.

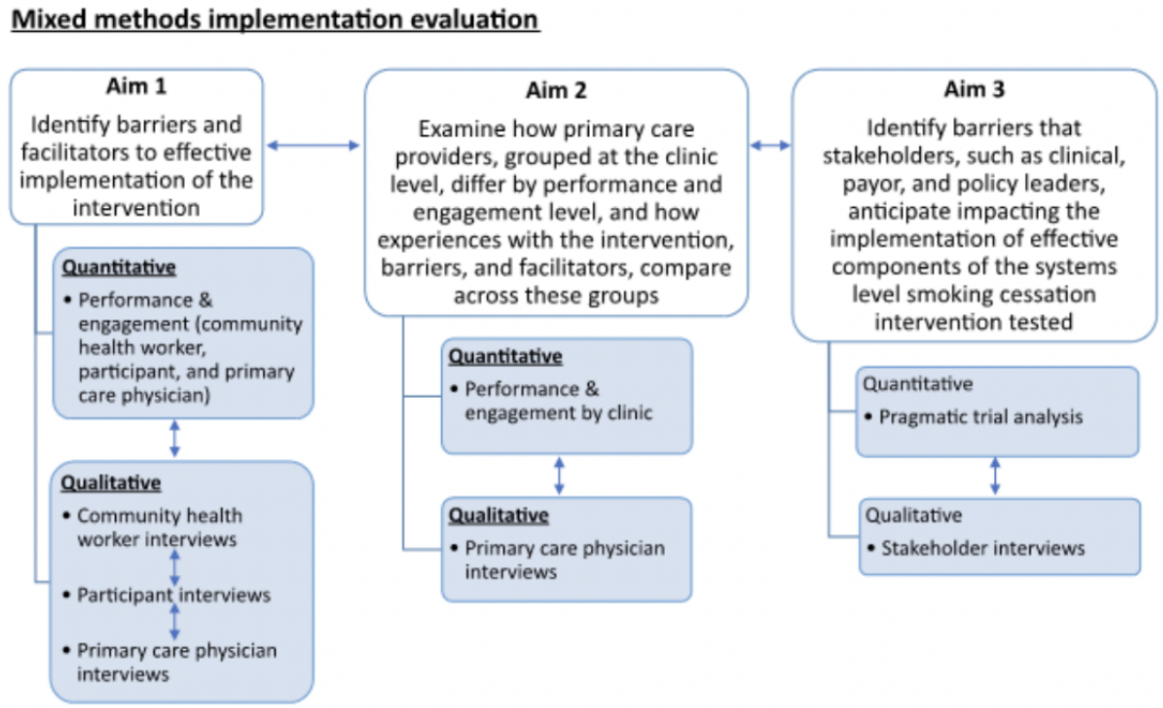
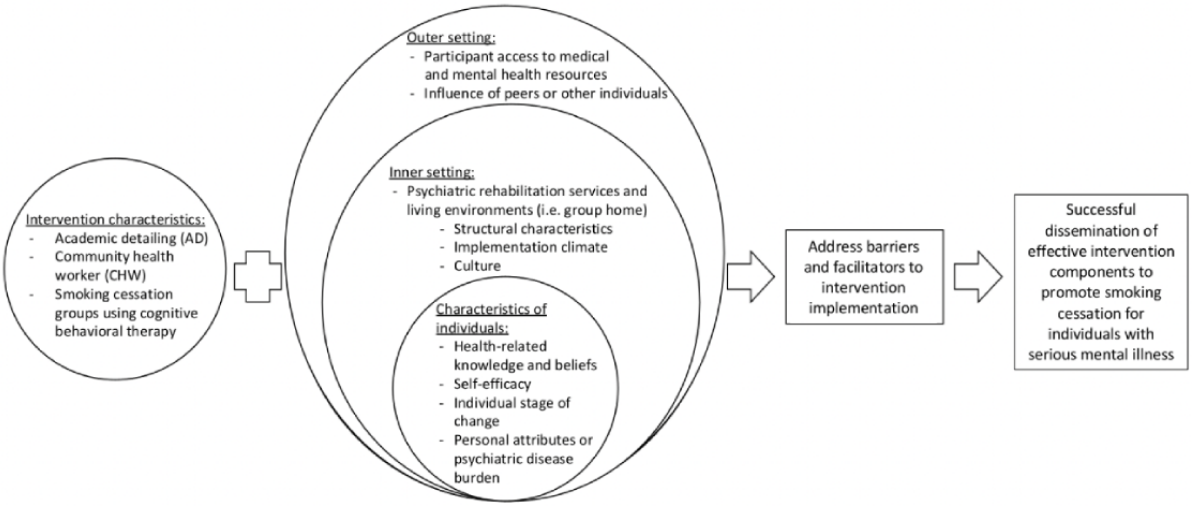


Figure 3. Logic diagram of the mixed methods intervention evaluation illustrating the structure of the Consolidated Framework for Implementation Research.



Quantitative Data

The quantitative data for this evaluation will be derived from the pragmatic clinical trial and process data from both interventions (ie, community health worker and academic detailing). Enrolled smoker participants were asked to complete three surveys: a baseline survey conducted at enrollment, followed by 2 surveys administered annually. Survey questions assessed self-reported current tobacco use, behaviors related to smoking cessation medications (eg, receipt of prescriptions from primary care physicians, prescription fills, and use of medications), smoking-related health issues, and rating of overall health. Demographic data were collected in the baseline survey. Additionally, smoker participants were asked to provide expired-air carbon monoxide measurements at each survey, which is used as biological confirmation of tobacco abstinence. Relevant process data include goal attainment during sessions with community health workers, the number of sessions with community health workers per smoker participant, attendance of the cessation group in cognitive behavioral therapy sessions, visits among primary care providers to address smoking cessation, and the attendance of primary care providers in academic detailing presentations.

Using these existing quantitative data, we anticipate creating matrices using 3-level measures (none or low, moderate, and high) of intervention engagement and performance to inform our purposive sampling for qualitative testing and future hypothesis testing. We will conduct quantitative analyses appropriate to establish thresholds for each measure of engagement and performance for community health workers, smoker participants, and primary care providers. We also anticipate conducting additional quantitative data analysis in testing hypotheses generated from the results of the qualitative data analysis.

Qualitative Data

Eligibility, Setting, and Sampling

All community health workers paired with smoker participants in the trial (n=12) will be recruited to participate in qualitative interviews. Those eligible for qualitative interviews include smoker participants who provided consent to work with a community health worker and provided smoking behavior data at the year 2 survey (n=201). Primary care providers from clinics randomized to receive academic detailing, who treat smoker participants who provided information regarding prescriptions for smoking cessation medications at baseline and year 2 surveys, will be eligible to participate in the qualitative interviews (n=459). We intend to recruit stakeholder interviewees who are considered key opinion leaders in policy, payor, and clinical administration. Interviews will be conducted in person or in the community setting, depending on interviewee preferences.

Purposive sampling involves the intentional selection of study participants based on preselected criteria that relate to the research questions of interest; that is, barriers and facilitators. As described above, we will establish matrices based on 3-level categorical measures of engagement and performance, which will be used to frame our qualitative purposive sampling and ensure representation from a range of qualitative interview participants [29].

Interview Process

Basic concepts and the purpose of the study will be reviewed with all interviewees by a doctoral-level qualitative interviewer. Study staff will review the consent form with all interviewees and provide an opportunity to the participants to ask questions before signing the form. Additionally, smoker participants from the pragmatic clinical trial will be required to successfully complete a competency assessment in the form of a short quiz on facts about participation in the research qualitative interview. All individuals who complete the qualitative interview will receive US $15 as compensation for their participation.

Community health worker interviews will be conducted by authors DA, MCM, and KS, who are trained in qualitative interviewing techniques. Smoker participant interviews will be conducted by authors MCM and KS to minimize bias, as author DA interacted with many smoker participants during smoking cessation groups. Immediately following each qualitative interview, interviewers will document and organize field observations into 3 categories—"context, content, and

concepts"—as described by Fetters and Rubenstein in 2019 [30]. This approach supports the integration of quantitative data (ie, inclusion of the number of smoker participant–completed community health worker or group visits in the "context" category), highlighting salient interview content and interviewer-identified important concepts, thus providing a foundation for future data integration. These field observations will be reviewed weekly throughout the data collection process to ensure that team members understand what information is emerging iteratively. This approach will allow for real-time adjustments in interview questions and provide the interviewer with an up-to-date sense of salient topics emerging from the interviews, which cannot be easily gleaned from a transcript.

Data Cleaning, Coding, and Analysis

All audio-recorded interviews will be transcribed verbatim. All transcripts will be checked for accuracy and completeness and edited where necessary. Final transcripts will be uploaded to NVivo software (version 12, QSR International) for organizing the text and supporting the analysis.

We will use a theory-driven approach in which we will explore the relationship between the findings and the Consolidated Framework for Implementation Research. Our study will be carried out in 5 stages outlined in the framework approach to qualitative analysis [31]: (1) familiarization, (2) identifying a thematic framework, (3) indexing, (4) charting, and (5) mapping and interpretation. Consolidated Framework for Implementation Research categories will form the basis for deductive analysis based on identified categories at the beginning of the study design, while new codes will be developed inductively by identifying those that emerge gradually from the data [32]. Based on the research questions, we will inductively identify themes and look for commonalities and variations in individual perspectives of the barriers and facilitators to study implementation. We will integrate quantitative and qualitative data for the purposes of convergence, contextualization, and expansion to gain a detailed understanding of processes and characteristics that can influence future scale-up and dissemination initiatives [30].

All analyses will follow procedures to ensure robust qualitative data analysis, including the establishment and training of the coding team and ongoing recalibration meetings to ensure reliability and to reduce coding drift. Interrater agreement will be assessed using a second rater coding a subset of interviews during initial data analysis until a high level of reliability ($\kappa \geq 0.80$) is established. Weekly consensus meetings will be held to resolve disagreements. The analytic process will be documented, and all coding decisions will be recorded for further review. Field observations will be reviewed to develop a macroscopic view of the data, assist the process of coding, and explore emerging hypotheses [31].

We will conduct joint displays analysis, in which quantitative and qualitative concepts will be merged and displayed together in an organized structure known as a "joint display" [33-35]. Combining quantitative and qualitative data in this way allows for broader interpretations across both types of data, so called "meta-inferences," [29] to be drawn for the outcomes of interest, ideally achieving an integrated whole greater than a sum of the individual qualitative and quantitative aspects [24].

Modification: the COVID-19 Pandemic

The COVID-19 pandemic and resultant social distancing measures took effect during preparation for qualitative interviews. Consequently, the protocol has been adapted to allow for interviews to be conducted via telephone or videoconferencing. All in-person team meetings have been transitioned to videoconferencing platforms.

Results

The 3-year cluster-randomized trial has concluded, and the analysis of primary outcomes is underway. Results from the pragmatic trial as well as this mixed methods implementation evaluation will be utilized to facilitate dissemination, scaling, and expansion of a systems intervention. The results of this evaluation will be published in a peer-reviewed journal and presented at scientific conferences.

Discussion

This study aims to evaluate barriers and facilitators in implementing a smoking cessation intervention for individuals with serious mental illness. This study will also broadly evaluate the real-world implementation of academic detailing and community health workers in the role of smoking cessation and provide insights into engagement strategies and the smoking cessation process for individuals with serious mental illness. Through close examination of outcomes and particular challenges by subgroup, identification of effective and unique intervention components, and setting-specific factors in this study, our analysis will inform future health interventions for those with serious mental illness as well as the general population.

Acknowledgments

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Conflicts of Interest

AEE receives NIDA Grant subcontracts from Brain Solutions, and Charles River Analytics, is on the Data Safety and Monitoring Board for Karuna Pharmaceuticals, and performs Advisory Board work for Alkermes.

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Protocol

The Digital Engagement of Older People: Systematic Scoping Review Protocol

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Abstract

Background: There is an ongoing negative narrative about aging that portrays older people as a socioeconomic burden on society. However, increased longevity and good health will allow older adults to contribute meaningfully to society and maximize their well-being. As such, a paradigm shift toward healthy and successful aging can be potentially facilitated by the growing digital technology use for mainstream (day-to-day activities) and assisted living (health and social care). Despite the rising digital engagement trend, digital inequality between the age groups persists.

Objective: The aims of this scoping review are to identify the extent and breadth of existing literature of older people's perspectives on digital engagement and summarize the barriers and facilitators for technological nonuse, initial adoption, and sustained digital technology engagement.

Methods: This review will be based on the Arksey and O'Malley framework for scoping reviews. The 6-stage framework includes: identifying research questions, identifying relevant studies, study selection, charting the data, summarizing and reporting the results, and a consultation exercise. Published literature will be searched on primary electronic databases such as the Association of Computing Machinery, Web of Science, MEDLINE, PsycINFO, CINAHL, and ScienceDirect. Common grey literature sources will complement the database search on the topic. A two-stage (title/abstract and full article) screening will be conducted to obtain eligible studies for final inclusion. A standardized data extraction tool will be used to extract variables such as the profile of the study population, technologies under investigation, stage of digital engagement, and the barriers and facilitators. Identified and eligible studies will be analyzed using a quantitative (ie, frequency analysis) and qualitative (ie, content analysis) approach suitable for comparing and evaluating literature to provide an evaluation of the current state of the older person's digital engagement. Inclusion will be based on the Joanna Briggs Institute–recommended participant, concept, and context framework. Articles on older people (65 years and older), on digital technology engagement, and from a global context will be included in our review.

Results: The results of this review are expected in July 2021.

Conclusions: The findings from this review will identify the extent and nature of empirical evidence on how older people digitally engage and the associated barriers and facilitators.

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KEYWORDS

digital divide; digital engagement; digital inclusion; initial adoption; older people; older users; sustained engagement; technological nonuse; older adults

Introduction

Background

Global demographic trends show that the worldwide age structure is rapidly changing more than ever before. The United Nations defines older people as those aged 65 years or older based on people's chronological age. Currently, there are over 703 million older people, and it is expected to reach 2.1 billion by the year 2050 [1,2]. Population projections have indicated Europe and North America have the fastest growing aging population, and by 2050, the population percentage of older adults is expected to reach 34% in Europe and 28% in North America [3].

There is an ongoing negative narrative about aging that age-related changes, disability, and dependency among older people with poor and deteriorating health conditions imply an increased expenditure on health and its burden on the socioeconomic aspects of society [4]. Further, the COVID-19 pandemic has also underlined how older people are generally perceived and valued in our contemporary society [5-7]. This crisis exacerbated existing and deeply rooted inequalities such as underfinancing in the care sector and the chronic shortage of caregivers (both in the health and social sector) [8]. However, contrary to the negative narrative, increased longevity and good health allow older adults to meaningfully contribute socially and economically, and maximize their well-being late into life [9-11]. To facilitate healthy and successful aging, the fast-growing digital technology, with all its drawbacks, barriers, and challenges, offers a staggering promise and opportunity [12].

Despite substantial mixed and inconclusive findings, several studies and reviews have demonstrated the positive impact of digital technologies on different dimensions of an older person's life, including health, housing, services and transactions, mobility and transportation, access to information, communication and work, recreation, and self-fulfillment [13-15]. Moreover, digital technologies play a substantial role in improving older people's quality of life and independence [16-18]. However, a review reported an ambivalence toward digital technology due to negative effects such as a sense of privacy and personal security breaches. Whereas, personal safety during emergencies was reported as a positive effect of owning a mobile phone [18].

Over the past decades, digital technology use among older populations has grown exponentially both in the mainstream (day-to-day lives) and assisted care (health and social care) [19,20]. Changes in the workplace and the "digital by default" strategy for delivering public services are among contributing factors *forcing* older people to engage digitally [21]. Digital engagement in health promotion and social support through health information is also growing. However, the breadth and the extent of digital technology use among older people remains limited to communications such as sending or receiving emails, instant messaging, video calls (Skype), and making voice calls [14]. A perceived or actual lack of interest, skill gaps, and socioeconomic factors were mentioned as possible reasons for the limited use of digital technologies [14]. Besides, the age-related decline in vision, hearing, cognition, and dexterity also attribute to the limited use of digital technologies [22-24].

Comparatively, there is a discrepancy in digital involvement, access, and connectivity between the younger and older populations [16,24]. For instance, in the United Kingdom between 2014 and 2019, a significant proportion of the older population never connected digitally at all or had not used the internet over the past 3 months. The 2019 Office for National Statistics (ONS) survey showed 13.5% of older people aged 65 to 74 years old and 47% of those 75 years and older never used the internet [16]. A similar population-based study in 7 European countries reported only 12% internet use among older people (60 years and older), of whom 64% used it for health-related issues [25]. In the United States, smartphone ownership among older people 65 years and older is significantly lower in comparison to the national average (81%; ie, 59% of those between the ages of 65 and 74 years are smartphone owners, but it falls to 40% among those 75 years and older) [26].

To create a digitally inclusive and accessible world, the International Organization for Standardization recommends human-centered and accessible designs (ISO 9241-11:2018) [27]. Adaptation guidelines such as text font size, screen setting, contrast, and color adjustments are among the recommended standards. These modalities enable older people with physical disabilities to engage digitally [28]. However, technology designs are mostly driven by technology push rather than user demand pull factors. Additionally, the fast-evolving nature of digital technology makes it challenging for older people to catch up and sustain engagement with the adaptation guidelines.

Digital Engagement Later in Life

To thrive in the increasingly digitalized world, an acquaintance with technology is inadvertently becoming a mandatory way of life [21]. Despite the current assumption that older people are not using digital technologies, many studies have indicated that older people are competent and skilled digital technology users [29,30]. Still, there is a gap in evidence, with some key questions that require illumination:

1. What are the contributing factors to the digital inequality between the age groups?
2. How can we understand older people's digital technology use?
3. What constitutes the diversity of digital technology use?

The term "digital engagement or disengagement" has been widely used in marketing research with an aim toward promoting marketing strategies to end consumers [31-33]. Factors like brand factor, product factor, consumer factors, and content factors have been the main focus of these studies [34]. Though the factors are intertwined, this review will focus on studies that explore drivers of technological nonuse, initial adoption, and sustained digital engagement from older people's perspectives.

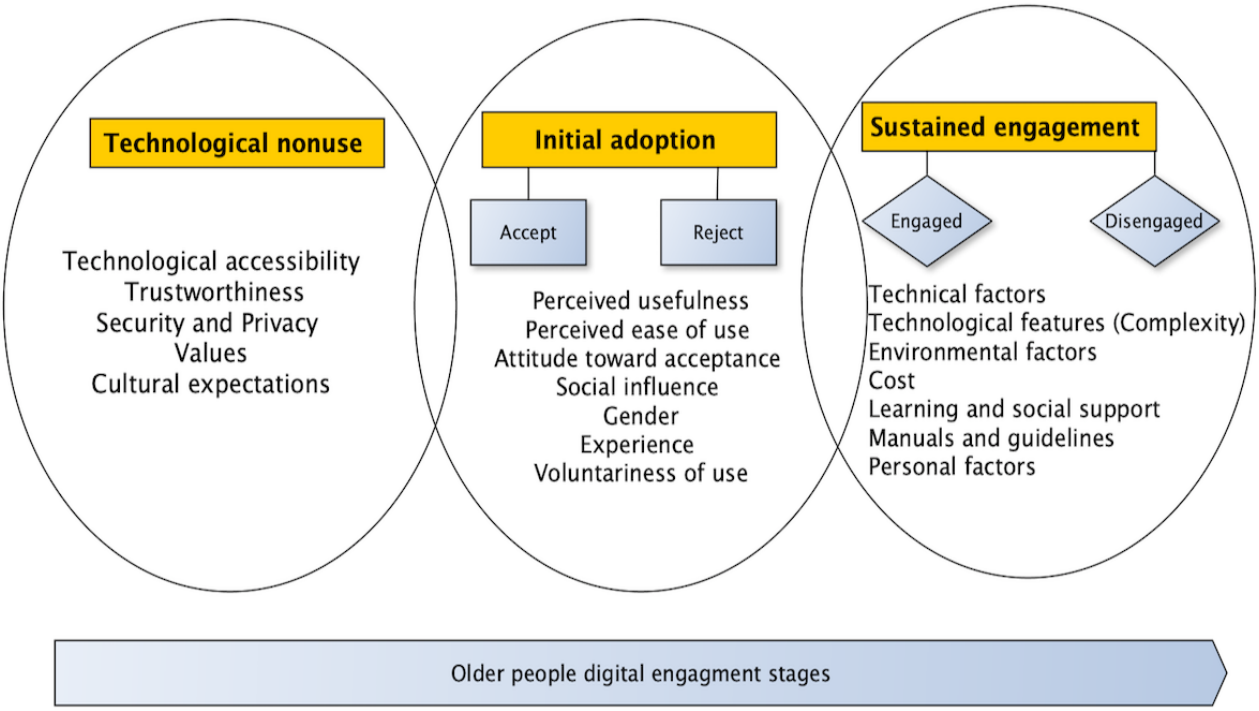
Overall, we propose to understand the current state of knowledge about older people's digital engagement through the stages of digital engagement (nonuse, initial adoption, and sustained engagement). This will facilitate an ongoing drive to reduce digital inequality and, in doing so, provide new understandings to promote the well-being of older people. It will also help

identify potential alternatives for older people who remain nonusers of digital technology.

Digital Engagement Dimensions

To facilitate this review, operationalizing older people's digital engagement and disengagement is considered an important step in deciphering the continuum (Figure 1). This continuum with a three-stage approach involves technological nonuse, initial adoption or acceptance, and sustained digital engagement. This categorization will enrich the evidence mapping and the identification of barriers and facilitators for each dimension (initial adoption, sustained engagement, and technology nonuse). The description for each digital engagement dimension is provided in the following sections.

Figure 1. Older people's digital engagement dimensions and stages later in life.



Stage I: Digital Technology Nonuse

Technological nonuse is not absolute as the term may suggest and goes beyond the absence of technology [35]. It is also a mistake to assume a person has not used a single digital technology, as use or nonuse is a constant negotiation and renegotiation to engage or disengage with technology. This also includes older people who access digital technology through their existing social support system (family and friends). To understand the possible factors affecting older people's engagement and disengagement, efforts to investigate the technological nonuse should be encouraged [35,36]. This will pave the way to understanding the bigger picture of digital exclusion among older people.

Governments across Europe (eg, the United Kingdom, Sweden, and Spain) have shown commitments to provide digital technologies through a framework (eg, universal service obligations for broadband) and accessible internet to citizens [37-39]. However, evidence has indicated that technological nonuse, later in life digital disengagement, and lower use rates are the main features of digital inequality among the older population [21,40]. The nonuse might involve technology, a service, an application, a platform, a communication medium, a set of practices, or some combination thereof. For example, the 2019 ONS survey in the United Kingdom showed 13.5% of older people aged 65 to 74 years and 47% of those 75 years and older never used the internet [16].

The drivers of technological nonuse are not only limited to sociodemographic and economic characteristics, but also the absence of tailored instructions and guidance, a lack of knowledge and confidence, and health-related barriers and costs [41]. According to Knowles and Hanson [17], accessibility and trustworthiness of the digital technologies, values, and religious and cultural expectations are salient determinants for older people's technological nonuse. Moreover, complexity, security, and privacy issues also contribute to the technological nonuse among this age group.

Stage II: Initial Adoption

Studies dealing with user (older person) decisions to accept or reject digital technology and the drivers that influence the user decision will inform this stage. This will answer questions such as, "What influences users' decision to use a particular digital technology?"

A considerable range of models and theories such as the Theory of Reasoned Action (TRA) [42], the Technological Acceptance Model (TAM) [43], the Unified Theory of Acceptance and Use of Technology (UTAUT) [44], the Diffusion of Innovations Theory [45], and Igbaria's model [46] have been developed to facilitate an understanding of the drivers toward the

favorableness and the unfavorableness of technology initial adoption [47]. The TAM [43,48] and UTAUT [44], a derivative of TRA, are among the prevailing theories. The TAM developed antecedent factors such as perceived usefulness, perceived ease of use, and attitude toward technological acceptance. Whereas, UTAUT, which is the extension of TAM, further developed the model by adding social influence and other moderating factors such as gender, age, experience, and voluntariness of use [44]. This review will scope studies that address these factors with age (65 years and older) as an important moderating factor [44]. Furthermore, this review will include qualitative accounts from older people's perspectives, unlike the TAM and UTAUT models, which are widely used to quantify acceptance [49].

Stage III: Sustained Digital Engagement

People who actively used technology start to disengage due to age or the generational effects of aging [30]. According to Damodaran et al [50], sustained digital engagement is affected by the complexity and fast-changing nature of digital technology. Additionally, user's low awareness about the availability of design adaptation modalities such as font size, color, and screen determined its sustained use. The manuals and guidelines on this design adaptation, which enhance older people's capacity to adapt to technologies, are frequently inaccessible and outdated. Learning and support from existing social support such as family play a crucial role at this stage [50]. A similar study reported that sustained mobile technology use among older people was influenced by personal factors (physical, cognitive, and mental changes), environmental factors (financial costs, social influence, and learning to use technology), and technical factors (complexity and usability, absence of feedback, and design challenge) [29].

Sustained use is vital in understanding the digital divide among different socioeconomic groups [50]. However, studies suggested that it is one of the underresearched areas of digital engagement. A growing body of evidence has focused on understanding the early adoption, with the assumption that once people subscribe to the technology, they will keep using it. However, there is evidence that there will be a digital engagement negotiation and renegotiation between use and nonuse and vice versa [21]. Therefore, this review will include studies focused on factors that prevent or promote sustained use among older people.

Scoping Review Rationale

There is a growing body of literature that often gives glowing reviews on the positive effect of digital technology engagement among older people. However, there is a gap in comprehensive reviews of evidence understanding the complexities of the barriers and facilitators of older people's digital engagement. This review will summarize the current state of knowledge concerning older people's perspectives on digital engagement and disengagement from technological nonuse, initial adoption, and sustained use. In addition, the varieties of technologies used or being used in social and health care for older people will be identified.

Studies have shown that the use of digital technology will have a great impact on different dimensions of older people's lives, for example, quality of life [18], decision making [29], and mobility and social connectedness [14]. However, there are no reviews of existing studies that summarized the state of knowledge from older people's perspectives, specifically the drivers of engagement and disengagement from technological nonuse to initial adoption and sustained use. This scoping review aims to provide a base for a more comprehensive understanding of digital engagement among older people. The findings will inform older people, designers, developers, and decision makers about practical implications. In addition, this review will set an agenda for future research and further in-depth understanding of older people's digital engagement.

The findings from this review will inform the extent of evidence on older people's digital engagement, inform the extent and the breadth of the knowledge about barriers and facilitators of older people's digital engagement, and delineate the scope of what we already know. Further, these findings will indicate the gaps in the ongoing research of the issue.

The Rationale in Light of the COVID-19 Pandemic

As of November 2020, there have been over 50 million COVID-19 cases and over 1 million deaths worldwide. Governments worldwide have implemented different levels of public health infrastructures such as lockdowns, social distancing, testing, contact tracing, and isolation measures [51]. As a result, digital technology use as a modality for coping with the crisis and socioeconomic continuity has substantially increased. For example, people are now using technology to work from home, to speak to their families and loved ones, and to source entertainment and information [52,53]. In addition, contact tracing apps were implemented in European countries, China, Singapore, and the United Kingdom [54,55]. Despite the unanticipated nature of the crisis and the higher vulnerability associated with age, the existing digital technology inequality among the age groups could imply low use or uptake of such services for the well-being of an older person, exacerbating the existing inequality [56]. In this new configuration of societal roles and innovative ways to tackle the transmission and stop the pandemic, future understanding of older people's digital engagement will shed light on existing efforts to make technologies equitable.

Methods

Overview

The methodology for this scoping review is informed mainly by the Arksey and O'Malley framework for scoping reviews and will examine the extent, range, and breadth of evidence for the drivers of digital engagement among older people [57]. Additional recent methodological development on scoping reviews by Levac et al [58] and Tricco et al [59] (ie, PRISMA-ScR [Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews] Checklist) will be incorporated in the main framework. The framework has 6 steps described in the following sections.

Stage 1: Identifying Research Questions

Identifying relevant and broader research questions is the first step in the process of a scoping review. Our review questions are as follows:

1. What is known from the existing literature about the perspectives of older people on digital technology engagement?
2. What digital technologies have been used in the health and social care of older people?

Stage 2: Identifying Relevant Studies

A comprehensive search of identified electronic databases will be conducted to locate relevant studies. Our search will include primary databases such as the Association for Computing Machinery Digital Library; Library, Information Science, and Technology Abstracts; MEDLINE; PsycINFO; CINAHL; and ScienceDirect. The search will be complemented by interdisciplinary (Web of Science, EBSCO, and Scopus) and secondary databases (Cochrane library and Joanna Briggs Institute [JBI] reviews). In addition, common grey literature sources from key journals (JMIR, the Journal of Gerontology, and the Journal of Gerontechnology) and Google Scholar will be included. Additional manual searches of peer-reviewed and grey source literature on the current COVID-19 crisis and the role of digital technology engagement among older people, published from December 2019 onward, will be included to support the review rationale.

Taking into consideration the research question and the JBI recommended population, concept, and context (PCC) approach, keywords and their synonyms, plurals, spellings, and acronyms will be used to develop a comprehensive search strategy as follows.

1. The population of this study is limited to studies conducted among older people 65 years and older. Terms such as “older person,” OR “older people,” OR “elderly,” OR “geriatric,” OR “old,” OR “frail,” OR “older user” will be used to form the population.
2. The concept will include studies dealing with digital engagement. Terms such as “digital,” OR “digital technology,” OR “digital engagement,” OR “digital technology engagement,” OR “technology” will form the concept.
3. There will be no restriction by context in terms of the geography of the studies.

All identified literature from our broad search strategy will be exported to the EndNote library manager and Evidence for Policy and Practice Information (EPPI) Reviewer 4 for the two-stage screening (title/abstract and full article).

Stage 3: Study Selection

Inclusion and exclusion criteria to select studies will be generated based on the scope of the inquiry. Accordingly, we will use the iterative search strategy as we go back and forth to refine the search strategy and study selection.

Inclusion Criteria

Peer-reviewed articles will be the primary target, but also, grey literature sources with important insights into the scope will also be included to enrich the review. The inclusion criteria will be in line with the PCC of the studies described as follows:

1. Participants/Population: In this scoping review, we will include only literature that focused on digital technology among older people aged 65 years and older. Technological research with different age groups or a cross-age categorization will be excluded.
2. Concept/Condition: The primary concept in this study will be digital engagement. Studies that investigated digital engagement among older people and the determinants for technological nonuse, initial adoption, and sustained digital use will be included. In addition, studies that investigated different aspects of older people’s digital technology engagement, digital inclusion and divide, and other intersection features between old age and digital technology will be included.
3. Context: The context of this study will be global.

Study Identification

The study selection will involve two stages of screening. EPPI Reviewer software version 4 (from Evidence for Policy and Practice Information and Co-ordinating Centre) will be used to facilitate the screening process.

1. Title and abstract screening will be performed according to the inclusion and exclusion criteria.
2. Articles qualified by the title and abstract screening will be further considered for full article appraisal. Full articles will be accessed through the University of Brighton library, interuniversity library resources, and contacting the authors. The search results, screening process, and reasons for exclusion will be presented using the PRISMA-ScR flow diagram.

Stage 4: Charting the Data

Important variables from studies found to be eligible for final inclusion in the scoping review will be extracted using a customized data extraction tool. The extracted variables will inform the scope and the breadth of the existing literature on older people’s digital engagement (Textbox 1). Variables such as study design, source of data, study size, study setting, study population, digital technology used, stage of digital engagement under study, and the barriers and facilitators of digital engagement among older people will be extracted.

Textbox 1. Variables to be extracted by review questions.

- Authors
- Year of publication
- Aim of the research
- Research setting or place
- Methodology (study design, interventions, description, and analysis techniques)
- Outcomes
- Study population and sociodemographic characteristics (sample size, mean age, gender, and economic conditions)
- Digital technology under investigation (everyday and health technologies)
- Stage of digital engagement explored
- Barriers and facilitators identified
- Older people's experience
- Research gaps and recommendations
- Keywords used for the study

Stage 5: Collating, Summarizing, and Reporting the Results

An extension of the PRISMA-ScR flow diagram and guideline for reporting scoping reviews will be used to describe and collate the results of the final review [58,59]. The scoping will involve quantitative analysis (ie, frequency analysis), numerical description and common characterization of the studies by a study setting (geography or distribution), type of the study designs, the mean age of the study participants, and other features. Finally, the qualitative analysis will be conducted using the content analysis technique. Conceptual categories and definitions will be formed to inform the meanings, barriers, facilitators, and experiences of older people related to digital technology engagement. These categories will be used to generate themes. Levac et al [58] recommended qualitative content analysis to facilitate the summary and make sense of the extracted variables. This relational conceptual analysis will help explore relationships between the concepts extracted from the articles in the field. Charting of important variables and a narrative description of the findings will be presented in the review report.

Stage 6: Consultation Exercise

We will conduct a consultation based on the identified preliminary literature findings on the topic of interest with identified stakeholders including advocacy groups, older people, academicians, digital developers, practitioners, and other early-stage researchers. This consultation exercise will be done after the preliminary electronic search on the common databases. The findings from the consultation exercise will inform our revision of the research question and refine the search strategy. The findings from the consultation exercise will be thematically presented.

Dissemination and Ethical Requirements

We will comment on the ethical approval status of the included studies. However, for this review, ethical approval is not required since it uses publicly available sources. The key finding from this scoping review will be made available online and will be disseminated to key stakeholders.

Results

We have conducted a preliminary search of the primary databases. We expect the final database search of this review to be completed in May 2021. We envisage disseminating the findings from this systematic scoping review in a scientific peer-reviewed journal.

Discussion

We conceptualized older people's digital engagement in a three-stage continuum from nonuse and initial adoption to sustained engagement. The findings from this review will identify the extent and nature of empirical evidence on how older people digitally engage and the associated barriers and facilitators at each stage of the continuum.

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Authors' Contributions

ASK developed the research questions and study methods and designed this protocol. KG refined the research questions and helped develop the research and study methods. KG, LLO, and HH reviewed the methodology and contributed meaningfully to the drafting and editing of the manuscript. The final manuscript version was read and approved by all authors.

Conflicts of Interest

None declared.

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Abbreviations

EPPI: Evidence for Policy and Practice Information
JBI: Joanna Briggs Institute
ONS: Office for National Statistics
PCC: population, concept, and context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
TAM: Technological Acceptance Model
TRA: Theory of Reasoned Action
UTAUT: Unified Theory of Acceptance and Use of Technology

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Protocol

Descriptive Review of Online Information Resources for People With Stroke: Protocol for a Scoping Review

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Abstract

Background: People with stroke and their caregivers experience numerous information needs; internet-based resources may offer cost-effective ways to improve access to information about this condition and its management, including the availability of resources and support. The quality of online health information is, therefore, an important consideration for both developers and consumers of these online resources.

Objective: This study aims to map and evaluate the content, readability, understandability, design, and quality characteristics of freely available online information resources (ie, websites) that empower people with stroke and their caregivers with information and self-help strategies poststroke.

Methods: This descriptive review will follow the five systematic and rigorous methodological steps that are recommended for scoping reviews, which include the following: (1) identifying the research question, (2) identifying relevant studies, (3) selecting the studies, (4) charting the data, and (5) collating, summarizing, and reporting the results. Data will then be synthesized and analyzed thematically.

Results: As of February 2021, the scoping review is in the data extraction stage. Data will be synthesized, and the first results are expected to be submitted for publication in an open-access peer-reviewed journal in August 2021. In addition, we will develop an accessible summary of the results for stakeholder meetings. Ethical approval is not required for this review, as it will only include publicly available information.

Conclusions: This study is novel and will evaluate the typology, content, and design-related criteria, including accessibility, aesthetics, navigability, interactivity, privacy, and data protection, of online information resources for stroke. The review will be limited to online resources published in English.

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KEYWORDS

stroke; online resources; content; readability; design

Introduction

Online, internet, or web-based stroke resources could be beneficial for people with stroke and their caregivers, specifically for those with information and support needs living in the community who have limited access to stroke care and rehabilitation. Apart from the benefit of easy access, users or consumers of these online resources may still experience unmet

needs if other quality criteria, such as accuracy and readability, are not in place [1,2].

Stroke is the second most common cause of death [3], accounts for 102 million disability-adjusted life years (DALYs) globally [4], and is ranked as the third most common cause of DALYs worldwide [5]. In Africa specifically, stroke is increasingly "becoming a public health problem...as it causes high rates of disability and mortality" [6]. Motor-sensory dysfunction that impairs functioning, such as activities of daily living, transfers, and mobility, are concerning sequalae of stroke. In addition, depression, social isolation, and not being able to return to work and remain socioeconomically active citizens are also of great concern for people with stroke. The high levels of disability and care needs of stroke survivors impose a significant burden on carers who are often family members, resulting in a disruption of family functioning. Meeting the need for effective and efficient health and rehabilitation services poststroke is imperative to optimize functioning poststroke and to reduce the burden of care [7]. A recent review found that stroke rehabilitation services in Africa are generally poor, with challenges including "fragmented services, lack of trained personnel, and infrastructure limitations," which lead to incomplete social and community reintegration of people with stroke in these resource-constrained settings [6].

Other than rehabilitation interventions, stroke patients and caregivers, globally, experience numerous diverse information needs after the incident, many of which are not met [8]. These needs include knowledge about the clinical aspects of stroke, prevention, treatment, functional recovery, and support services. Commonly reported needs of caregivers are related to transfers, exercises, psychological changes, and nutritional issues. With these needs addressed, people with stroke and their caregivers are empowered with information and strategies, which reduces psychosocial distress and caregiver burden and enhances self-efficacious behavioral changes [8]. Those affected by stroke will benefit from information tailored to their situational needs [8], but it is recognized that the provision of information and support remains poorly addressed globally [9]. Within resource-constrained environments, many barriers exist to equitable health care and rehabilitation service delivery and access [10]. Online or internet-based resources may offer cost-effective ways to improve awareness of, and access to, existing stroke care services, as well as self-management support for users of these digital health interventions [11].

The internet, or the World Wide Web, is increasingly being used for health-related inquiries by the general public [1]. There is also a growing body of literature into the use of technology as an adjunct or replacement for face-to-face stroke rehabilitation, education, and self-management strategies [12,13]. Digital health in stroke may take the form of various technologies, including websites; computer software; health apps, which could be used on mobile devices, such as smartphones or tablets; and even gaming consoles. Overall, online information on health conditions and their management has become accessible and inexpensive, which attracts the general public to use it for self-diagnosis or management [1], sometimes well before seeking assistance from health care professionals. A few benefits for users of using digital health include patient empowerment and engaging patients in their own health care [14]. Being able to source information based on recognized health needs not only empowers patients or users with information but helps them to make decisions about their own well-being and health care choices [13,15]. Using the internet provides users with several resources that assist them in gaining information and insight into their conditions. Users of online resources will be able to engage in searching for information even after a consultation with a health care provider, as they may not have fully comprehended what was relayed during the session. Breast cancer patients who conducted personal research on the internet, in books, and via other media, for example, had improved knowledge of their conditions, and this proactive approach was deemed an independent predictor of active engagement in the choice of future therapy [16]. Unfortunately, low health literacy levels may influence how users, in general, are able to engage with information that is available online. This may lead to misunderstanding online information and, subsequently, inappropriate use of this information during health care decision making [17].

Health literacy has been defined as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and the services needed to make appropriate health decisions" [18]. Poor health literacy has been linked to poorer health outcomes and increased health care costs and is, therefore, an important predictor of health status [19]. The quality of online health information in terms of readability and understandability is, therefore, an important consideration for both developers and consumers of these resources. Several evaluation tools are available to assess quality criteria such as the readability and understandability of health content that is available on the internet. Readability is "characterized according to the level of understanding a person must have to comprehend written materials, as determined by a set formula" [17] and may include algorithm systems, such as the Flesch-Kincaid Grade Level, the Simple Measure of Gobbledygook, or an overall electronic grading system that summarizes the various tools found online [20]. Another tool, the Patient Education Materials Assessment Tool, assesses the overall understandability and actionability of any audio-visual or written information for patients [21]. The Health On the Net code instrument [22] assesses the quality of information provided on websites [23], whereas web analytics services, like the Alexa analysis software, can be used to assess website visibility [24].

Previous studies evaluating online resources for stroke found that the quality, content, and readability of these websites were highly variable [1,2,13,24]. Even though internet connectivity and access to the internet through improved telecommunications, such as cellular phones and faster fiber-optic cables, have been improving, information on stroke will continue to remain inaccessible to users if it is not at an appropriate reading level [13]. Sharma et al [25] reported that "most consumer-oriented stroke information web pages were written at the 12th-grade level or above and that none complied with the...maximum recommended sixth-grade level." In addition to readability, the accountability and reliability of education information on stroke websites have been investigated [2]. Accountability criteria entailed disclosure of authorship, ownership, and currency of

information, while reliability was related to evidence-based practice as compared to the local clinical practice guidelines in the United Kingdom. Again, many stroke websites failed to conform to these quality standards, and few provided complete and accurate information regarding stroke [2]. Criteria such as trustworthiness (ie, timing, publisher, and contact information) and suitability for stroke prevention and self-management were explored more recently [1]. The Suitability Assessment of Materials instrument was used to evaluate content, literacy demands, graphics, layout, typography, learning stimulation and motivation, and cultural appropriateness for Korean Americans, including availability of multiple translations on the site. It is further recommended that the use of "graphical examples, multimedia, and interactive features can reduce the reading burden of stroke patients and caregivers, as well as build more confidence...when applying the information for condition management and rehabilitation in daily living" [1]. Examples include practical demonstration of behavior and daily skills, which the person with stroke could practice, cultivating greater self-efficacy, overall health, and well-being. Many different evaluation criteria and tools have been incorporated to assess online resources, with newer, more robust instruments continually being developed, to align with the evolving functionalities of this medium [26]. It has also been recommended that users and consumers should become partners in the co-design process of stroke-related websites to ensure that their needs are successfully met [2].

This study will, therefore, aim to map and evaluate freely available, current, online health information resources (ie, websites) that can empower people with stroke and their caregivers with information and self-help strategies poststroke. This comprehensive evaluation will review the content, readability, understandability, design, and quality characteristics of these online stroke health information resources.

Methods

Overview

When searching for educational information on stroke, information sources such as websites and social media pages are regularly accessed and will influence the knowledge and behavior of people with stroke and their caregivers. The search for online guidance has become a preferred strategy for many individuals globally, even more so during the COVID-19 pandemic, where fear, social distancing restrictions, and lack of accessible health services frequently influence their health-seeking behavior. Online resources reflect a new and current data source available to people with stroke and their caregivers in their search for information postincident. Following the rigorous approach of a scoping review framework will allow us to search, locate, and evaluate the contents and quality of these novel data sources in a systematic manner. The review will, therefore, be conducted according to a methodological framework for scoping reviews [27] involving five steps: (1) research question identification, (2) study identification, (3) study selection, (4) data charting, and (5) collating, summarizing, and reporting results.

Review Framework

Overview

A scoping review approach will be used to locate, collate, and evaluate all relevant information on freely available online health information resources (ie, websites) that seek to empower people with stroke and their caregivers with information and self-help strategies poststroke. The reviewers will follow the guidelines of a scoping review methodological framework using a five-step process recommended by Levac et al [27], which is outlined below.

Step 1: Identifying the Review Question and Defining the Objectives

The initial stage of this review provides a roadmap for the entire process, as it clearly defines the breadth and depth of the scoping review process. The main constructs of the scoping review include synthesis of evidence relating to the information content, readability, understandability, and design characteristics of freely available online health information resources for stroke globally.

Therefore, the primary objectives of this scoping review will be to conduct the following:

1. Systematically search, summarize, and synthesize existing literature on the various freely available websites for stroke globally.
2. Describe these online resources in terms of typology (ie, type of resource) and geographic location.
3. Describe the information content in terms of its currency and credibility (ie, authoritativeness and trustworthiness).
4. Describe the design characteristics of these online health information resources in terms of readability, understandability, accessibility, aesthetics, navigability, interactivity, privacy, and data protection.
5. Identify exemplars of freely available websites for stroke globally. These exemplars may offer valuable insights and design elements to emulate for developers of new online resources for people with stroke and their caregivers.

Step 2: Searching, Eligibility Screening, and Selection of Relevant Online Stroke Resources

A structured online search will be conducted via Google by the primary researcher (GIJ) to obtain all freely accessible online educational resources and tools designed for people with stroke and their caregivers. Every step of the process will be recorded. In addition, websites of international organizations like the World Stroke Organization [28] will be specifically searched to identify potential online resources or links to other global stroke organizations or associations. The following combination of key search terms will be used: "stroke" AND "information," "advice," "help," OR "support."

The search will be conducted under the *private browsing* setting for the searches, in order to avoid being influenced by previous browsing history. The search will be limited to a time span of 2 years (2019 to 2021), representing the most recent and up-to-date online resources currently available to public users interested in this information (ie, people with stroke or those caring for survivors of stroke). Only the first three pages of

results, containing 50 records each, generated by the search engine will be reviewed. This imitates the behavior of general internet users, where the majority (71.33%) may only view the first page, followed by fewer users (5.59%) looking at the second and third pages of search results [29]. Websites will be screened to identify resources that (1) contain information designed for people with stroke and their caregivers, (2) are available in the English language, and (3) do not have access or subscription charges.

Exclusion criteria include duplicate webpages, commercial sites or advertisements, commentary type webpages, and webpages that do not contain any relevant information about stroke or its management. Peer-reviewed primary literature will be excluded because it would likely exceed the comprehension and readability level of most patients and the general public. It is also assumed that most patients may not have access to scientific literature. Specific content for medical professionals will be excluded because of its intended target audience.

Step 3: Selection of Online Stroke Resources

One reviewer (GIJ) will screen the results generated via the Google search and apply the selection criteria to identify relevant websites. When in doubt, a final determination will be made through discussion with a second reviewer (TC) until consensus has been reached.

Step 4: Data Charting

Data will be extracted and captured on a custom Microsoft Excel spreadsheet. Extracted data items may include descriptions, content-related categories, and design-related categories, including but not restricted to typology, geographic location, credibility, and understandability. Definitions and descriptions of content and design characteristics are provided in Table 1 [26]. Data extracted will be cross-checked for completeness and accuracy.

Table 1. Definitions of quality criteria of online resources.

Criterion	Definition
Accessibility	Refers to “whether or not a site can be easily accessed. Widely used indicators included whether: a site is available, the links are active, special software is required for viewing the content, website contact information is clearly presented, and the site attends to users with disabilities” [26].
Aesthetics	Refers to “the look and feel of a site...major indicators are site layout (e.g., whether the layout is easy-to-follow, attractive, clear, simple, clean, and appealing), the use of images (e.g., whether they are relevant, appropriate, useful, and of high quality), and the use of headings (whether headings and subheadings are used)” [26].
Currency	Refers to “whether or not the content is up-to-date,” usually identified by the publication date and the time of the last update [26].
Credibility	Refers to “two components, authoritativeness and trustworthiness” [26].
Interactivity	Refers to the “capacity of a site to allow users to communicate with the system or with other users...including whether the site offers internal search functions, supports user input (e.g., commenting on content) and information exchange (e.g., chat rooms and links to social media), provides multimedia content, and personalizes content based on consumer characteristics” [26].
Navigability	Refers to “how easily a consumer can move around within a site...and includes whether the information architecture of a site is logical, supports easy navigation, and provides a site map” [26].
Privacy and data protection	Refers to “whether a site respects the privacy and confidentiality of personal data submitted by visitors.” Most studies used the indicator outlined in HONcode’s (Health On the Net Foundation Code of Conduct) privacy criterion; that is, the presence of policy statements describing what information is collected and how it is used—for example, whether users were given the opportunity to opt out of sharing personal information [26].
Readability	Refers to “whether or not the content of a site is understandable for general consumers without medical background” [26].
Cultural contextualization	For this review, the investigators will identify whether any of the online resources provide evidence of and/or information on aspects that were designed or adapted to make it culturally appropriate for diverse users. Some of the cultural indicators may include surface elements (eg, formats, pictures, and language) [26]. In addition, latent messages and themes (eg, whether examples for patients from diverse sociodemographic backgrounds are included) will be identified.

As the field of digital health is expanding, so is the plethora of evaluation tools and criteria checklists available to assess the quality of online resources and webpages. The researcher is interested in whether the information content included in these online stroke information resources is comprehensive, current, and evidence based, as well as whether appropriate and accessible formats are being used. The description of the contents of each data source may include currency and credibility of the information, while design characteristics may include readability, understandability, accessibility, aesthetics, navigability, interactivity, privacy, and data protection. Data items will be extracted and summarized narratively and, where available, appraisal tools will be used. Selection of the appraisal tool will be determined by the specific criteria or characteristics to be appraised. Table 2 provides more details of the various quality criteria and indicators, along with appraisal tools or systems as described by Zhang et al [26].

Table 2. Quality criteria and indicators to assess online information sources and resources, as described by Zhang et al [26].

Characteristics and criteria	Examples of indicators	Validated evaluation tools (where applicable)
Content-related characteristics		
Currency	Publication date	N/A[a]
	Time of last update	
Credibility (authoritativeness and trustworthiness)	Authorship	HONcode (Health On the Net Foundation Code of Conduct) conformity developed by the Health On the Net Foundation
	Author name and professional credentials	
	Editorial process	
	Site domain and site type	Alexa web analytics software to assess domain popularity and visibility
	Disclosure	
	Aims of the website	
	Owner or sponsor of the site	
	Financial disclosure and conflict of interest	
	Contact information disclosed	
	Advertising policy	
	Target audience disclosed	
	Bias disclosed	
	Attribution	
	Source of the content and references	
	Additional source of support	
	Copyright, logo, or page title disclosed	
	Links to other related sites	
	Third-party accreditation	
	Health On the Net certified	
	Site popularity	
	Page rank in search engine results list	
	Site traffic statistics	
	Presentation of the content	
	Balanced content	
	Spelling errors	
Design-related characteristics		
Readability	Site content should be understandable for general consumers without medical background	Patient Education Materials Assessment Tool
Accessibility	Operational: sites available, no dead links, and browser independent	N/A
	Clear presentation of website contact information	
	Registration and accessing fee	
	Accessible for people with disabilities (eg, font size and graphics with captions)	
	Other languages offered	
	Website technical support available	
Aesthetics	Site layout	N/A
	Appropriate use of images	
	Use of headings	
	Color schema	
	Design consistency	
Navigability	Navigation structure: information presented in a logical order and easy navigation between links	N/A
	Site map	

Characteristics and criteria	Examples of indicators	Validated evaluation tools (where applicable)
Interactivity	Information exchange (eg, forums and emails)	N/A
	Internal search engines	
	Multimedia capability	
	FAQ (frequently asked questions) section	
	Personalization	
Privacy and data protection	Policy on the collection and use of personal data	N/A

[a]N/A: not applicable; there were no validated evaluation tools for this criterion.

Step 5: Collating, Summarizing, and Reporting Results

One reviewer (GIJ) will extract all the information related to content and design characteristics of stroke websites and will cross-check the entries in a reviewer-developed Microsoft Excel data sheet. A random selection of 10% of the extracted data will be checked by a second reviewer (TC). After comparison, any discrepancies will be resolved via discussion between the reviewers; if necessary, a third reviewer (KG) will be consulted. The extracted data will be summarized narratively using text and tables; where appropriate, thematic content analysis will be employed.

Results

As of February 2021, the scoping review is in the data extraction stage. Data will be synthesized, and the first results are expected to be submitted for publication in an open-access peer-reviewed journal in August 2021. We will develop an accessible summary of the results for stakeholder meetings. Ethical approval is not required for this scoping review, as it will only include publicly available information or data. Data generated from this review will be made available upon reasonable request.

Discussion

Potential Limitations of the Review

Only English-language websites will be reviewed in this study. This may result in missing potentially good-quality resources available in other languages as well as excluding end users with limited English proficiency. Even though Google is one of the most common and well-known search engines available internationally, limiting the search to only this search engine may be a limitation of our study. The use of computer-based analysis of readability may overestimate the difficult level of online information on websites, but more than one readability index will be used in this review to provide a broader interpretation of this quality criterion.

Conclusions

This review will attempt to map and evaluate the quality of the content, readability, and design of current, freely available, online health information resources (ie, websites) that empower people with stroke and their caregivers with information and self-help strategies poststroke, globally. Comprehensively mapping existing resources will assist developers with gaining insight into gaps across a range of quality criteria. The results of this review will be used to identify exemplar online health information resources of good quality and which specific aspects may need to be improved. An evaluation of these exemplar online stroke resources by target users will be incorporated in a follow-up study to validate the obtained results of the review from the user's perspective. The exemplar online stroke resources, identified during the review, will also inform the design of a South African–specific stroke-related digital health intervention. The envisaged co-design of the new contextually appropriate digital health intervention will, therefore, be informed by explicit quality criteria, international exemplar information resources, and, finally, input from end users, including people with stroke, their caregivers, and health care professionals involved in stroke care in South Africa.

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Authors' Contributions

GIJ drafted and revised the protocol with suggestions from KG and QL, who reviewed the protocol and provided feedback on the draft. GIJ, in consultation with the other authors, constructed the search protocol. TC assisted with data charting and cross-checking of preliminary results. All authors read and approved the final protocol.

Conflicts of Interest

None declared.

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Abbreviations

DALY: disability-adjusted life year
NRF: National Research Foundation

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Protocol

Choice of Behavioral Change Techniques in Health Care Conversational Agents: Protocol for a Scoping Review

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Abstract

Background: Conversational agents or chatbots are computer programs that simulate conversations with users. Conversational agents are increasingly used for delivery of behavior change interventions in health care. Behavior change is complex and comprises the use of one or several components collectively known as behavioral change techniques (BCTs).

Objective: The objective of this scoping review is to identify the BCTs that are used in behavior change–focused interventions delivered via conversational agents in health care.

Methods: This scoping review will be performed in line with the Joanna Briggs Institute methodology and will be reported according to the PRISMA extension for scoping reviews guidelines. We will perform a comprehensive search of electronic databases and grey literature sources, and will check the reference lists of included studies for additional relevant studies. The screening and data extraction will be performed independently and in parallel by two review authors. Discrepancies will be resolved through consensus or discussion with a third review author. We will use a data extraction form congruent with the key themes and aims of this scoping review. BCTs employed in the included studies will be coded in line with BCT Taxonomy v1. We will analyze the data qualitatively and present it in diagrammatic or tabular form, alongside a narrative summary.

Results: To date, we have designed the search strategy and performed the search on April 26, 2021. The first round of screening of retrieved articles is planned to begin soon.

Conclusions: Using appropriate BCTs in the design and delivery of health care interventions via conversational agents is essential to improve long-term outcomes. Our findings will serve to inform the development of future interventions in this area.

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KEYWORDS

behavior change; behavioral change technique; chatbot; conversational agent; health care; protocol; scoping review; long-term outcomes; behavior

Introduction

Background

Conversational agents (CAs), also known as chatbots, are computer programs that simulate conversations with users [1]. CAs are multimodal and can be deployed via messaging apps such as Telegram, Facebook Messenger, and Slack [2]; as standalone apps or websites; or integrated into cars or television sets. CAs may operate using simple text interfaces as the most basic form, as voice assistants, or as embodied CAs that use virtual characters to simulate both verbal and nonverbal human

behavior [3]. CAs are multifunctional and can automate a variety of tasks such as provision of information or news, web-based shopping, or as symptom checkers.

Health care is an ideal candidate for CA-delivered interventions [4]. CAs can assist patients by providing timely information [5], support mental health disorder management [6,7], and assist with triage in clinical settings [8,9] by harnessing the increasing ubiquity of smartphones [10] and other digital media [11,12].

CAs are increasingly being used for delivery of interventions focusing on disease treatment, management, and prevention [13]. An important component of such interventions is behavior change. Behavioral change interventions are defined as "coordinated sets of activities designed to change specified behavior patterns" [14]. Most behavior change interventions are complex, comprising the interaction of one or several smaller components, often referred to as behavioral change techniques (BCTs) [15]. A BCT is "an observable and replicable component designed to change behavior" [15], with descriptors as the smallest component compatible with retaining the postulated active ingredients of components designed to alter or regulate behavior, enabling easy coding and extraction of data in the intervention context [15]. Although various BCT taxonomy systems have been developed, BCT Taxonomy v1 (BCTTv1) [16] is widely used to provide a shared, standardized terminology to specify the active ingredients to support behavior change in health care interventions. BCTTv1 consists of 93 distinct BCTs divided into 19 major groups such as "goals and planning" and "feedback and monitoring" [16].

Existing reviews on CAs are largely descriptive and focus on effectiveness [17,18]. Systematic reviews on BCTs found that incorporating certain BCTs in the design of health care interventions increased their effectiveness [17-19]. Examples include action planning to enhance physical activity [20] or self-monitoring to increase physical activity and healthy eating [21]. Given the increasing use of CAs in health care and delivery of behavior change interventions, it is crucial to understand the way BCTs are incorporated in their design, including what BCTs are most commonly used and the behavior they intend to change [22]. By identifying what BCTs are employed, to what outcomes, and for what function according to experimental studies, this review seeks to advance understanding of the types of BCTs used in CAs in health care.

Identifying the Research Question (Stage 1)

The aim of this scoping review is to identify and present BCTs that have been included in behavior change interventions delivered via CAs. Specifically, the review will try to answer the following questions: (1) Which BCTs are used in CA-delivered interventions in health care? (2) What are the target behaviors the CA in health care aims to modify? (3) What were the theories/frameworks guiding the design of behavior change interventions delivered via CAs in health care? (4) Which BCTs have been incorporated into the effective CA interventions?

Methods

Design

This scoping review will follow the Joanna Briggs Institute scoping review guidelines [23] and will be reported in line with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) reporting guidelines [24].

Identifying Relevant Studies (Stage 2)

A systematic search will be performed of both peer-reviewed and grey literature. Peer-reviewed articles will be searched on the following databases: PubMed, Embase (Ovid), and Cochrane Central Register of Controlled Trials (CENTRAL). Grey literature will be identified by searching the first 10 pages in Google and Google Scholar.

The search strategy includes an extensive list of related words and phrases that define "conversational agents," which was updated from a search strategy used in a previous scoping review on CAs published by our research group [2] (see Multimedia Appendix 1).

All studies retrieved from the searches will be uploaded to EndNote X9 (Clarivate) and further imported to Covidence [25], an online tool to assist in the production of systematic reviews, to facilitate the screening of eligible articles. Screening will be performed in two stages, according to inclusion and exclusion criteria. In the first stage, the titles and abstracts will be screened by two independent reviewers. In the second stage, the full texts of all studies included will be acquired and reviewed by two independent investigators. Discrepancies resulting from any screening stage will be resolved by discussion between the reviewers or by engaging a third reviewer if discrepancies cannot be resolved by discussion alone. Interrater agreement will be determined using the Cohen κ coefficient in which $\kappa \geq 0.6$ (substantial or almost perfect agreement) will be considered to be acceptable [26]. The search and screening processes will be documented using a study selection flowchart [27].

Study Selection (Stage 3)

This scoping review will include primary experimental studies on a CA-delivered health care intervention focusing on behavior change. The eligible study designs comprise randomized controlled trials, quasirandomized controlled trials, cluster-randomized trials, controlled before-and-after studies, uncontrolled before-and-after studies, interrupted time series, pilot, and feasibility studies. Nonexperimental study designs, including observational studies, qualitative studies, reviews, personal communications, editorials, as well as conference abstracts and studies where it was not possible to access the full text report, will be excluded. The study population will include interventions featuring any kind of CA, including a text-based, voice-based, or embodied CA. Embodied CAs are defined as conversational interfaces that include a human-like avatar mimicking human movements and facial expressions. The eligible interventions will include any health care intervention focused on behavior change. This includes interventions focusing on improving or promoting a healthy lifestyle (eg, increase physical activity, weight loss, healthy eating) or

managing physical or mental health disorders (eg, depression, diabetes, asthma, hypertension). These interventions should include a clear reference to behavior change as an essential aspect of the intervention, with or without reference to an associated behavioral change theory.

Charting the Data (Stage 4)

A data extraction form will be developed by the research team, which will include the following items: first author, year of publication, source of literature, title of article, study design and methods, geographic focus, health care sector, CA name, accessibility of CA, dialogue technique, input and output modalities, nature of the CA's end goal, behavioral change theories or frameworks guiding the intervention, and BCTs used, mapped according to BCTTv1 [16].

Data from included studies will be extracted into a Microsoft Excel spreadsheet. Before starting the data extraction process, the table will be piloted by all members of the research team involved in this step, and amendments to the table will be made according to researchers' feedback.

Data extraction for each paper will be performed by two researchers working independently, and the results will subsequently be compared. If disagreements arise, these will be resolved through consensus or consultation with a third reviewer acting as an arbiter.

Data will be tabulated and analyzed using descriptive statistics.

Collating, Summarizing, and Reporting the Results (Stage 5)

The data extracted from the included papers will be presented in a diagrammatic or tabular form accompanied by a narrative summary. We will provide an overview of the choice of BCTs in the included studies, the use of BCTs across different types of CAs and health care areas, the BCTs employed in the interventions that have been shown to be effective, and the theories or frameworks used in the development of behavior change interventions. We will also discuss any gaps in the evidence and provide recommendations for future use of BCTs in CA-delivered interventions.

Stakeholder Consultation (Stage 6)

We will also undertake a stakeholder consultation to inform the analysis and presentation of our findings. Stakeholders will include researchers in the field of CAs in health care. We will organize a seminar with the stakeholders, present our findings, and invite comments from the attendants. We will use the collated feedback to guide our analysis and reporting in our manuscript.

Ethics and Dissemination

Ethical approval is not required for this study. We will disseminate our findings via a publication in a peer-reviewed journal and presentations at conferences.

Results

This protocol is being submitted prior to data collection and is registered on the Open Science Framework (osf.io/487jd). To date, we have designed the search strategy (see Multimedia Appendix 1 for the PubMed search strategy), and performed the initial search in PubMed (447 articles retrieved), Embase (858 articles retrieved), CENTRAL (1003 articles retrieved), and the first 10 pages of Google and Google Scholar search results on April 26, 2021 for a total of 3303 articles. After removing duplicates, a total of 2579 articles remain for screening. The first round of screening is planned to begin shortly.

Discussion

Behavior change is an essential yet complex aspect of many health care interventions. The aim of this scoping review is to provide insight into how behavior change interventions can be delivered via CAs. To provide a systematic and transparent analysis of this complex concept, we will identify and map the choice and use of BCTs in CA-delivered interventions. Using appropriate BCTs could potentially increase engagement and improve long-term outcomes. Our findings will serve to inform the development of future interventions in this area.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
PubMed search strategy.
[DOCX File , 13 KB - resprot_v10i7e30166_app1.docx]

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Abbreviations

BCT: behavior change technique
BCTTv1: BCT Taxonomy v1
CA: conversational agent
CENTRAL: Cochrane Central Register of Controlled Trials
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Career Development of Academic Staff in Faculties of Dentistry by Means of Mentorship Programs: Protocol for a Scoping Review

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Abstract

Background: Globally, the demands on dental educators continue to diversify and expand. Due to their importance and value, mentoring programs have been acknowledged as a means of recruiting, developing, and retaining academics in dental education.

Objective: This protocol is for a scoping review that aims to identify the goals of mentoring programs for academic staff in dental faculties and determine how these programs were structured, delivered, and evaluated.

Methods: The review will be performed in accordance with the Joanna Briggs Institute's methodology for scoping reviews, which covers both qualitative and quantitative scientific literature as well as grey literature written in English and published between 2000 and 2020. The databases will include PubMed, Ovid, the Educational Resources Information Center database, Science Direct, Scopus, Google Scholar, Trove, Web of Science, Openthesis.org, and the website of the American Dental Education Association. A manual search will also be conducted by using the reference lists of included studies to identify additional articles. Working independently, the authors will participate iteratively in literature screening, paper selection, and data extraction. Disagreements between the reviewers will be resolved by discussion until a consensus is reached or after consultation with the research team. Key information that is relevant to the review questions will be extracted from the selected articles and imported into a Microsoft Excel file. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) will be used to guide the reporting of this protocol.

Results: The search for appropriate literature has commenced, and we aim to present the results before the end of the 2021 academic year.

Conclusions: The development of formal mentorship programs for academics in dental education will enhance the retention of academic staff.

International Registered Report Identifier (IRRID): PRR1-10.2196/27239

(JMIR Res Protoc 2021;10(7):e27239) doi:10.2196/27239

KEYWORDS

scoping review protocol; academic staff development; mentorship; capacity development; dental education; dentistry; dental educators

Introduction

Mentoring was first developed in the United States of America in the 1970s within large corporations to support junior staff [1] but has now extended to other contexts, including the university-based education platforms of health professionals [2-13]. Over the years, the reforms in the education of health professionals have contributed to the doubling of life expectancy during the 20th century [4]. However, in the beginning of the 21st century, health advances were not being shared equitably due to gaps and inequalities in health education that existed between and within countries. To advance opportunities for

health equity within and between countries, a call for redesigning the curricula of health professionals was made. Instructional and institutional reforms were proposed, and these would be guided by two outcomes—transformative learning and interdependence in education [5]. As transformative learning is considered an outcome of instructional reforms, specific recommendations were made, such as the strengthening of educational resources with special emphasis on the capacity development of faculty and academic staff, including those of medical schools in Africa. Through the provision of rewarding and stable career trajectories and performance-based constructive assessment, the need to increase investments in the education of educators was highlighted.

Mentoring is difficult to define, but the Standing Committee on Postgraduate Medical and Dental Education described it as a process "whereby an experienced, highly regarded, empathetic person (the mentor) guides another (usually younger) individual (the mentee) in the development and re-examination of their own ideas, learning, and personal and professional development. The mentor, who often works in the same field as the mentee, achieves this by listening or talking in confidence to the mentee" [14]. Although mentoring is considered to be central to education in academic medicine and other health professions, it is inhibited by the increased number of clinical, administrative, research, and other educational demands on academics, thus reducing the time they need to devote to a mentoring relationship [11-14]. Unfortunately, the unique challenges encountered by women in academics have not yet been satisfactorily addressed [1,5,8,12]. The absence of mentorship has often resulted in a failure to retain junior academics in higher education institutions or within academia altogether.

It is helpful to gain some insight into the global context of dental education to appreciate the need for mentorship programs that enhance the careers of academic staff who are preparing for the future generation of oral health care professionals. It has been estimated that under 3 to 5 billion people across the world are affected by oral diseases [15]. The World Health Organization has therefore focused on increasing the awareness of oral health worldwide, as it is considered to be an important component of people's general health and quality of life. Unfortunately, oral disease is still a major public health problem in high- and low-income countries, and the burden of oral disease is growing in many low - and middle-income countries [16,17]. Untreated oral disease is a visible reminder of existing health inequalities, and ensuring access to adequately trained oral health professionals has become critical [18].

The following two approaches have influenced the practice of dentistry globally: the odontology and stomatology models [19-21]. Odontology is the study of oral disease and disorders of the oral cavity, including their diagnosis, treatment, and prevention. Stomatology is the study of the mouth, and it connects general medical health and disease with diseases of the mouth [21]. The duration of dental education across the world ranges from 5 to 9 years [20]. Unfortunately, there are limited details about dental education in Africa despite the oral health challenges in this continent [22-24] and in other countries where inequities in access to oral care are also evident [25]. The presumption that colonization influences dental education in Africa and other places could have contributed to the calls for the decolonization, indigenization, and transformation of oral dental education [26-28].

In light of the recommendation to transform the education of health professionals in order to strengthen health systems in the 21st century [5], professional bodies like the American Dental Education Association have made calls for major changes in the training of oral health professionals [26-31]. A 2-phase project named "Advancing Dental Education in the 21st century" is a current driver of change in the United States of America. The project aims to develop practical strategies that dental and allied dental educational institutions can implement to address long-range challenges related to finances, education, scholarship, diversity, and the need to change disease and practice trends by 2040 [32-36]. Similarly, a partnership between the American Dental Education Association and the Association for Dental Education in Europe, which have strong historical relationships, led to the creation of another project named "Shaping the future of Dental Education" [37-41]. The first meeting between the two associations was attended by over 180 participants who represented 39 countries and sought to explore the roles and capabilities of dental educators in impacting global dental health education.

Curriculum changes were recommended by the two projects to prepare oral health professionals to address more diverse, multicultural patient populations; older patients with dental needs and comorbidities; younger patients with fewer restorative and prosthodontic treatment needs; and vulnerable, disadvantaged populations with unmet needs [32-41]. These professionals would require skills for serving as good team members and team leaders of intra- and interprofessional teams as well as skills in communication, collaboration, supervision, critical thinking, and problem solving. These professionals would also need to understand scientific methods, evaluate research findings, and decide what to incorporate into patient care. Additional factors that would impact dental education in preparing oral health professionals for 2040 and beyond would include skills for addressing the social determinants of health [36] and adapting to different teaching and learning methodologies [41,42]. To achieve the goals of the change processes that were set out for the 21st century, the capacity development of academic staff was considered to be essential for their recruitment and retention. This was in line with earlier recommendations of the American Dental Education Association [5,35,43,44].

The quality of academics and their willingness to lead the transformative changes in dental education have become essential. Due to having little to no previous experience and coming from diverse backgrounds, novice academics can readily feel overwhelmed, unsupported, and discouraged in their attempts to meet the demands of success in academics [6,7,26]. Therefore, the objective of this paper is to present a protocol for a scoping review that aims to map out literature and produce an evidence-based synthesis of data regarding the mentorship of academic staff in dental faculties.

Methods

Summary of the Scoping Review

The overall objective of the proposed scoping review is to explore formal and informal mentorship programs in dental faculties that are designed to develop academic staff members' careers. The review will be conducted in accordance with the Joanna Briggs Institute (JBI) framework for scoping reviews, which acknowledges the following six methodological stages: (1) the identification of the research question; (2) the identification of relevant studies; (3) the selection of studies; (4) the extraction and charting of the results; (5) the collation, summarization, and reporting of results; and (6) consultation with stakeholders (optional) [45].

Identifying the Research Questions

The proposed scoping review aims to answer the following three questions: within existing literature, (1) what were the goals of mentoring programs for academic staff in dental faculties, (2) how were these programs structured and delivered, and (3) how were the programs evaluated?

Identification of Relevant Studies

Search Strategy

In consultation with the librarian of the Faculty of Dentistry at the University Western Cape, the electronic search for literature will focus on retrieving articles that were published in peer-reviewed journals between 2000 and 2020 via a systematic search of the following bibliographic databases: PubMed, Ovid, the Educational Resources Information Center database, Science Direct, Scopus, Google Scholar, Trove, Web of Science, Openthesis.org, and the website of the American Dental Education Association [46]. In addition, a manual search will be conducted by using the reference lists of included studies to identify additional articles. Articles in grey literature that are considered to be relevant to the research questions and objectives will also be included, and if this is done, the information sources will be reported. Only articles written in English will be considered.

The 3-step search strategy, which is explained in the JBI Reviewer's Manual, was followed [45]. The first step involved consulting a librarian in the Faculty of Dentistry. The librarian conducted pilot searches by searching for the terms *mentor*, *training*, and *dental* in the abstracts of relevant articles and grey literature from a predefined list and tested the search strategy with different databases. Articles published before the year 2000 often conflated mentoring with supervision, role modelling, coaching, advising, networking, and sponsorship [5,8,12]. Based on the outcome of the pilot searches (Table 1), we determined the search strategy that will be used when the scoping review is conducted. With the assistance of the faculty librarian, the search strategy was drafted and further refined through team discussion.

Table 1. Search strategy for PubMed. The search was conducted on April 7, 2021.[a]

Search number	Query terms	Records retrieved, n
1	*Training*	1,283,644
2	*Mentorship OR mentor*	16,936
3	*Dental OR dentistry*	479,241
4	*Training AND mentorship OR mentor AND dental OR dentistry*	574

[a]The search was limited to literature published from 2000 to 2020, those written in English only, and those that involved human subjects only.

Selection of Studies

Two reviewers (SLA and FKD) will conduct searches in all identified databases, and all search results will be imported into Rayyan Qatar Computing Research Institute software to ensure that a systematic and comprehensive search is performed and to document the selection process [47]. Working independently, the same reviewers will manage Rayyan and review the titles and abstracts to identify and remove duplicate citations. If necessary, full-text copies of the short-listed studies will be obtained to find more details. The reviewers will consider studies that focused on the mentoring of academic staff in the dental faculties of the following departments and specialties: orthodontics, maxillofacial and oral surgery, prosthodontics, periodontics, pediatric dentistry, maxillofacial and oral radiology, oral pathology, oral forensic pathology, clinicians, specialists, oral hygienists, and dental therapists. However, the considered studies will not be limited to these topics. Studies that focus on allied health specialties (dietetics, nursing, occupational therapy, physiotherapy, psychology, chiropractic, midwifery, social work, etc) and nondental professionals (medical professionals and veterinary science professionals) and studies that do not fit into the conceptual framework of the proposed scoping review will be excluded.

The proposed scoping review will consider both experimental and quasi-experimental study designs, including randomized controlled trials, nonrandomized controlled trials, before-and-after studies, and interrupted time series studies. In addition, analytical observational studies, including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies, will be considered for inclusion. This review will also consider descriptive observational study designs, including case series, individual case reports, and descriptive cross-sectional studies, for inclusion. Qualitative studies that focus on but are not limited to qualitative data, including phenomenology data, grounded theory, ethnography data, qualitative descriptions, action research, and feminist research, will also be considered. In addition, systematic reviews and texts and opinion papers that meet the inclusion criteria will also be considered for inclusion. All references from identified grey reports will be

hand-reviewed to determine if the literature is appropriate for inclusion in the scoping review.

Any disagreements between the two reviewers will be resolved by discussion until a consensus is reached or after consultation with the research team. Once a decision is reached on the final list of selected articles, the full texts of the articles will be accessed. The reference management software Mendeley Desktop for Windows will be used to store, organize, cite, and manage all selected references [48]. Two reviewers (SLA and FKD) will independently review the articles to determine whether they meet the inclusion criteria. Disagreements regarding inclusion will again be discussed and resolved by consensus among the reviewers or with the other two authors (RB and GG). A PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) flow diagram will be used to delineate the search decision process for the scoping review [49]. The full texts of selected citations will then be independently assessed by two reviewers (SLA and FKD) in detail against the inclusion criteria. Reasons for the exclusion of full-text studies that do not meet the inclusion criteria will be recorded and reported in the scoping review. Again, any disagreements that may arise between the two reviewers will be resolved via consultation with the other two authors (RB and GG) to reach a consensus.

Extracting and Charting the Results

A Microsoft Excel file will be developed by the two reviewers (SLA and FKD) and pilot tested to determine whether it satisfactorily captures information that is consistent with the purpose and questions of the scoping review. General information that will be included in the Excel chart will include a description of study characteristics—the year of publication, the country of origin, the geographical location in which the research was conducted, study aims and purposes, the methodology and sample size, and descriptions of study populations. Key information that is relevant to the review questions will be independently extracted from the selected articles by the two reviewers and imported into the Microsoft Excel file. This will be an iterative process conducted by the two reviewers, and the file will be continuously updated.

Data Availability

The data generated for this scoping review protocol will be made available upon reasonable request.

Results

The fifth stage of the JBI framework for scoping reviews is collating, summarizing, and reporting the results. The PRISMA-ScR [49] will be used to guide the reporting of the scoping review protocol and will subsequently be used to structure the reporting of the full review.

The search for appropriate literature has commenced, though it has been delayed due to the sudden death of the librarian during the peak of the COVID-19 pandemic. However, we aim to present the results before the end of the 2021 academic year.

Discussion

The sixth stage of the JBI framework for scoping reviews (consultation with stakeholders) is incorporated into this section. The prevalence of oral diseases across the world is still a major concern, and there are calls for additional oral health professionals to improve access to care [15-17]. The two change projects that are referred to in this paper [32-42] provide a framework for the training of oral health professionals during the 21st century that is in line with the recommendations of the Lancet Commission [5]. Higher education institutions cannot ignore these transformational drivers of change in dental education. Upon entering a career in academia, there is the expectation that novice academics can meet the increasing demands of teaching, scholarly activity, and research; perform administrative tasks; and participate in both university and community services [7]. Oral and dental care play an important role in the health and well-being of the population. Further, mentorship will help mentees to fulfill their career aspirations and will contribute to meeting the oral health needs of the population. Therefore, the purpose of the proposed review is to identify the goals of mentoring programs for academics in dental faculties and determine how these programs were structured, delivered, and evaluated**.** As this review will only include data that are already in the public domain, ethics approval will not be sought. The data generated from the scoping review will be accessible upon request, as the library of the University of Western Cape is developing a data management plan for storing and sharing research data securely on the university's research data repository [50]. However, the articles selected for review will be selected regardless of methodological quality and the risk of bias, as analyzing these factors is outside of the scope of the review. This may be a limitation of the study.

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Authors' Contributions

SLA, FKD, and GG contributed to the conception and design of the review. SLA drafted the review protocol with suggestions from FKD, GG, and RB. SLA and FKD constructed the search strategy and performed a preliminary search. SLA, FKD, GG, and RB contributed to and approved the final draft of the review protocol.

Conflicts of Interest

None declared.

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Abbreviations

JBI: Joanna Briggs Institute
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Bioethics in Childbirth Care: Protocol for a Scoping Review

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Abstract

Background: Ensuring women's rights during childbirth care based on humanized and bioethical principles results in better quality of care and patient safety and provides positive childbirth experiences.

Objective: We aim to explore the available evidence on the application of bioethical principles in the general context of childbirth care.

Methods: Our scoping review will follow the Joanna Briggs Institute Reviewer's Manual. Published and unpublished bibliographic materials will be considered based on the following inclusion criteria: reports of the application of bioethical principles (concept) in assistance to the predelivery, childbirth, and postpartum periods (population) in the hospital context (context). We will search for relevant studies in PubMed and the Virtual Health Library, including MEDLINE, LILACS, BDENF, SCiELO, Web of Science, and Google Scholar. Two reviewers will perform the screening of titles and abstracts, read the full texts, and extract data from the selected articles. The data will then be organized and expressed into categories based on their content.

Results: The analyzed data will be presented through flowcharts, tables, and descriptive narratives. A paper summarizing the findings from this review will be published in a peer-reviewed journal. In addition, a synthesis of the key findings will be disseminated to health services linked to university hospitals in Brazil. They will also be shared with the academic community and policy makers involved in the Childbirth Assistance Network, which will potentially adopt our recommendations in their decision-making process regarding childbirth care practice in Brazil.

Conclusions: The findings from this review will inform, through the translation of knowledge, childbirth support groups, feminist movements, movements in favor of humanization of childbirth, and other childbirth support networks in the country.

Trial Registration: Open Science Framework; https://osf.io/kczyr/

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KEYWORDS

childbirth care; bioethics; scoping review; childbirth; parturition; labor

Introduction

Background

In 2014, the World Health Organization (WHO) released a statement on the abuse and disrespect that many women suffer during childbirth globally. Professionals in the field and researchers have frequently demonstrated patterns of mistreatment and disrespect for women during childbirth. These patterns, conceptualized as obstetric violence in many countries [1], have varied from psychological and physical aggression such as verbal abuse to neglect and abandonment, humiliation and punishment, and coercive and forced care.

The WHO's declaration shows the real dimension of these ill-treatments, that is, the violation of human rights. Health and

human rights in maternal law should always reflect the bioethical issues that involve childbirth assistance, especially in doctor-patient conflicts and the abusive use of technologies that can make the risk greater than the benefit [1].

The high morbidity and mortality rates made the search for respectful and better-quality care necessary [2]. Thus, the goals of a sustainable development aimed at reducing these rates have been sought since the implementation of the millennium goals in 2003 [3]. The increasing changes toward the promotion and protection of maternal rights in the clinical and care scenarios should be accompanied by reflections on bioethics and human rights in childbirth [4].

Research Question and Objective

In this context, we used the acronym PCC (population, concept, and context), defined below, to elaborate the research question:

- P (population): women in labor, delivery, and the postpartum period
- C (concept): bioethics and health care
- C (context): childbirth care in the hospital context

Thus, the following question was raised: "Do women in labor, delivery, and the postpartum period have their rights ensured, through health care based on bioethics during care?"

Based on this research question, the main objective of this review is to map the available evidence on the application of bioethical principles in the general context of childbirth care.

Many studies have addressed bioethical issues during childbirth care. However, after conducting a search with the descriptors "bioethics," "ethics," "birth," and "childbirth" in the Joanna Briggs Institute Evidence-Based Practice Database, Cochrane Library, and PubMed, no systematic reviews, overviews, or scoping overviews were found in this context. Only one systematic review was found in the Web of Science database that addresses the effectiveness of respectful care during childbirth and birth services, but it does not address bioethical issues.

Methods

Study Design

To achieve the proposed objective in accordance with the research question, we decided to use the scoping review methodology, which is a type of systematic review, mapping concepts and findings related to the topic of interest available in the main data sources by using the knowledge synthesis approach [5]. The scoping review uses all types of evidence at various levels.

Protocol

This scoping review will be conducted according to the guidelines and methodological framework published by the Joanna Briggs Institute for scoping reviews. The expected development time and duration of the study is 6 months.

Prior to the elaboration of this protocol, a search of review articles already published on the topic to be studied was carried out, as described below.

Search Strategy

The search strategy (Table 1) covered the following aspects:

- Type of studies: systematic review, overview, and scoping review
- Descriptors: bioethics and midwifery; bioethics and (delivery or "natural childbirth" or labor or obstetric or parturition or "perinatal care"); "human rights" and childbirth
- Filters: year of publication (last 10 years), type of study

Table 1. Review articles identified in electronic databases.

Search strategy	Joanna Briggs Institute Evidence-Based Practice Database	PubMed	Cochrane	Web of Science	Health Systems Evidence	Google Scholar	Findings	Excluded	Met the inclusion criteria
Bioethics and childbirth	1	5	0	12	0	200 early[a]	218	218	0
"Human rights" and childbirth	3	20	1	89	2	200 early	315	315	0
Bioethics and (delivery or "natural childbirth" or labor or obstetric or parturition or "perinatal care")	6	382	11	169	0	8	576	576	0
Bioethics and midwifery	3	39	0	7	0	200 early	249	249	0

[a]For searches performed on Google Scholar, we analyzed the first 200 articles due to the large number of random findings.

Inclusion Criteria

Participants

Studies that included participants who are women; are of any age; and received labor, delivery, and postpartum care in any hospital, maternity, or delivery house will be included in the review. Studies that included participants who received care during home birth will be excluded.

Concept

The central concept of the included studies is that they should address bioethical issues. They should include details related to bioethical principles; feminist-inspired bioethics; principled

theory; or any bioethical or human, maternal, or women's rights foundation.

Context

The context to be observed should be assistance during labor, delivery, and postpartum, regardless of the country, state, city, or region. The abuses and mistreatment of women during childbirth care as a global issue is important, as well as different perspectives from different locations need to be considered. Only hospital birth care services are of interest in terms of the context of the research question in this review.

Study Types

The source of information will remain open to allow the inclusion of any type of study. All studies will undergo a methodological quality assessment, using the Joanna Briggs Institute Critical Appraisal Tools, with the scores described in tables next to the description of the selected articles.

Period

Studies published in the last 10 years, developed in any year and duration, will be eligible for the review.

Language

Full articles published in English, Portuguese, and Spanish will be considered for inclusion.

Results

Information Sources and Search Strategy

First Stage

An initial search was performed in two electronic databases, MEDLINE (PubMed) and Virtual Health Library. After this initial search, words contained in the title, summary or abstract, and keywords of the articles found were analyzed. The descriptors found will be compared to the descriptors registered in the descriptor bases: Medical Subject Headings (MeSH) for searches in PubMed and DeCS (Descriptores en Ciencias de la Salud [Health Sciences Descriptors]) for searches to be carried out in the Virtual Health Library (Table 2).

Table 2. Descriptors selected for search strategy.

DeCS[a]			MeSH[b]
Portuguese	English	Spanish	
Bioética	Bioethics	Bioética	Bioethics
Ética Médica	Ethics	Ética Médica	Ethics
Direitos Humanos	Human Rights	Derechos Humanos	Human rights
Autonomia	Autonomy	Autonomía Personal	Autonomy
Beneficência	Beneficence	Beneficencia	Beneficence
Não maleficência	Non-maleficence	No maleficencia	Non-maleficence
Justiça	Justice	Justicia	Justice
Eficiência	Efficiency	Eficiencia	Efficiency
Proporcionalidade	Proportionality	Proporcionalidad	Proportionality
Obstetrícia	Obstetric	Obstetricia	Obstetric
Parto	Childbirth	Parto	Childbirth; parturition; labour; labor
Parto Normal	Natural childbirth	Parto Normal	Delivery; perinatal care; natural childbirth
Assistência ao Parto	Midwifery	Partería	Midwifery

[a]DeCS: Descriptores en Ciencias de la Salud (Health Sciences Descriptors).

[b]MeSH: Medical Subject Headings.

Second Stage

A second search using all identified keywords and descriptors will be carried out in all databases: PubMed, Virtual Health Library, SCiELO, and Web of Science, following the search strategy described in Table 3.

Table 3. Search strategy across different databases.

Database	Search strategy
PubMed	("bioethics"[MeSH Terms] OR "bioethics"[All Fields]) AND (("delivery, obstetric"[MeSH Terms] OR ("delivery"[All Fields] AND "obstetric"[All Fields]) OR "obstetric delivery"[All Fields] OR "delivery"[All Fields]) OR "natural childbirth"[All Fields] OR ("labour"[All Fields] OR "work"[MeSH Terms] OR "work"[All Fields] OR "labor"[All Fields] OR "labor, obstetric"[MeSH Terms] OR ("labor"[All Fields] AND "obstetric"[All Fields]) OR "obstetric labor"[All Fields]) OR obstetric[All Fields] OR ("parturition"[MeSH Terms] OR "parturition"[All Fields] OR "delivery, obstetric"[MeSH Terms] OR ("delivery"[All Fields] AND "obstetric"[All Fields]) OR "obstetric delivery"[All Fields]) OR "perinatal care"[All Fields])
	([Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Autonomy[All Fields])
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Beneficence
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Non-maleficence
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Justice
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Efficiency
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Proportionality
Web of Science	[bioethics and (delivery or “natural childbirth” or labor or obstetric or parturition or “perinatal care”)] or ["human rights" and childbirth]
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Beneficence
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Non-maleficence
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Justice
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Efficiency
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Proportionality
SCiELO	bioethics and (delivery or “natural childbirth” or labor or obstetric or parturition or “perinatal care”)
	"human rights" and childbirth
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Beneficence
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Non-maleficence
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Justice
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Efficiency
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Proportionality
BVS[a]	bioética and ("assistência ao parto" or nascimento or parto)
	"direitos humanos" and ("assistência ao parto" or nascimento or parto)
	autonomia and ("assistência ao parto" or nascimento or parto)
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Beneficence
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Non-maleficence
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Justice
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Efficiency
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Proportionality
Google Acadêmico (Google Scholar)	bioética and "assistência ao parto"
	bioética and parto
	direitos humanos and "assistência ao parto"
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Beneficence
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Non-maleficence
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Justice
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Efficiency
	(Midwifery OR Natural Childbirth OR Childbirth OR Obstetric) AND Proportionality

[a]BVS: Biblioteca Virtual en Salud (Virtual Health Library).

Third Stage

A third search will be carried out in the grey literature through Google Scholar. Thus, the search will be complete in five different databases. If necessary, the list of references used in all articles selected from the full text and included in the review will be consolidated. We will contact authors of primary studies or reviews to obtain more information about published studies, if relevant. All these steps and care will be undertaken to maximize the scope of the search and the scope of the important studies to be considered in this review. Thus, articles published in any language will be considered eligible if they meet the remaining eligibility criteria.

Selection of Studies

The following steps will be undertaken to select published articles based on prespecified inclusion criteria: (1) screening by year of publication, (2) sorting by title, (3) screening by summary or abstract, and (4) full-text screening.

The selection process of the studies to be included will be carried out by two independent researchers. Doubts or divergences will be resolved through consensus, or a third researcher will be called for a final decision regarding the inclusion or exclusion of a study.

Data Extraction

The important information that will be mapped is as follows: article title, year of publication, study objective, population or sample, study design, main conclusions, and key findings related to the scoping review's research question.

Records that identify each study will be preserved, should further checks be required. In the course of data extraction, it may become important to add unanticipated information that will be additional if useful to help answer the review question. Thus, the data table will be continuously updated by the research team. The data to be extracted will be tested by one or two team members to make sure that all relevant results are extracted.

Summary of Results

The results of this scoping review will be presented in a diagram or table as well as in a descriptive format. Analyses of the general data of the included studies will also be presented as graphs or tables, indicating the distribution of the studies by year or period of publication, countries of origin, and research methods. A narrative summary will accompany the results displayed in graphs or tables, describing how the results of each included study are related to the objective and question of this review. Research gaps found and possible limitations of this review will also be highlighted.

Discussion

Implications

The main aim of this review is to explore the available evidence on the application of bioethical principles in the general context of childbirth care. We believe that having a clearer picture of how women in labor, delivery, and the postpartum period have their rights ensured through health care based on bioethics, as well as investigating what further actions have been suggested, is critical to addressing the problem of ensuring these women's rights.

The conclusions from this scoping review will inform decision-makers, health services, and health professionals on bioethics in childbirth care. The findings will also be shared with the entire academic community and public policy makers involved with the Childbirth Assistance Network in Brazil. This, in turn, may result in the implementation of decision-making regarding a safe and humanized childbirth care practice, based on ethical and bioethical principles and ensuring the rights of women.

Dissemination

The summary of the results will be disseminated through the publication of data in a free-of-charge format and through the translation of knowledge to women, childbirth support groups, feminist movements, movements in favor of the humanization of childbirth, and birth and support networks. We will use social networks and electronic correspondence, in addition to presentations at congresses and scientific events and publication in peer-reviewed scientific journals.

Conclusions

The strengths of this study relate to a very comprehensive bibliographic search of various databases, electronic sources for difficult-to-locate and unpublished studies (or the grey literature), and publications in any language following Joanna Briggs Institute's methodologically rigorous manual. We will also use different strategies to disseminate our results widely. As a potential limitation, we could cite the time needed to evaluate a large number of articles related to assistance and bioethics.

Acknowledgments

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Authors' Contributions

GIF conceived the idea, the research question, and the methods of study and contributed to the writing and editing of the manuscript. GIF also approved the final manuscript. KHB, AD, CO, and DG assisted in the development of the research question and study methods, and they also contributed to the writing, editing, revision, and approval of the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

DeCS: Descriptores en Ciencias de la Salud [Health Sciences Descriptors]
MESH: Medical Subjects Headings
WHO: World Health Organization

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Protocol

The Role of Occupational Therapy in Pulmonary Rehabilitation Programs: Protocol for a Scoping Review

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Abstract

Background: Chronic respiratory diseases are highly prevalent and compromise an individual's ability to perform activities of daily living (ADLs) and participate in meaningful life roles. Pulmonary rehabilitation (PR) is a well-established intervention aimed at restoring an individual's exercise capacity and improving their ability to complete their ADLs. Occupational therapists help individuals engage in meaningful "occupations," improving their health and well-being. Given the concordance in the aims of PR and the occupational therapy (OT) scope of practice, occupational therapists appear to be well suited as key players in PR programs. However, the benefits of adding OT to PR programs have been sparsely reported in the literature and the role of OT in PR has never been synthesized or reported in national and international guidelines.

Objective: The aim of this review is to explore the role of OT in PR programs, the current guideline recommendations for the inclusion of OT in PR programs, the estimated prevalence of OT in PR programs, and the reported or anticipated effects of OT interventions in PR programs.

Methods: The review will be conducted following the Joanna Briggs Institute (JBI) methodology for scoping reviews. A comprehensive search will be undertaken in the Cochrane Database of Systematic Reviews, EMBASE, MEDLINE, and CINAHL (EBSCO) to identify and retrieve relevant literature published in English, French, or Portuguese. Gray literature on international OT association websites will also be identified, including position statements and guidelines relevant to PR programs. All literature published since the establishment of the effectiveness of PR for chronic respiratory disease in 1994 that explores OT in PR programs for these patients will be included. Search results will be exported to Covidence for title, abstract, and full-text screening by two independent reviewers. Data will be extracted by two independent reviewers using a pilot-tested template including the following: the number of PR programs including OT (specifically from surveys), the purpose of the study, the study design, patient characteristics, respiratory conditions included, PR components, OT role, outcomes, and results. Findings will be presented using a narrative summary, supplemented by figures and/or tables. Key themes will be displayed in an infographic or schematic.

Results: The study was initiated in January 2021 and registered with the Open Science Framework (OSF) in February 2021, prior to title and abstract screening. Data collection and analysis and drafting of the manuscript will occur throughout 2021, with expected publication in 2022.

Conclusions: The results of this scoping review will help health care professionals improve patient care by broadening their understanding and awareness of the role of OT in PR programs. This role clarification may help to inform program development

and clinical decision making and will serve to optimize the delivery of multidisciplinary care for patients in PR programs, ultimately improving patient outcomes.

Trial Registration: OSF Registries ZH63W; https://osf.io/zh63w

International Registered Report Identifier (IRRID): DERR1-10.2196/30244

(JMIR Res Protoc 2021;10(7):e30244) doi:10.2196/30244

KEYWORDS

chronic respiratory disease; COPD; lung diseases; occupational therapy; pulmonary rehabilitation program

Introduction

Chronic respiratory diseases are chronic diseases of the airways and structures of the lung [1]. In 2017, an estimated 545 million people globally were impacted by chronic respiratory diseases; in Canada, approximately 1 in 10 adults are affected [2,3]. Chronic respiratory diseases impose a high burden of morbidity and mortality worldwide [2]. In recent years, chronic respiratory diseases represented the third-leading cause of death globally [2] and chronic obstructive pulmonary disease (COPD) represented the sixth greatest contributor to global disability-adjusted life years (DALYs) [4]. As such, people with chronic respiratory diseases present with multifaceted physical, psychological, and social impairments, compromising their ability to perform activities of daily living (ADLs) and threatening their participation in meaningful life roles [5].

Pulmonary rehabilitation (PR) is a core component of the management of respiratory diseases, and there is strong evidence to support its effectiveness in people with COPD [6], interstitial lung disease (ILD) [7], lung cancer [8], pulmonary arterial hypertension [9], and COVID-19 [10], as well as those who are pre–lung transplantation or post–lung transplantation [11,12], among others [6]. PR has been shown to relieve dyspnea and fatigue, improve overall exercise capacity, reduce hospital readmissions, enhance the sense of control that an individual has over their condition, and improve health-related quality of life [13,14]. A PR program generally involves a thorough individual assessment, followed by a comprehensive, multidisciplinary, person-centered intervention that may include education, exercise, and self-management strategies targeting healthy behavior change [6,15]. These interventions aim to restore an individual's exercise capacity and improve their ability to complete ADLs [16].

Occupational therapists are rehabilitation professionals who work to help individuals engage in ADLs and other meaningful "occupations" that affect their health, well-being, and participation in life roles [16,17]. Given the concordance in the aims of PR and the occupational therapy (OT) scope of practice, occupational therapists appear to be well suited as key players in PR programs [18]. The benefits of adding OT to PR programs have been sparsely reported in small studies of patients with COPD [19-21] but have never been synthesized or reported in national and international guidelines [6,22]. The lack of knowledge about OT roles and benefits may be hampering its inclusion in PR programs and preventing people with chronic respiratory diseases from getting the best evidence-based care. Indeed, the most recent Canadian survey found that less than 40% of PR programs in Canada report having occupational therapists on their team [22].

In preparation for this review protocol, an initial search of the literature was conducted in EMBASE, MEDLINE, CINAHL, the Cochrane Database of Systematic Reviews, and the JBI Evidence Synthesis; no current or underway scoping reviews or systematic reviews on OT in PR were identified. However, the terms "occupational therapy," "cardiopulmonary rehabilitation programs," "respiratory rehabilitation programs," and "pulmonary rehabilitation programs" yielded a wide breadth of literature. These preliminary search findings support the need for a scoping review to map the available research; explore the extent, range, and nature of the research activity; and identify gaps in the available evidence [23].

The main objective of this scoping review is to explore the role of OT in PR programs. The secondary objectives are the following: (1) systematically map the recommendations of current guidelines for the inclusion and roles of OT in PR programs, if any, (2) estimate the prevalence of OT as part of PR programs, and (3) summarize the reported effects of OT as part of PR.

Methods

Overview

The protocol is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guideline [24]. The scoping review will be conducted in accordance with the JBI methodology for scoping reviews and will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) for the reporting of results [25,26]. The protocol was registered with the Open Science Framework (OSF) from the Center for Open Science prior to title and abstract screening to improve research transparency and reduce risk of bias [27,28].

Review Questions

This review will seek to answer the following questions:

1. What are the recommendations of current guidelines for the inclusion and roles of OT in PR programs, if any?
2. What is the estimated prevalence of OT in PR programs?
3. What are the reported effects of OT as part of PR?

Inclusion Criteria

Participants

This review will consider literature pertaining to patients with chronic respiratory diseases who are receiving OT services in PR programs. Only studies in adult populations (aged ≥18 years) will be included to provide a more coherent summary of the available literature, since OT interventions differ significantly between children and adults. Additionally, pulmonary rehabilitation is currently primarily provided to adult patients and thus we estimate that literature in children will be too scarce for fulsome review. Chronic respiratory diseases include, but are not limited to, COPD, ILD, cystic fibrosis, bronchiectasis, and lung cancer.

Concept

This review will consider studies that explore the concept of OT in PR programs. These programs may be described as "cardiopulmonary rehabilitation programs," "respiratory rehabilitation programs," or "PR programs" in order to capture a wide range of possible interventions with similar therapeutic goals that may be described using different terms. To be considered for inclusion, studies have to report on PR programs as defined by Spruit and colleagues [6] (ie, delivered over a minimum of 4 weeks, and including exercise, education, and self-management or behavior change interventions) and must include and describe the role of OT in a PR program. An exception will be made for survey studies of PR programs, in which all surveys of PR programs will be included, even if OT is not part of the PR program or if programs surveyed did not meet the PR definition established. This decision was made since a preliminary search revealed that surveys on PR programs usually use a broader definition of PR, for example by including programs that only provide exercise training as well as programs established according to the international guidelines. Thus, including all surveys will allow more accurate conclusions about the prevalence of OT in PR programs. Additionally, if only surveys including OT were to be included it could skew the estimation toward an inflated estimation of OT inclusion in PR programs.

Context

To ensure the scope of the review has both breadth and depth, this review will consider studies where PR programs are delivered in institutional or noninstitutional settings including the home and community. Some context examples may be inpatient, outpatient, or home PR programs. Included studies will not be limited by sample location, culture, or race.

Types of Sources

Quantitative, qualitative, and mixed methods study designs will be considered for inclusion, as well as clinical practice guidelines, systematic reviews, and PR program surveys. Where systematic reviews meet inclusion criteria at title and abstract screening, the individual studies included in the review will be screened for the eligibility criteria. The systematic review will only be included in data extraction if novel findings for the role of OT in PR programs are reported. Finally, gray literature will be searched from OT association websites for position statements and other practice guidance relating to PR. The OT association websites of Canada, the United States, Australia, and the United Kingdom were searched because these countries are pioneers and leaders in PR and thus more likely to have published guidelines on PR implementation. In addition, the OT association websites of Portugal, Brazil, and France were searched for consistency with our language inclusion criteria.

Exclusion Criteria

The exclusion criteria were established a priori. Conference abstracts will not be included. Given the language competencies of the research team members, included literature may be published in English, Portuguese, and French. Studies published in any other languages will be excluded. Studies published prior to 1994 will be excluded, as prior to this time the efficacy of PR for the management of chronic lung disease was not yet established [29].

Search Strategy

The search strategy will be collaboratively developed by the research team, in consultation with an experienced librarian at the McMaster University Health Sciences Library (Ontario, Canada). An initial limited search of the JBI Evidence-Based Practice Database, EMBASE, MEDLINE, and CINAHL (EBSCO) will be undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles as well as the keywords and index terms used to describe the articles will be used to assist in developing the full search strategy. The search strategy, including all identified keywords and index terms, will be adapted for each database. Furthermore, the reference lists of articles selected for full-text review will be hand-searched for additional studies.

Information Sources

Four databases will be searched: MEDLINE via Ovid (1946 to 2021), EMBASE via Ovid (1974 to 2021), CINAHL via EBSCOHost (1937-2020), and the Cochrane database (1995-2021). Multimedia Appendix 1 contains a complete description of search strategies for each database.

Study Selection

Following the search, all identified records will be collated, uploaded into Zotero reference management software (Center for History and New Media, George Mason University), and duplicates removed. All records will then be uploaded to the Covidence screening and data extraction tool (Veritas Health Innovation). Two independent reviewers will perform a pilot test of the proposed eligibility criteria with 10 articles to achieve full understanding of the criteria and solve any disagreements before screening. Titles and abstracts will then be screened by two independent reviewers for assessment against the eligibility criteria for the review. Literature meeting the criteria will be retrieved in full and assessed against the eligibility criteria by two independent reviewers. Any disagreements that arise between the reviewers during title and abstract screening or full-text screening will be resolved through discussion with a third reviewer. Search results and reasons for exclusion of full-text papers that do not meet the eligibility criteria will be recorded and reported in a PRISMA-ScR flow diagram [26].

Data Extraction

Data from papers included in the scoping review will be extracted to predefined tables by two independent reviewers. Tables will be created using the data extraction instrument from Peters and colleagues [30] adapted to address the review objectives and to take into consideration the different study designs [30]. Multimedia Appendix 2 contains full details of which data will be sought. The data extracted will include specific details describing the population, concept, and context of the study, as well as its methods and results relevant to our scoping review. A draft of the data extraction tables is provided in Multimedia Appendix 2. The draft data extraction tables will be modified and revised as necessary during the process of data extraction. Modifications will be detailed in the full scoping review. The first three references will be extracted together by two reviewers as a pilot test to ensure consistency and reliability. Data from all remaining studies will then be extracted by two independent reviewers and compared once all are complete, with a third reviewer available to consult in case of disagreement.

Data Analysis and Presentation

The findings of the scoping review will be classified under conceptual domains based on the primary and secondary research questions and the Canadian Model of Occupational Performance and Engagement (CMOP-E) [31]. The CMOP-E was originally developed by the Canadian Association of Occupational Therapists and outlines the primary domains of interest to the scope of practice of OT. It has three components: (1) the person, situated at the center of the model, (2) the environment (the physical, cultural, institutional, and social spaces where the "occupations" occur), and (3) occupation, including the subcategories of self-care, productivity, and leisure. In this model, the occupation is seen as the connection between the person and their environment [31]. Describing the results in this manner will ensure clarity when reporting key findings. Furthermore, given that this model is consistent with the International Classification of Functioning Disability and Health (ICF), our findings will be presented in a manner that is in line with internationals standards [31]. A summary of extracted data will be provided in predefined tables (Multimedia Appendix 2). The extracted data will be reported in a narrative summary providing the answers to our research questions, and key findings will be presented in a table within the manuscript. We will also illustrate themes and their relationships in an infographic or schematic.

Results

The project was initiated in January 2021. After formalizing the study methods, and prior to title and abstract screening, the protocol was registered with the Open Science Framework (OSF) from the Center for Open Science in February 2021. Data collection commenced in March 2021 and is ongoing at the time of submission. Data collection is expected to be completed by June 2021. Data analysis and drafting of the manuscript will occur throughout 2021, with expected publication in 2022.

Discussion

To the author's knowledge, this is the first scoping review to explore the role of OT in PR programs. By exploring a breadth of literature, including quantitative, qualitative, and mixed methods study designs, as well as clinical practice guidelines, systematic reviews, and PR program surveys, this study will provide a comprehensive description of the role of OT in PR programs. In addition, this study will systematically map the recommendations of current guidelines for the inclusion and roles of OT in PR programs, if any; estimate the prevalence of OT as part of PR programs; and summarize the reported effects of OT as part of PR. In doing so, this study will complement several guidelines that emphasize the importance of multidisciplinary care in PR [32-34] and may provide more specification and clarification for the role of OT in these multidisciplinary programs.

The results of this study will be of interest to all health care professionals and policy makers involved in the delivery of PR programs across many health care settings. The findings of this scoping review will allow these stakeholders to better understand the scope, roles, and responsibilities of OT within PR care pathways. This role clarification will inform program development and clinical decision making and will serve to optimize the delivery of multidisciplinary care for patients in PR programs, ultimately improving patient and health care services outcomes.

This proposed scoping review has many strengths. Preregistering the protocol prior to title and abstract screening reduces risk of bias and ensures research transparency [35]. Furthermore, using the JBI methodological framework and PRISMA guidelines for reporting results optimizes the rigor of this scoping review. Additionally, a comprehensive search strategy was developed in consultation with an experienced librarian, and the broad scope of the inclusion criteria was chosen to provide the most breadth and depth of information relating to the role of OT in PR programs. Finally, targeted gray literature searching will capture the most relevant information from OT association websites.

This scoping review is limited by language criteria, which restricts our ability to examine the role of OT in PR programs delivered in languages other than English, French, or Portuguese. There is a possibility that important roles of OT in PR programs exist in literature inaccessible to our group due to language barriers. Furthermore, though intentionally targeted, the search of gray literature will be minimal due to time constraints. Additionally, the literature search will be limited to four databases. It is likely that the majority of the relevant literature on the topic is included in these databases, but the possibility remains that additional literature of interest may be missed. Finally, and inherent to all scoping review methodology, this review will not include a critical appraisal of the evidence, which limits the ability of this review to make recommendations based on the literature or identify gaps on the basis of low-quality evidence.

In conclusion, this study will enhance our understanding of the role, extent, and effect of OT in PR programs, which has the

potential for OT role enrichment or expansion, ameliorated interdisciplinary patient care and, most importantly, improved patient outcomes.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 16 KB - resprot_v10i7e30244_app1.docx]

Multimedia Appendix 2
Data extraction tables.
[DOCX File , 9 KB - resprot_v10i7e30244_app2.docx]

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Abbreviations

ADL: activities of daily living
CMOP-E: Canadian Model of Occupational Performance and Engagement
COPD: chronic obstructive pulmonary disease
DALY: disability-adjusted life year
ILD: interstitial lung disease
JBI: Joanna Briggs Institute
OSF: Open Science Framework
OT: occupational therapy
PR: pulmonary rehabilitation
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Cranial Nerve Noninvasive Neuromodulation in Adults With Neurological Conditions: Protocol for a Scoping Review

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Abstract

Background: Cranial nerve noninvasive neuromodulation (CN-NINM) via translingual nerve stimulation (TLNS) is a promising new intervention combined with neurological rehabilitation to improve outcomes for persons with neurological conditions. A portable neuromodulation stimulation (PoNS) device rests on the tongue and stimulates cranial nerves V and VII (trigeminal and facial nerves, respectively). Emerging evidence suggests that CN-NINM using the PoNS device, combined with targeted physical therapy, improves balance and gait outcomes but has not yet been comprehensively reviewed.

Objective: This review will describe CN-NINM via TLNS and its applications, effects, and implications for rehabilitation science in adult populations with neurological conditions. We will identify how CN-NINM via TLNS is currently being incorporated into neurological rehabilitation and identify gaps in evidence with respect to this novel technology.

Methods: Joanna Briggs Institute methodology will be used to conduct this scoping review. Electronic databases MEDLINE, AMED, CINAHL, Embase, and Web of Science will be searched, as well as gray literature databases ProQuest, DuckDuckGo, and Google. Studies published in English and French between 2000 and 2021 will be included. Two reviewers will independently screen all titles and abstracts and full-text papers that meet the inclusion criteria. Data will be extracted and collated in a table to synthesize the results. Extracted data will be reported in a comprehensive summary.

Results: The final manuscript is intended for submission to an indexed journal in September 2021.

Conclusions: This scoping review will be the first, to our knowledge, to address the current evidence on CN-NINM. The results will inform the use of CN-NINM in neurological rehabilitation and the development of recommendations for future research.

Trial Registration: Open Science Framework 10.17605/OSF.IO/XZQFM; https://osf.io/xzqfm

International Registered Report Identifier (IRRID): PRR1-10.2196/29965

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KEYWORDS

cranial nerve; neurological conditions; neurology; neuromodulation; neurorehabilitation; physical therapy; portable neuromodulation stimulation device; rehabilitation; scoping review; translingual neurostimulation

Introduction

Background

Neurological disorders are currently the leading cause of disability worldwide, and the burden of death and disability caused by them is increasing [1,2]. Stroke, multiple sclerosis (MS), and traumatic brain injury (TBI) are among the largest contributors to disability and mortality worldwide [1,3]. Although the global age-standardized incidence, mortality, and prevalence rates of neurological conditions have been decreasing from 1990 to 2015, years lived with disability and death from neurological conditions has been increasing over the same period [1]. This is consistent with a continually aging population and suggests that people with neurological conditions are living longer with persistent disability [1].

Recent literature has explored the burden of disability among patients with neurological conditions [4-6]. Older adults living with neurological disorders are at a significantly higher risk of falls compared to healthy older adults [4]. A systematic review by Lai et al [4] reported that approximately 73% of individuals who have sustained a stroke will experience a fall in the first 6 months after discharge from hospital. Additionally, motor function deficits make common activities challenging for stroke survivors, such as reaching, grasping, and holding onto household objects [5]. Similar functional impairments have been observed in people with MS. Coote et al [6] reported that over a 6-month period, 71% of older adults with MS sustained a fall compared to 41% of age-matched healthy controls. Individuals with MS who experienced a fall were much more likely to sustain serious injury [6]. As the neurological burden of disease is expected to grow over the coming decades, the development of new, effective rehabilitation interventions to improve the lives of people with neurological conditions is of utmost importance [1].

Cranial nerve noninvasive neuromodulation (CN-NINM) is a novel and emerging technology, grounded in mechanisms that facilitate neuroplasticity, for targeted use in individuals with neurological conditions [7-12]. CN-NINM involves translingual neurostimulation (TLNS) with a portable neuromodulation stimulation (PoNS) device [13-16]. Use of the PoNS device, combined with targeted physical therapy, aims to address longstanding balance and gait deficits in people with neurological conditions [13,14,16].

The PoNS device is equipped with an electrode array that is placed on the anterior dorsal surface of the individual's tongue [10,13,17]. Electrical impulses are delivered via the PoNS device to the tongue, which stimulate the trigeminal (CN V) and the facial (CN VII) nerves [16,18-20]. Other CNs have been reported to be stimulated as well, including the glossopharyngeal (CN IX), vagal (CN X), and hypoglossal (CN XII) nerves [11,18]. Stimulation of the CNs subsequently leads to the stimulation of targeted areas in the brainstem and cerebellum through the lingual branch of CN V and chorda tympani branch of CN VII [18]. Repetitive stimulation of structures in the brainstem and cerebellum potentiates a cascade of central nervous system neuromodulation [21,22]. Combined with physical therapy, this procedure potentiates significant long-term neuroplastic change [10].

There are a number of advantages to TLNS using the PoNS device for neurological rehabilitation. First, it is a portable noninvasive therapy amenable to home use and can enable higher-frequency and -intensity rehabilitation programs [13,15,17]. Second, to date, there have been no reports of serious adverse events with the use of the PoNS device [23]. Third, this procedure has broad applicability to a wide variety of neurological conditions [23]. Finally, CN-NINM has a rapid effect; neuroplastic changes have been demonstrated in several brain regions after only 5 days of use [11].

The PoNS device uses a biphasic waveform designed to ensure net 0 direct current to minimize tissue irritation [16,23-25]. Voltage and timing are preprogrammed and cannot be adjusted by the user, but the user can adjust the intensity by changing the pulse width [24,25]. There are a wide range of parameters (pulse width, frequency, and intensity) used in the literature; however, optimal parameters remain to be established [7,25]. Intensity of the intervention is variable, ranging 1-3 times per day, while treatment duration ranges between 2 weeks to 7 months [25-33]. Treatment sessions range 20-90 minutes and are typically combined with an active physical rehabilitation program [25,29,31,32]. Two frequencies have been reported in the literature, a high-frequency pulse (150 pulses/second) and a low-frequency pulse (0.08 pulses/second) [32]. Low-frequency pulses, however, are only delivered by the low stimulation pulse device that has been developed exclusively for research purposes (personal communication from Helius Medical Technologies, May 2021).

Case studies and case series have elucidated promising initial clinical applications of CN-NINM via TLNS in a variety of neurological conditions. For example, significant improvements in chronic balance deficits, reducing falls, and improving gait have been reported in individuals living with moderate TBI [7,8,14,15]. Improvements have also been demonstrated in mobility, incidence of falls, and balance in individuals living with stroke [15,27-29]. Lastly, CN-NINM has demonstrated improvements in gait, balance, posture, and self-observed disability in individuals with balance disorders [7].

A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews, and Joanna Briggs Institute (JBI) Evidence Synthesis was conducted on February 14, 2021. In the preliminary search, no current or ongoing scoping reviews were identified. Papa et al [11] identified a systematic review that assessed the efficacy of CN-NINM for nervous system disorders [11]. A recent narrative review by Diep et al [7] summarized and appraised the available evidence for TLNS. However, considering the nature of narrative reviews, there is an inherent high risk of bias [34]. This scoping review of CN-NINM will expand on these previous reviews by systematically searching both peer-reviewed and gray literature. Here we performed a scoping review because it involves the analysis, synthesis, and reinterpretation of a broad range of evidence, including different study designs and nonresearch articles, to provide clarity on the emerging field of CN-NINM [35,36]. This will enable clinicians and researchers to gain an

understanding of the current state of knowledge with respect to CN-NINM.

Objectives

The objectives of this scoping review are to assess and understand the evidence available for CN-NINM, including a description of CN-NINM and its mechanism of action, the devices utilized, and for which conditions or clinical symptoms evidence is currently available. Furthermore, we will explore the effects of CN-NINM outlined by previous research efforts, and how CN-NINM is being incorporated into neurological rehabilitation. The current gaps in the literature will be identified, and the implications for rehabilitation science and future research directions will be discussed. This will be the first scoping review of the CN-NINM evidence base; therefore, it will be essential for informing future research and health care policies. The objectives, inclusion criteria, and methods for this scoping review were specified in advance and documented on Open Sciences Framework registries [37].

Review Questions

The following questions have been addressed in this review:

1. What is CN-NINM, and how is CN-NINM being delivered?
2. What are typical parameters used in CN-NINM?
3. Which conditions or clinical symptoms have evidence supporting the use of CN-NINM?
4. How is CN-NINM being incorporated into neurological rehabilitation?
5. What has previous research shown on the effects of CN-NINM in neurorehabilitation?
6. What are the current gaps in the evidence base and the implications for rehabilitation science?

Methods

Study Design and Ethics Approval

The proposed scoping review will follow the JBI methodology for scoping reviews [38]. The study is designed and will be conducted in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) framework [39]. The objectives, inclusion criteria, and methods for this scoping review were specified in advance and documented on Open Sciences Framework registries [37].

Inclusion and Exclusion Criteria

Eligibility criteria were established a priori using the population, concept, context framework. Studies will be selected in accordance with the following criteria.

Population

This review will consider studies that involve adults with neurological conditions (≥18 years of age) including but not limited to MS, mild TBI including concussions, moderate TBI, severe TBI, and stroke.

Concept

The concepts to be explored include CN-NINM, PoNS, and TLNS. We will exclude other forms of invasive and noninvasive brain stimulation such as functional electrical stimulation, transcranial magnetic stimulation, deep-brain stimulation, and transcranial electrical stimulation techniques.

Context

This review will consider studies conducted in any context and geographical location to widely explore its application in neurological rehabilitation.

Types of Sources

In lieu of the exploratory nature of this scoping review, no restrictions will be placed on the types of sources included in this review. This scoping review will consider including studies with quantitative, qualitative, and mixed methods designs. Furthermore, systematic reviews and gray literature including nonresearch articles, opinion papers, texts, as well as documents from relevant websites will be considered. Studies in English and French published since 2000 will be included.

Search Strategy

The search strategy will identify peer-reviewed articles and gray literature to explore the full breadth and depth of available evidence. An initial limited search of MEDLINE and CINAHL databases was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles were used to develop a full search strategy for MEDLINE (Multimedia Appendix 1). An academic librarian was consulted for suggestions regarding key concepts and Medical Subject Headings. The academic librarian approved the search strategy for MEDLINE, which will be adapted for the other respective databases. Boolean operators (ie, “OR” and “AND”) will be used to combine and refine search terms and concepts. The search will be iterative in nature; therefore, additional search terms may be identified and incorporated into the search strategy. The review team will hand-search all reference lists of the included articles to identify additional studies of relevance.

Articles in English and French, published from January 2000 to the present will be included. This time frame is deemed appropriate as CN-NINM is a novel neuromodulation technique that emerged from the sensory substitution research performed in the early 1990s at the Tactile Communication and Neurorehabilitation Laboratory at the University of Wisconsin-Madison [16,40].

The databases to be searched include MEDLINE, AMED, CINAHL, Embase, and Web of Science. Sources of unpublished studies and gray literature will include ProQuest, DuckDuckGo, and Google. Gray literature will also be targeted from relevant health or scientific organizations pertinent to CN-NINM (eg, Helius Medical Technologies Inc).

For the gray literature search strategy, consistent terms will be used for each browser. The date and time as well as the results of the search will be documented. The first 5 pages of results will be screened. If a document meets the inclusion criteria, a backward and forward reference search will be performed to identify other relevant documents.

Selection Process

After the search, all identified records will be collated and imported to Zotero reference management software (Center for History and New Media, George Mason University) and duplicates will be removed. The research team will screen the first 10 citations of the initial MEDLINE search to assess the inclusion and exclusion criteria and researcher agreement. Any discrepancies will be discussed and resolved collectively among the research team. The titles and abstracts of the remaining articles will be screened by groups of 2 researchers for assessment against the inclusion criteria identified a priori. Screening differences will be resolved between the 2 researchers, and in cases where an agreement cannot be reached, senior researchers will be consulted. Researchers will categorize studies as "include" or "exclude" to identify articles for full-text screening. Potentially relevant papers will be retrieved in full, and their citation details imported into Covidence screening and data extraction tool (Veritas Health Innovation). Full-text review will be undertaken by groups of 2 researchers. Any disagreements between researchers with regard to the inclusion and exclusion criteria will be resolved through discussion and debate; if a consensus is not reached, a senior researcher will be consulted. Reasons for exclusion of full-text papers that do not meet the inclusion criteria will be recorded and reported in the scoping review.

Articles published in French will undergo 2-stage screening by a senior researcher and 1 author. Any disagreements during the full-text review will be resolved through discussion with the entire research team.

The results of the search will be reported in full and presented in a PRISMA-ScR flow diagram [39].

Data Extraction

Data extraction will be completed by groups of 2 researchers by using a data extraction tool developed by the research team. To ensure accurate data collection, the extracted data will be compared; discrepancies will be resolved through consensus, or a third researcher will serve as an arbitrator. The data extracted will include specific details about the study population, concept, context, study methods, and key findings relevant to the research questions. Authors of those articles will be contacted to request missing or additional data, where required.

A draft extraction table is provided in Multimedia Appendix 2 and includes minor revisions to the original JBI template [38]. Revisions include examples of details or results extracted from studies to align with the objective of this scoping review. The research team will trial the data extraction table on 2 or 3 sources to ensure that all relevant results are extracted [38]. Modifications will be identified in the full scoping review report.

Data Presentation

The collected data will be presented in a tabular or graphical format that aligns with the scoping review's proposed research questions. A summary and synthesis of the findings and discussion of the review will accompany the tabulated or charted data. The full scoping review will be reported in accordance with the PRISMA-ScR checklist [39].

Results

The collated results will be presented in a scoping review publication. The research team has already initiated study activities, and the results will be available by September 2021.

Discussion

Overview

People living with neurological conditions are living longer, often with persistent disabilities that have become refractory to rehabilitation [1]. CN-NINM is a promising new intervention designed to augment physical rehabilitation by harnessing neuroplastic mechanisms to ameliorate persistent movement disabilities related to neurological conditions [1]. It is important for clinicians and researchers to understand the current state of knowledge with respect to CN-NINM, and a scoping review allows for comprehensive exploration of the available literature. This will be, to our knowledge, the first scoping review to comprehensively map the available literature on the use of CN-NINM in neurological rehabilitation. Mapping the literature will yield an outline of current studies and resources within the field, identify current gaps in the evidence base, and provide recommendations for future research. Furthermore, the review will explore how CN-NINM is being incorporated into neurological rehabilitation and its effects, with implications for both researchers and clinicians.

A systematic review by Papa et al [11] reported numerous studies that used the PoNS device and investigated its effects on balance and sensory-motor coordination in a variety of central and peripheral nervous system conditions. Papa et al [11] highlighted the advantages of the device, its noninvasive nature and portability, and its effects on several brain regions. Similarly, the narrative review by Diep et al [7] acknowledges that CN-NINM can be feasibly and safely administered to people with diverse neurological conditions. CN-NINM was found to improve balance and gait symptoms secondary to chronic mild-to-moderate TBI, balance disorders, spinal cord injuries, and Parkinson disease [7]. Both Papa et al [11] and Diep et al [7] highlighted the need for further studies to examine the use, applications, and effects of CN-NINM. As such, our rigorous scoping review will expand on these previous, but different, review methods to provide clarity on the breadth of the available evidence. Furthermore, it will identify research gaps by specifically exploring typical parameters used (pulse-width, frequency, and intensity), length of rehabilitation programs, and whether CN-NINM is typically incorporated as an adjunct intervention within neurological rehabilitation programs.

Limitations

The limitations of this scoping review include the following. First, the search was limited to 5 databases and 3 gray literature sources; hence, it is possible that pertinent literature may have been missed. However, these databases were chosen on the recommendation of an academic librarian at the McMaster University Health Sciences Library and represent the most extensive health science databases. Second, the gray literature search results may not be reproducible owing to the date, time,

and location of its conductance. Third, the articles screened and selected will be restricted to those published in English and French, which is an inherent limitation as pertinent literature on the topic may be published in other languages, thus being potentially missed in our search.

Conclusions

This scoping review will provide a comprehensive analysis, synthesis, and interpretation of the available literature on the use of CN-NINM in adults with neurological conditions. It will provide an up-to-date evidence summary for neurological rehabilitation specialists and will identify research gaps and limitations in the current literature. This knowledge is essential to guide future studies on CN-NINM.

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Authors' Contributions

Senior authors JVG and DB conceived the idea of the scoping review and developed the research questions; both contributed meaningfully to drafting and editing the manuscript along with the rest of the research team. TN and SD wrote the introduction. Lead author KB developed the study methods and wrote the discussion. KL, TH, and AB formalized the search and created the search strategy table.

Conflicts of Interest

None declared.

Multimedia Appendix 1
MEDLINE search conducted on February 19, 2021.
[DOCX File , 14 KB - resprot_v10i7e29965_app1.docx]

Multimedia Appendix 2
Data extraction instrument.
[DOCX File , 14 KB - resprot_v10i7e29965_app2.docx]

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Abbreviations

CN-NINM: cranial nerve noninvasive neuromodulation
JBI: Joanna Briggs Institute
MS: multiple sclerosis
PoNS: portable neuromodulation stimulator
PRIMSA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
TBI: traumatic brain injury
TLNS: translingual nerve stimulation

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